Psychophysiological responses to emotional stimuli and their alterations in stress-related mental disorders

Dissertation submitted for the degree of
Doctor of Natural Sciences

Presented by
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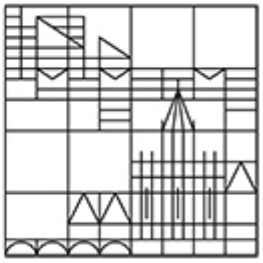
at the

Universität Konstanz



Faculty of Sciences

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Date of the oral examination: 10 October 2014
First referee: Prof. Dr. Thomas Elbert
Second referee: Prof. Dr. Chantal Martin Sölch

Konstanzer Online-Publikations-System (KOPS)
URL: http://nbn-resolving.de/urn:nbn:de:bsz:352-0-258442

DANK

Zunächst möchte ich mich ganz herzlich bedanken bei *Chantal Martin Sölch* und *Ueli Schnyder* für meine erste Stelle nach dem Studium und für die Förderung in den vergangenen Jahren. Thomas Elbert möchte ich herzlich danken für die Möglichkeit, in Konstanz zu promovieren und für seine unkomplizierte Unterstützung.

Des Weiteren geht mein Dank an *Annette Brühl* und *Monique Pfaltz* für die Unterstützung beim Schreiben der Artikel und an *Hanspeter Mörgeli* für die vielen Statistik-Besprechungen in den letzten Jahren. Ein besonderer Dank geht auch an *Misari Oe* für die Zusammenarbeit und den spannenden Kulturaustausch. Auch allen übrigen an den Projekten beteiligten möchte ich danken für die Zusammenarbeit und meinen Mitdoktoranden für den Austausch.

Nicht zuletzt geht ein grosses Dankeschön an meine Familie – ganz besonders an meine Eltern – und an meine Freunde für die moralische Unterstützung in dieser wie auch in anderen Zeiten. Danke dafür, dass ihr immer hinter mir steht.

Sonja Schumacher

Konstanz/Zürich, im Mai 2014

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Abbreviations

Ag/AgCl	silver/silver-chloride
AIC	Akaike's Information Criterion
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BIC	Schwartz's Bayesian Criterion
BPD	borderline personality disorder
bpm	beats per minute
CAPS	Clinician-Administered PTSD Scale
dB	decibel
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
EMG	electromyography
fMRI	functional magnetic resonance imaging
HPA	hypothalamic-pituitary-adrenal axis
HR	heart rate
HRR	heart rate response
Hz	Hertz
IADS	International Affective Digitized Sounds
IAPS	International Affective Picture System
IQ	intelligence quotient
M.I.N.I.	Mini-International Neuropsychiatric Interview
ms	millisecond
mV	millivolt
µS	microsiemens
OXT	oxytocin
PDS	Posttraumatic Stress Diagnostic Scale
PTSD	post-traumatic stress disorder
s	second
SAM	Self-Assessment Manikin

SC	skin conductance
SCID	Structured Clinical Interview for DSM-IV
SCL	skin conductance level
SCR	skin conductance response
SSNRI	selective serotonin/noradrenalin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAI	State Trait Anxiety Inventory

Summary

Peripheral physiological parameters can be measured easily and noninvasively and they can be used as an objective measure of information processing in addition to subjective self-report data. Peripheral physiological measures are often used in research about stress and emotions by investigating reactions to the perception of pictures or sounds with emotional content or to startling stimuli. Several mental disorders are associated with alterations in peripheral physiological reactions. Therefore, information about these reactions and how they change in psychopathology might be useful to better understand psychopathological processes.

This thesis aims at illustrating psychological and physiological processes, how they interact, and how they are modified in psychopathology. In a first study, the psychophysiological reactions of 32 healthy subjects to the anticipation and perception of emotional pictures were studied. Valence specific reactions could be measured already during anticipation. While anticipating pictures of unknown valence subjects showed a reaction pattern which is compatible with a pessimistic bias. In a second study, the modification of the startle response by emotional pictures, social content of the pictures and oxytocin as well as the influence of trait anxiety were tested with 44 healthy men. Results showed that oxytocin can reduce as well as enhance startle reactions, and that specific aspects of stimuli and individual differences in trait anxiety can lead to complex interactions with oxytocin. In a total of 41 subjects, the third study investigated differences in the startle reactions of healthy subjects, traumatized participants and remitted post-traumatic stress disorder (PTSD) patients. Traumatized subjects who had never developed a PTSD showed stronger startle responses than non-traumatized controls 10 years after the traumatic event. The fourth study examined the emotional processing in borderline personality disorder. Acoustic emotional stimuli were presented to 41 female subjects. Borderline patients showed lower skin conductance responses to negative stimuli than non-clinical controls. In addition, patients rated positive stimuli less positive and differentiated less physiologically between different valence categories than controls. The findings of these studies show that immediate emotional experiences as well as stressful experiences dating back a long time can influence physiological reactivity. The results also show that specific aspects of personality characteristics play an important role and should be taken into account in future research as these aspects might partly explain contradictory outcomes of previous studies.

Zusammenfassung

Peripherphysiologische Masse können mit wenig Aufwand gemessen werden, sind nicht invasiv und ermöglichen die objektive Messung von Informationsverarbeitungsprozessen als Ergänzung zu Befunde aus subjektiven Selbstberichten. Peripherpyhsiologische Messungen werden häufig eingesetzt in der Stress- und Emotionsforschung. Meist werden hier die Reaktionen auf Bilder oder Geräusche mit emotionalem Inhalt oder auf Schreckreize untersucht. Verschiedene psychische Störungen sind mit Veränderungen in diesen Reaktionen assoziiert. Die Erforschung dieser Veränderungen könnten möglicherweise Informationen liefern, die helfen, psychische Störungen besser zu verstehen.

Diese Dissertation hat das Ziel, psychische und physiologische Prozesse, deren Zusammenhänge sowie deren Veränderungen im Zusammenhang mit psychischen Störungen zu beleuchten. Zu diesem Zweck wurden in der ersten Studie physiologische Reaktionen auf die Erwartung und die Präsentation von emotionalen Bildern von 32 gesunden Probanden untersucht. Es zeigte sich, dass bereits in der Erwartungsphase valenzspezifische Reaktionen auftreten, und dass die Reaktionen auf eine unklare Valenz mit einem pessimistischen Bias vereinbar sind. Die Modifikation des Schreckreflexes durch emotionale Bilder, sozialen Inhalt der Bilder, die Ängstlichkeit der Person und Oxytocin wurde in der zweiten Studie an 44 gesunden Männern untersucht. Es zeigte sich, dass Oxytocin nicht nur schreckreflexreduzierende sondern auch -verstärkende Effekte haben kann, und dass Merkmale der Reize und der Person zu komplexen Interaktionen mit Oxytocin führen können. In der dritten Studie wurde an insgesamt 41 Probanden untersucht, ob sich der Schreckreflex bei Gesunden, bei Traumatisierten und bei Probanden mit einer remittierten post-traumtischen Belastungsstörung unterscheidet. Traumatisierte, die keine posttraumatische Belastungsstörung entwickelt hatten, zeigten 10 Jahre nach dem traumatischen Ereignis eine stärkere Schreckreaktion als nicht traumatisierte Kontrollprobanden. Die Veränderung der emotionalen Verarbeitung durch die Borderline Persönlichkeitsstörung wurde in der vierten Studie anhand von akustischen Stimuli an insgesamt 43 Frauen untersucht. Borderline-Patientinnen zeigten geringere Reaktionen auf negative Reize in der Hautleitfähigkeit als nicht-klinische Kontrollprobanden. Ausserdem zeigte sich, dass Borderline-Patientinnen positive Reize weniger positiv bewerten, sich an weniger positive Reize erinnern und dass sie physiologisch weniger zwischen verschiedenen Valenzen unterscheiden als Kontrollprobanden.

Die Ergebnisse dieser Studien zeigen, dass sowohl unmittelbare emotionale Reize als auch weit zurück liegende Stress-Erfahrungen physiologische Reaktionen beeinflussen können. Ausserdem zeigen die Resultate, dass auch spezifische Aspekte der Persönlichkeit die physiologische Reaktivität beeinflussen können und eventuell bisherige widersprüchliche Befunde erklären könnten.

1. General introduction

The dualistic philosophy by René Descartes (1596-1650) regarded body and mind as two separate entities. On the other hand, Descartes also raised the question of how these two entities interact (Descartes, 1649). Even today somatic and psychological problems are often treated separately, although a shift towards a more holistic view of health has started several decades ago (Suter, 1986). It is well known by now that psychological and physiological processes are closely linked. Evidence for this link is specifically clear with regard to stress and emotions. There is a large literature on the fact that physical as well as psychological stress can induce health problems of psychological and somatic nature (Banerjee, Das, & Foujdar, 2013; B. S. Dohrenwend, 1973; Hendrix, Ovalle, & Troxler, 1985; Marx, Garrity, & Bowers, 1975; Mather, Blom, & Svedberg, 2014; Rahe, Mahan, & Arthur, 1970). There are a number of open questions, though, about how exactly we are affected by stress and emotions. Stress and emotions have a clear physiological component and were first conceptualized as physiological responses (Lange & James, 1922; Selye, 1956). One central question in emotion theories is whether physiological reactions cause the experience of emotions or the other way around. There are numerous perspectives on this topic and there is a long history of debate in many disciplines about “whether the mind governs the body or the body governs the mind” (Adler, 1931). Several approaches and methods are needed to investigate the complex interactions of body and mind. This thesis focuses on the psychophysiological approach. This thesis investigates basic physiological response patterns under different emotional conditions and their alterations through psychological disorders. The link between psychological and physiological processes in healthy subjects and alterations of these processes in psychopathology might help to better understand mental disorders. In this introduction I will first outline some of the most important psychological theories of emotions and stress. Then I will address different aspects of the psychophysiology of emotions and stress. Next I will highlight alterations of emotional processing in two psychiatric disorders. Subsequently I will give an overview on the peripheral physiological measurements used in the studies of this thesis.

1.1. Emotion theories

Although emotions are ubiquitous and an important part of everyday life, it is not trivial to give a clear definition of what an emotion is. Working definitions are often given as a list of different aspects that compose emotions; four levels that are commonly mentioned are physiological, cognitive, behavioral

and affective aspects (Euler & Mandl, 1983). Therefore, an emotion could be defined as a subjectively experienced affect, which can be accompanied by physiological changes, cognitive processes and behavioral expressions (e.g. mimic expression). Physiological changes can be directly measured and behavioral components can be observed while the cognitive and affective levels are inner processes of the subject which can only be explored indirectly by asking questions. Emotion theories pivot around these levels, trying to put them into a causal order. At the same time, emotion theories try to explain where emotions come from (innate or learned). I will now take a look at some of the most important theories form evolutionary, learning, physiological, and cognitive perspectives.

1.1.1. Evolutionary perspective

Evolutionary theories see emotions as adaptive processes which support survival. Evolutionary theories of emotions were first recognized by the work of Darwin (1809-1882). He collected evidence that emotional expressions are interculturally universal (Darwin, 1872). The exact function of emotional expression has been debated though. While Darwin concentrated more on physical aspects (e.g. wide opened eyes to see better), newer theories like Ekman's emphasize communication as its main function (Ekman, 1971). Although John Watson (1878-1958) was a behaviorist, also his theory of emotions is partly evolutionary. Watson assumed that emotions are hereditary reaction patterns which are elicited by stimuli from the environment (Watson, 1919, 1929). He thought of emotions as something that has lost its adaptive value and which disturbs organized activity. As today humans live in a fast changing environment it might well be that some evolutionarily developed emotional reactions are not adaptive anymore.

1.1.2. Learning perspective

The focus of behavioristic theories was on learning and motivation (Meyer, Reisenzein, & Schützwohl, 2001). Therefore, behavioristic theories of emotions also focused on learning. In addition to the innate basic emotions anger, fear and love, John Watson postulated secondary emotions that are learned (Watson, 1919, 1929). According to Watson, these learned emotions are built on the three basic emotions. They are formed through classical conditioning (association of an originally neutral stimulus with a pleasant or unpleasant experience), which alters inherited behavior (Meyer et al., 2001). Watson & Rayner (1920) proved that emotional reactions can be learned by conditioning a fear response in a 9 months old child (known as "little Albert"). They also described procedures to delete the conditioned fear response, which have been tested later (Jones, 1924). Systematic desensitization

is a technique in behavioral therapy, which has developed from these experimental methods (Davison & Neale, 1998). Also, Mowrer's two-factor theory explains fear responses by learning processes (Mowrer, 1947). He focused on avoidance learning in phobias and argued that after a stimulus has been associated with an unpleasant experience (fear learning by classical conditioning) this stimulus is avoided in order to remove unpleasant emotions (operant conditioning).

1.1.3. Physiological perspective

Carl Lange and William James (1922) characterized emotions as reflexes that are caused by physiological processes. Cognition was not considered as a cause for emotions because an appraisal would occur, if at all, only after the emotional experience and could contradict the emotion. According to the James-Lange theory the perception of a certain situation leads to arousal which in turn leads to the emotion (Lange & James, 1922).

Walter Cannon (1927) did not agree with the James-Lange theory because many different emotions are associated with the same physiological arousal pattern. So if the physiological arousal was the cause it would not be possible to differentiate between these emotions. In animal experiments Cannon also showed that the central nervous system is necessary for emotional experiences but that the emotional experience remained unchanged even if the viscera were disconnected from the central nervous system (Cannon, Lewis, & Britton, 1927). Therefore, Cannon's theory postulates that emotional processes need the central nervous system to develop and that physiological processes and emotions are both caused by the perception of a situation and develop in parallel. As behaviorists considered only observable aspects in their theories, according to John Watson the most important component of emotions is physiological and triggers for basic emotions can be objectively described without relation to psychological conditions (Watson, 1919, 1929).

1.1.4. Cognitive perspective

A problem with a mechanistic view of stimulus and response in the context of emotions is that emotional processes cannot be explained by observable aspects alone. For example the emotion of surprise depends on a stimulus which was not expected. But a stimulus can only be unexpected in relation to a non-observable inner condition of an individual (English, 1929).

According to Stanley Schachter's two factor theory of emotion (Schachter, 1964; Schachter & Singer, 1962) the emotional experience originates in the interaction of physiological arousal and a cognitive interpretation. As soon as we notice physiological arousal, we search for an explanation and the

interpretation depends on the context. According to this theory cognitive interpretation explains why the same arousal pattern can be experienced as different emotions. Newer theories focus even more on the cognitive level. They postulate that emotions arise only in association with personal goals and appraisal processes which determine a goal-relevant meaning to a given situation (Ellsworth & Scherer, 2003; Gross, 2014; Scherer, 2001). In addition, strategies to regulate emotions might be necessary when emotions compromise the achievement of a goal, like for example anxiety before a talk (Gross, 2013). Modern emotion theories also account for the complexity of emotional phenomena. For example the modal model of emotion (see Figure 1) mentions person-situation interactions, attention, meaning, goals, and a multisystem response to be involved in emotional processes and that the response loops back to change the original situation (Gross, 2014). Strategies to regulate emotions can take place at different stages (see Figure 1) within emotional processing (Gross, 2013). According to Lazarus, stress and emotional processes are closely linked (Lazarus, 1993). Lazarus' theory of emotions developed from his stress theory. Stress theories will be discussed in the next section.

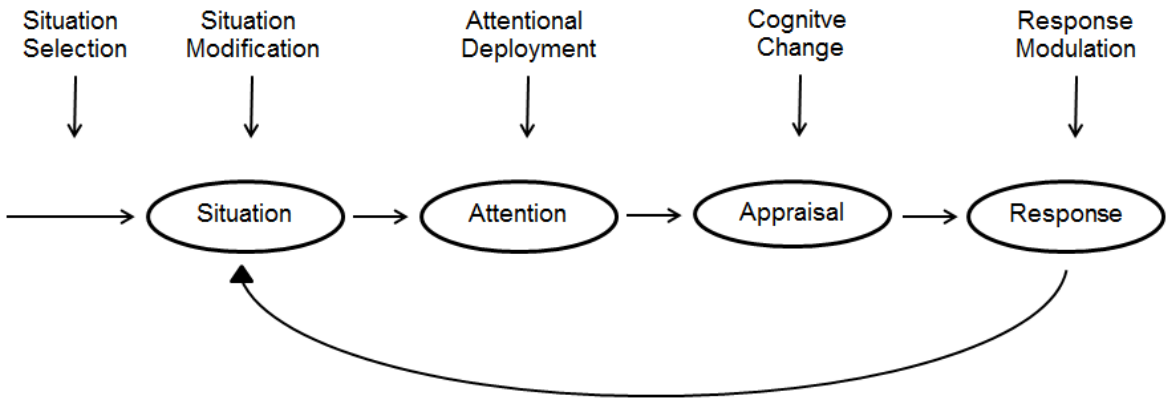

Figure 1. Illustration of the modal model of emotions with *situation*, *attention*, *appraisal* and *response* as stages in emotional processing and the response looping back at the situation (Gross, 2014). Five stages are illustrated at which emotions can be regulated (Gross, 2013).

1.2. Stress theories

Stress can be defined as a tension caused by a force on a system which will cause damage on the system, unless the system is able to compensate (Lovallo, 2005). In the 17th century, Robert Hooke defined stress in technical terms as the area over which a load is placed (Hinkle, 1973). He was concerned about how bridges must be constructed to carry heavy loads. This definition has often been

used as a metaphor in psychology (Lazarus, 1993). Analogous to emotion theories, also stress theories can be looked at from evolutionary, physiological and cognitive perspectives.

1.2.1. Evolutionary perspective

Walter Cannon introduced the concept of the “fight or flight reaction” (Cannon, 1929), which helps the organism to survive in the face of threat by activating the necessary resources to handle the situation. He used the term “homeostasis” to describe the state of a healthy organism that has to be maintained by taking action against stimuli or conditions that threaten this state (called stressors). Cannon was first to use the word “stress” in this context (Lovallo, 2005). While acute stress can be handled by the fight or flight reaction, this reaction is not adaptive in long-term stress situations which are typical for our modern environment. Therefore, the evolutionarily developed reactions of the human body in response to the modern world long-term stress can lead to exhaustion and illness (Chrousos & Gold, 1992). Therefore, analogous to emotions, there is also the notion of an evolutionarily developed mechanism which is not adaptive anymore in certain situations of modern life (Chrousos, 1998; Chrousos & Kino, 2007).

1.2.2. Physiological perspective

According to Hans Selye, stress is “the nonspecific response of the body to any demand” (Selye, 1956). The general adaption syndrome is a model, developed by Hans Selye, of the reaction to long lasting stress. In this model there are three stages in the adaptation process: alarm, resistance and exhaustion. Each of these stages is associated with specific physiological processes (Selye, 1974): In the alarm stage a danger is recognized and the organism prepares for action. The hypothalamic-pituitary-adrenal axis (HPA axis) is activated and cortisol, adrenaline and noradrenaline are released. In the resistance stage the organism tries to restore homeostasis through recovery. If this is not possible because the stressor is not eliminated the organism falls into the third stage of exhaustion. In this stage the energy needed for recovery is used up. The general adaptation syndrome is illustrated in Figure 2).

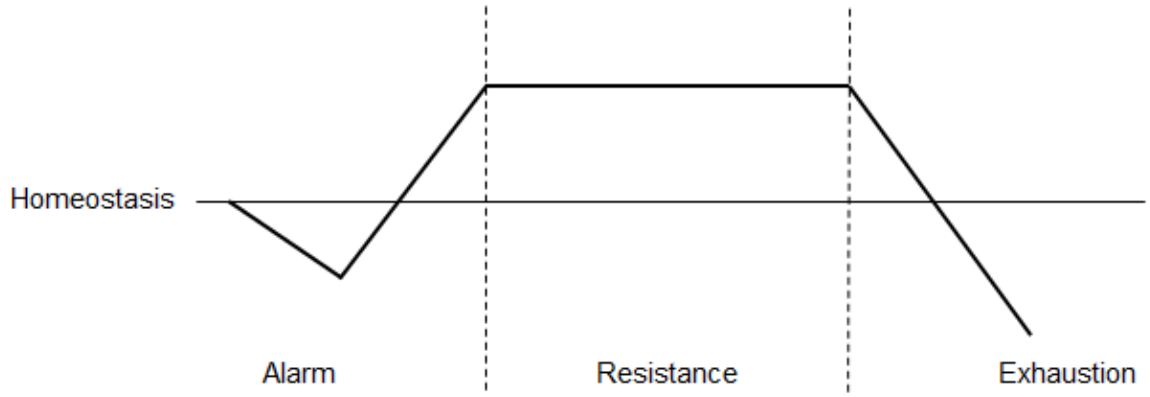

Figure 2. Illustration of the three stages of the general adaptation syndrome (Selye, 1974). In the alarm stage homeostasis is affected by a stressor and the individual prepares for action. In the resistance stage the organism tries to restore homeostasis through recovery. If this is not possible the organism falls into the third stage of exhaustion.

1.2.3. Cognitive perspective

Clearly the same situation does not lead to the same response in all individuals. So there must be something that mediates between condition and outcome. While Selye used a physiological definition of stress, Lazarus defined it in psychological terms to be able to explain why the same situation has different impact on different people. According to Lazarus the subjective appraisal of a situation determines the consequences much more than the objective characteristics of the situation. A first evaluation of a situation is necessary to distinguish between irrelevant, harmless or even positive, and dangerous situations (Lazarus & Folkman, 1984). Lazarus calls this process the primary appraisal. A secondary appraisal becomes necessary if the situation is a threat or a challenge. This process evaluates the things that can be done to handle the given situation, the so called coping options (Lazarus & Folkman, 1984). From this perspective, psychological stress can be defined as the consequence of a situation that exceeds the perceived ability to cope with it (Cohen, Tyrrell, & Smith, 1991). Coping in turn is an important factor for health outcomes (see section 1.2.3.).

In the literature, stress and emotions are often treated as separate fields. But according to Lazarus they belong together. In his opinion the concept of stress is included within the concept of emotion and psychological stress is in fact a subset of emotions (Lazarus, 1993). Another link from stress to emotions can be seen in Selye's distinction between "distress" and "eustress" (Selye, 1974). Whereas distress refers to severe threats which can lead to diseases, milder challenges that are regarded as positive are called eustress. Therefore stress is not exclusively associated with negative but also with positive emotions.

As this overview shows there are many ways of looking at emotions and stress and many aspects to investigate. Focusing on just one of the many components can never give a comprehensive understanding of emotions. Therefore, all sorts of different research approaches are needed. The physiological level of the emotional experience is probably the most objective one to measure as these reactions cannot easily be influenced consciously. It is the level this thesis focuses on. In the next section I will take a closer look at the psychophysiological level of stress and emotions.

1.3. Psychophysiology of stress and emotions

1.3.1. Orienting, defensive and startle responses

Novelty in the environment elicits an orienting response which was first described by Pavlov (1927). Among other components, like for example an orientation of the eyes towards the novel stimulus, the orienting response comprises an increase in skin conductance and a deceleration in heart rate. If the eliciting stimulus is repeated but of no threat and constant in its properties (like for example loudness, pitch and so on), the orienting response habituates quickly (Sokolov, 1963).

On the other hand, more intense, sustained, and potentially threatening stimuli can elicit a defensive response. In contrast to the orienting response, the defensive response increases heart rate (Viken, Johnson, & Knutson, 1991) and habituates slowly (Sokolov, 1963). The defensive response prepares the body for a fight-or-flight reaction. Heart rate acceleration might also help to tune out negative stimuli (Lacy, 1967). Although tones are most often mentioned to induce orienting and defensive responses, for example Hare (1973) showed that visual stimuli can also induce them. In his study pictures of spiders elicited orienting responses in non-phobic subjects while spider-phobic subjects showed defensive responses (Hare, 1973).

Very intense, brief, and unexpected stimuli can elicit a startle response. The startle reaction is a reflex that involves muscle movements of the whole body to protect it from harm (Landis & Hunt, 1939). It interrupts ongoing behavior in the presence of a sudden intense stimulus (Graham, 1992). The eye-blink reflex is a part of the startle reaction which can easily be triggered, for example by a loud tone or noise (Landis & Hunt, 1939). It can be measured by placing two small electrodes below the eye, over the musculus orbicularis oculi (Fridlund & Cacioppo, 1986). The two most important components of the eye-blink that can be measured are the amplitude of the blink and its onset latency. The amplitude measures the strength of the muscle contraction, the onset latency how quickly the contraction occurs. Stronger reactions are characterized by higher amplitudes and shorter onsets. The

startle reflex is also associated with autonomic responses like increased heart rate and skin conductance (Orr, Lasko, Metzger, & Pitman, 1997; Orr, Lasko, Shalev, & Pitman, 1995; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Shalev, Orr, Peri, Schreiber, & Pitman, 1992)..

Several characteristics of a stimulus determine the strength of the startle reaction. Loudness, duration, and suddenness seem to be important (Graham, 1975). Whether white noise or a pure tone is more effective depends on stimulus length. While at very short length (shorter than 32ms) a pure tone elicits a stronger reaction (Graham, 1975), with longer stimulus duration white noise was found to be more startling (Graham & Slaby, 1973). In healthy subjects the eye-blink reflex habituates if the same stimulus is presented several times (Geyer & Braff, 1982). This means that the reaction becomes weaker and slower as the stimulus becomes more familiar. Because habituation is quicker to predictable stimuli (Davis, 1970) repetitions of the same startle stimulus within an experimental session have to be presented in variable inter-stimulus intervals so that the subject cannot anticipate an upcoming stimulus event. The habituation that can be observed within an experimental session is called short-term habituation while habituation occurring between sessions is called long-term habituation (Stern, Ray, & Quigley, 2001).

The startle reaction can be modulated in several ways (Filion, Dawson, & Schell, 1998). Emotional states, for example, can alter the startle reaction. A positive emotional state can lower the startle response while a negative emotional state can increase it (Lang, Bradley, & Cuthbert, 1990). A negative affect (or a stressful situation) is congruent with the startle reflex because both are driven by an aversive motivational system. Therefore, the reflex is augmented because its motivational system is already active. At the same time, a positive emotional state is driven by an appetitive motivational system and will therefore inhibit aversive reflexes (Lang et al., 1990). Positive and negative pictures, for example, were shown to be able to induce affective states that modulate the startle response accordingly (Vrana, Spence, & Lang, 1988). Some studies also demonstrated that phobic patients show heightened startle responses to phobia-relevant stimuli (deJong, Visser, & Merckelbach, 1996; Hamm, Cuthbert, Globisch, & Vaitl, 1997; Vrana, Constantine, & Westman, 1992). Therefore, the startle reaction can be used to indirectly investigate emotional processing and emotion regulation (Grillon & Baas, 2003). Another way to modulate the startle response is by prepulse inhibition. A prepulse is a weak stimulus given shortly before the startle probe, which reduces or eliminates the response to the startle stimulus (Graham, 1975; Hoffman & Ison, 1980). This effect is seen as a mechanism to protect preattentive processing (Graham, 1975) and is deficient in pathologies

characterized by problems in filtering out unwanted thoughts, as e.g. schizophrenia or obsessive compulsive disorder (Braff, Grillon, & Geyer, 1992).

1.3.2. Hormones

Cortisol is a glucocorticoid hormone associated with the stress response. As already mentioned in section 1.1.2., stress activates the hypothalamic-pituitary-adrenal (HPA) axis which leads to the release of cortisol from the adrenal cortex (Foley & Kirschbaum, 2010). The HPA axis is illustrated in Figure 3.

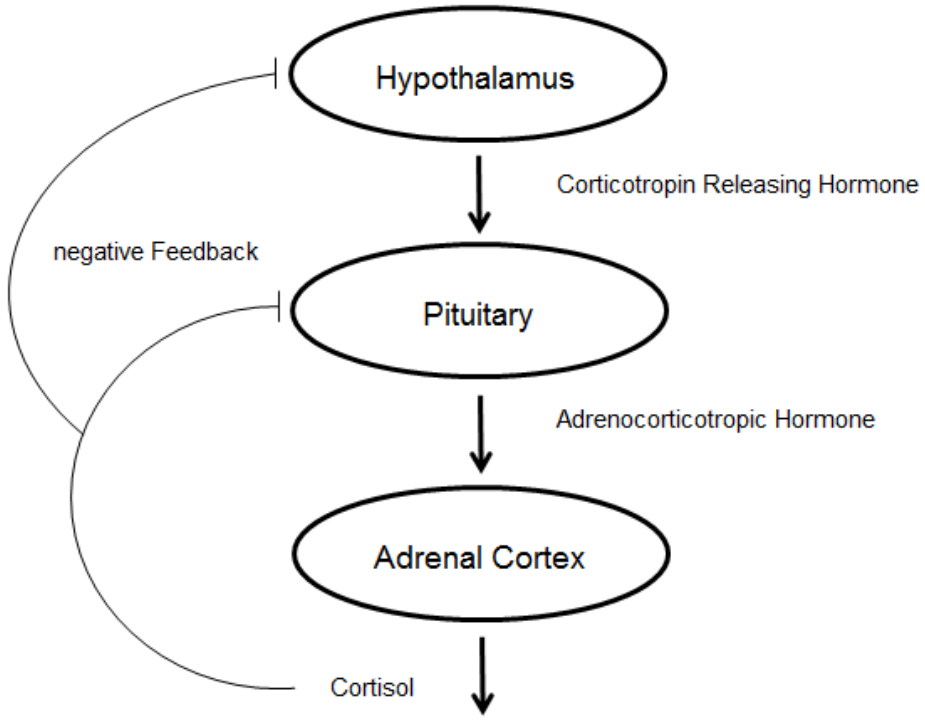

Figure 3. Illustration of the hypothalamus-pituitary-adrenal (HPA) axis. The release of corticotropin releasing hormone from the hypothalamus leads to the release of adrenocorticotropic hormone from the pituitary, which in turn leads to the release of cortisol from the adrenal cortex. The release of cortisol leads to negative feedback to build a regulatory circuit (Gauggel & Hermann, 2008).

Cortisol activates metabolic processes that provide the body with energy (Chiras, 2008). Therefore, cortisol is important in the first stage of Selye's model of the general adaptation syndrome, which is the alarm stage that prepares the body for action (Selye, 1956, 1974). A dysregulation of the HPA axis has been found in several mental disorders like depression (Vreeburg et al., 2009), post-traumatic stress disorder (Olff, Guzelcan, de Vries, Assies, & Gersons, 2006), panic disorder (de Kloet, Joels, & Holsboer, 2005), and borderline personality disorder (Lieb et al., 2004). Stressful life events as well as chronic stress (like e.g. chronic pain), were shown to be related to elevated concentrations of cortisol

measured in participants' hair (Karlen, Ludvigsson, Frostell, Theodorsson, & Faresjo, 2011; Van Uum et al., 2008). Oxytocin (OXT) on the other hand is a neuropeptide which is synthesized in the hypothalamus (Gimpl & Fahrenholz, 2001). OXT was first investigated in the context of birth and breast feeding (Nissen, Lilja, Widstrom, & Uvnas-Moberg, 1995; Uvnas-Moberg, Widstrom, Werner, Matthiesen, & Winberg, 1990), but it is also associated with social behavior and bonding (Benarroch, 2013; Campbell, 2010) and with recovery from stress exposure (Kubzansky, Mendes, Appleton, Block, & Adler, 2012; Onaka, Takayanagi, & Yoshida, 2012). Therefore, OXT is important in the second stage of Selye's model of the general adaptation syndrome (recovery; Selye, 1956, 1974). The release of OXT is able to reduce HPA axis activity and therefore to attenuate the stress response (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013). It has been hypothesized that social approach is promoted by OXT as it reduces arousal by acting on the HPA axis (Taylor et al., 2000). The positive effect of social support on health has been investigated extensively (Broadhead et al., 1983; Callaghan & Morrissey, 1993). OXT release during positive social interaction might account for the positive effect of social support in stressful situations (Uvnas-Moberg, 1998). The specific effect of endogenous OXT is hard to determine, however, as the release of other hormones cannot be controlled for (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Therefore, many studies have administered OXT intranasally as this allows a direct comparison of the same experimental conditions with and without a specific amount of exogenous oxytocin. OXT may have potential as a therapeutic agent as reduced plasma OXT has, for example, been associated with depression (Matsuzaki, Matsushita, Tomizawa, & Matsui, 2012). Administered OXT also dampens amygdala reactivity and might therefore also be able to reduce anxiety (Kirsch et al., 2005). But the effect of OXT is not always pro-social. Some studies have also shown an increase in envy, schadenfreude (Shamay-Tsoory et al., 2009), and ethnocentrism (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011) in response to administered OXT.

1.3.3. Emotions, stress, and health

As described in section 1.1., the evolutionarily developed responses to emotional events or stressors might not be adaptive anymore in our modern world environment. Evolutionarily developed mechanisms were probably designed to fight short-term threats while modern world stressors are in many cases long lasting (Chrousos, 1998; Chrousos & Kino, 2007). According to Hans Selye's general adaptation syndrome the danger of long-term stress for the organism sets in at the stage of resistance

(Selye, 1956, 1974). If the stressor cannot be eliminated the body continues to spend energy to resist the threat until the energy is depleted and the stage of exhaustion sets in. There is a large literature on the consequences of stress on health. Investigated stressors reach from public events (disasters like e.g. earthquakes) to private events (e.g. illness, or death of a relative; B. S. Dohrenwend, 1973). For example Sheatsley & Feldman (1964) showed that 89% of their population sample in the USA showed some sort of psychiatric symptoms after the assassination of President Kennedy. Other studies demonstrated the influence of more private events on mental health (B. P. Dohrenwend, 1969; Myers, Lindenthal, Pepper, & Ostrander, 1972). Long lasting stress can have severe consequences for the organism. It can lead to chronic diseases and even death (Lovallo, 2005). The stress response influences the cardiovascular system (e.g. leads to high blood pressure), so that long-term stress elevates the risk of heart attack and stroke (Chrousos & Kino, 2007). Stress and the negative emotions associated with it can also dysregulate the immune system and the suppression of the immune system in turn elevates the risk for infections and cancer (Glaser & Kiecolt-Glaser, 2005). In addition, stress might lead to behavior (e.g. not enough sleep, an unbalanced diet or smoking) that has a negative influence on health (Neylon et al., 2013). Furthermore, illness itself or the management of diseases can again produce psychological stress, which might induce further health problems (Golden et al., 2008). As described in section 1.1., emotion regulation or coping strategies can change the impact of a given situation. Studies have shown that high levels of negative emotions are associated with cardiovascular disease (Suls & Bunde, 2005) and that successful emotion regulation can decrease the risk of heart attacks (Kubzansky, Park, Peterson, Vokonas, & Sparrow, 2011). Also, the regulation of emotions is often disturbed in mental disorders (Gross & Munoz, 1995; Jazaieri, Urry, & Gross, 2013). In the next section I will look at emotional processing in psychopathology.

1.4. Emotional processing in mental disorders

Several psychological disorders are associated with emotional dysfunction, like for instance anhedonia in depression (Klein, 1974), hyporesponsiveness to aversive stimuli in psychopathy (Hare, 1965), or diminished expression of emotions in schizophrenia (Schneider et al., 1990). In the following I will focus on posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD). While, according to DSM-IV TR (American Psychiatric Association, 2000), PTSD is an axis I and BPD an axis II disorder, they exhibit several similarities. One similarity is that both disorders comprise symptoms of altered emotional processing by diagnostic definition (American Psychiatric Association, 2000). In

DSM-5 (American Psychiatric Association, 2013) disorders are not divided into different axes anymore and PTSD was moved from the section of anxiety disorders to a separate section of trauma- and stressor-related disorders.

1.4.1. Posttraumatic stress disorder

An extreme form of stress, a traumatic event, can lead to PTSD. According to DSM-5, a traumatic event is a necessary precursor of PTSD. A traumatic event is defined as an event where a person experiences or witnesses actual or threatened death, serious injury or sexual violence. PTSD is defined as a pattern of symptoms including intrusion symptoms, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity, caused by a traumatic event (American Psychiatric Association, 2013). Emotions can be influenced in two opposite ways in PTSD, either by attenuated or by exaggerated reactivity, which has led to debate in research (Wolf, Miller, & McKinney, 2009). According to Wolf et al. (2009), self-report measures revealed a whole range of conflicting results while psychophysiological studies mostly seem to support heightened emotional reactivity to trauma cues (Orr, Metzger, Miller, & Kaloupek, 2004).

In addition to direction of emotional responses, there is also the question of whether a specific pattern of emotional processing causes a traumatized person to develop PTSD or PTSD induces this pattern of emotional processing. As traumatic events do not necessarily lead to PTSD, there must be factors that influence resilience in the face of trauma. PTSD rates differ between types of traumatic events (Gill, Page, Sharps, & Campbell, 2008) but other factors must be taken into account to explain why a rather big proportion of people within most types of potentially traumatic events do not develop PTSD. Personality characteristics like, for example, optimism, extraversion, high positive and low negative emotionality have been identified as protective against PTSD symptoms (Jaksic, Brajkovic, Ivezic, Topic, & Jakovljevic, 2012). On the other hand prior traumatic events are a risk factor for developing PTSD (Neuner et al., 2004). Finally, physiological reactivity might also be a factor that influences the consequences of traumatic events. For example Guthrie & Bryant (2005) conducted a prospective study with firefighters and found heightened startle responses prior to trauma to be a predictor for PTSD severity after traumatic events. Other studies, however, indicate that heightened startle responses are a consequence rather than a precursor of PTSD (e.g. Shalev et al., 2000).

As postulated by Selye's general adaption syndrome (Selye, 1956, 1974), acute as well as chronic stress is associated with heightened levels of cortisol (Daskalakis, Lehrner, & Yehuda, 2013). PTSD

on the other hand has been associated with lowered levels of cortisol (Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007; Olff, de Vries, Guzelcan, Assies, & Gersons, 2007; Olff et al., 2006; Yehuda et al., 1990). At the same time glucocorticoid receptors were shown to be more sensitive in PTSD patients (Matic et al., 2013; Yehuda, Golier, Yang, & Tischler, 2004), which might explain the higher stress responsiveness. As with other parameters of physiological reactivity, it is unclear whether these findings point to a consequence or a precursor of PTSD (Daskalakis et al., 2013). For example a higher number of glucocorticoid receptors are at least partly seen as a risk factor for PTSD development (Yehuda, 2009).

OXT has also been investigated in PTSD. For example the diminished fear extinction seen in PTSD (Charney, Deutch, Krystal, Southwick, & Davis, 1993; Guthrie & Bryant, 2006) together with the finding that OXT might enhance fear extinction (Acheson et al., 2013) has led to studies testing the therapeutic potential of OXT for PTSD. A reduction in PTSD symptoms through intranasal OXT was found in a study by Yatzkar & Klein (2010). On the other hand, a study by Pitman, Orr, & Lasko (1993) showed a differentiation between physiological and psychological responses. They found that intranasal OXT reduced physiological but not psychological responses to imagery in Vietnam veterans (Pitman et al., 1993).

1.4.2. Borderline personality disorder

According to DSM-5 (American Psychiatric Association, 2013) BPD is characterized by impulsive behavior and instability in relationships, self-image and affect. Besides suicidal behavior and self-injury, emotional instability is a central characteristic (Linehan, 1993), which has often been investigated. Studies showing that BPD patients tend to interpret others' intentions as more negative than healthy controls (Westen, Lohr, Silk, Gold, & Kerber, 1990) indicate that these distorted cognitions make it difficult for BPD patients to maintain relationships. The inability to regulate negative emotions might contribute to this sort of disturbed social cognitions which in turn leads to disrupted relationships (Clarkin & De Panfilis, 2013). On the other hand, the perception of emotional stimuli and bodily responses to them might per se be disturbed. For example, BPD patients were shown to exhibit more intense facial muscle responses to negative and less intense responses to positive stimuli compared to healthy controls (Matzke, Herpertz, Berger, Fleischer, & Domes, 2013). But the general hyperreactivity of BPD patients postulated by Linehan (1993) has been challenged by contradictory findings in psychophysiological studies. For example, (Ebner-Priemer et al., 2005) found larger startle

responses and slower startle habituation in BPD patients compared to healthy controls. On the other hand, Herpertz, Kunert, Schwenger, & Sass (1999) found comparable startle responses for BPD patients and healthy controls. Some studies even found lower skin conductance responses to emotional pictures in BPD patients compared to healthy controls (Herpertz et al., 1999; Herpertz, Schwenger et al., 2000). Therefore, there is an ongoing debate in the literature whether BPD patients tend to show psychophysiological hyper- or hyporeactivity in response to emotional stimuli.

Lower plasma levels of OXT have been found in BPD and levels were negatively correlated with childhood abuse (Bertsch, Schmidinger, Neumann, & Herpertz, 2013). Therefore, studies started to investigate a possible beneficial effect of administration of OXT. In a study by Simeon et al. (2011) intranasal OXT was found to reduce the stress-induced cortisol increase in response to psychosocial stress in BPD patients. But not all results show beneficial effects for OXT. In a study by Bartz et al. (2011) OXT reduced trust and cooperative responses in BPD patients in a social dilemma game. Therefore, OXT might have some potential as a therapeutic agent but its exact mode of action has to be carefully explored to avoid unwanted negative effects.

BPD has several aspects in common with PTSD. A phenomenon often seen in BPD as well as PTSD patients is dissociation (Korzekwa, Dell, Links, Thabane, & Fougere, 2009). This refers to a separation of mental processes, like emotions, thoughts or memory, which are normally integrated (Spiegel & Cardena, 1991). Furthermore, a high rate of BPD patients report traumatic experiences, which have been hypothesized to be a possible cause for many of the symptoms seen in BPD (Holm & Severinsson, 2008). Finally, many BPD patients are also diagnosed with comorbid PTSD (Rusch et al., 2007). There was even a debate about redefining BPD as a trauma spectrum disorder (Lewis & Grenyer, 2009).

1.5. Research questions

On the basis of the background discussed so far, this thesis investigates the following research questions: 1) According to modern theories of emotion, cognitive aspects play a crucial role for emotional responses (Ellsworth & Scherer, 2003; Gross, 2014; Lazarus & Folkman, 1984; Scherer, 2001). The research question of the first study is whether these aspects are strong enough to evoke emotional responses in peripheral physiology by themselves. If such responses could already be measured in an anticipation period, where an actual emotional event is not yet present, this would further underline the importance of cognitive factors. 2) OXT is associated with social behavior

(Campbell, 2010) and it seems to have antagonistic effects on the stress response (Cardoso et al., 2013). Therefore, the research question of study 2 is whether the effect of OXT on the startle response is dependent on social content of affective stimuli or an interaction of social versus non-social content with emotional valence categories. 3) The second study also aims to investigate whether high versus low trait anxious subjects show differential effects of administered OXT on the affective modulation of the startle response. These two aspects might help to gain a better understanding of exogenous OXT effects. 4) The research question of the third study addresses the ongoing discussion in psychopathology whether altered physiological reactivity is a precursor or a consequence of disorders related to the experience of extreme stress. If it was a precursor, altered reactivity should be a stable trait characteristic of people at risk of developing PTSD. Therefore, also remitted PTSD patients should still differ in their reactivity from trauma survivors who never developed PTSD. The third study thus compares startle reactivity in trauma survivors with and without a history of PTSD and healthy controls. 5) The research question of the fourth study concerns the discussion of hyper- versus hyporeactivity in stress-related disorders and aims to expand existing findings in BPD to acoustic stimuli. Study 4 therefore investigates whether BPD patients' psychophysiological responses to acoustic emotional stimuli are stronger or weaker compared to non-clinical controls.

In the next section I will outline the physiological parameters which have been shown to be important in stress and emotional processes and were investigated in the studies of this thesis.

1.6. Assessment methods

1.6.1. Emotional stimuli

To investigate emotions, stimuli are needed that can be categorized according to their emotional content. For this purpose Lang, Bradley, & Cuthbert (2005) developed a collection of pictures called International Affective Picture System (IAPS) and a collection of sounds called International Affective Digitized Sounds (IADS; Bradley & Lang, 2000). These stimuli represent a wide range of human experiences. They have been rated by normative samples and are widely used in emotional research. These stimuli are rated along the dimensions of valence and arousal. Valence refers to the pleasantness (positive, negative or neutral) of a stimulus and arousal to how much activation it induces. Valence and arousal are rated independently but emotional stimuli (positive and negative) tend to be rated as more arousing than neutral ones. Positive as well as negative stimuli can be more or less arousing but negative stimuli tend to be more arousing than positive ones.

For the norm ratings, Bradley & Lang (1994) developed the self-assessment manikin (SAM), a rating scale with 9 steps for each dimension, which can also be used to collect ratings from subjects under investigation. Norm ratings can be used to select suitable stimuli for the current research question. Ratings by the current subject sample are used to confirm the categorization and as a subjective measure that can be compared to physiological responses.

1.6.2. Measurement of peripheral physiological parameters

For most applications reusable silver-silver chloride (Ag/AgCl) electrodes are used today. They need to be filled with electrode paste before each application and have to be carefully cleaned afterwards. Disposable electrodes which are already filled with gel are also available. Before electrodes are placed the skin needs to be cleaned to lower the impedance. Dirt and dead cells can be removed with alcohol or by abrading the skin (Stern et al., 2001).

The sampling rate has to be adjusted to the signal of interest. Data require more storage space than necessary if the sampling rate is set too high. A too low sampling rate, however, can have the more severe effect of aliasing. This means that frequencies higher than half the sampling rate (Nyquist frequency) in the originally analog signal are interpreted as lower frequencies in the digitalized signal. Therefore the sampling rate has to be at least twice the highest possible frequency in the signal of interest (Stern et al., 2001).

To get a clear signal and to distinguish signal from noise the data need to be filtered. The most common problem is noise from electrical equipment (50Hz in Europe) which interferes with the signal of interest. This can be eliminated by using a so called notch filter, which filters a specific frequency. Other noise can be filtered by high-pass, low-pass or band-pass filters. While high-pass filters erase frequencies below and low-pass filters those above a certain value, band-pass filters let a certain range of frequencies pass and cut frequencies above and below (Stern et al., 2001). Filters can be applied during data collection (online) or afterwards (offline). Subjects need to be instructed to sit still to avoid movement artifacts.

As every individual has a somewhat different tonic level of visceral activity it is common to calculate difference values for better comparison between subjects. A mean value of a baseline period shortly before a stimulus is applied is subtracted from a mean or maximum value of a certain time window after stimulus onset. With fast changing signals, like muscle tension or heart rate, it is more reliable to take the mean, for slowly changing signals, like skin conductance, it is more common to use the

maximum value within the time window of interest. Different measures also require different window lengths. The startle reaction for example is a fast reaction starting within about 20-40ms after the onset of the eliciting stimulus, while the onset of a skin conductance reaction takes 1-3s (Stern et al., 2001). In the next three sections I will take a closer look at specific measures.

1.6.3. Heart rate

The heart rate, given in beats per minute, is a common measure in psychophysiology. It can be measured by counting the R-waves in the electrocardiogram occurring within a given time interval. The adult human heart beats about 60-80 times per minute in a resting state and rises under stress (Schächinger, 2003). The inter-beat interval is inversely related to the heart rate. It measures the time between successive R-waves in milliseconds. The heart is innervated by the sympathetic as well as the parasympathetic nervous system. These two systems often work reciprocally, i.e. as one of them increases the other decreases. But they can also increase or decrease together or react independently. Therefore, if a change in heart rate is measured it is unclear from what sort of combination of activation in those two systems the change arose (Berntson, Cacioppo, & Quigley, 1991). Therefore, a change in heart rate can only be interpreted in combination with changes in other visceral measures.

1.6.4. Electrodermal activity

When sweat glands are activated the electrical resistance of the skin is reduced and conductance increased (Stern et al., 2001). Sweat glands are innervated by the sympathetic nervous system and can be found all over the body (Dawson, Schell, & Filion, 1990). On palms and foot soles eccrine sweat glands are especially numerous and, in contrast to sweat glands in other body regions, they primarily react to psychological stimuli (Stern et al., 2001). Therefore, in psychophysiological experiments skin conductance electrodes are most often placed on the palmar surface. Measures of tonic (long-lasting) and phasic (short-lasting) activity are used in research. Tonic activity is referred to as the skin conductance level, phasic activity as skin conductance reactions (Stern et al., 2001). Changes of skin conductance activity can occur spontaneous or in response to a certain stimulus (Boucsein et al., 2012). Interestingly, Jung already used the measurement of electrodermal activity to access unconscious processes (E. Neumann & Blanton, 1970).

1.6.5. Electromyogram

Muscle action potentials that can be measured by electrodes on the skin vary from a few microvolts to more than a millivolt in amplitude and from 1Hz to more than 1000Hz in frequency (Stern et al., 2001). The strongest signals can be obtained from big muscles that are used for movement. In research about stress and emotions facial muscles are of special interest. Strong emotions can be recognized by facial expressions. Less intense processes might be invisible to the eye but the underlying muscle activity can still be measured by the electromyogram. Activation of the zygomaticus mayor (the laughing muscle) is associated with appetitive stimuli and activation of the corrugator supercilii (the frowning muscle) can be measured in association with aversive stimuli (Dimberg, 1990). The orbicularis oculi is responsible for the eye-blink (Landis & Hunt, 1939; see also section 1.2.1). Measuring the activation of a specific muscle is difficult because there can always be contribution of other muscles nearby. Standardized electrode placement is therefore important. Placement sites corresponding to specific muscles can be found in the guidelines for electromyographic research (Fridlund & Cacioppo, 1986).

1.7. Studies description

This thesis comprises four studies, investigating different aspects of the psychophysiology of emotional processing and responses to stress. The first study focuses on the anticipation of emotional pictures in 32 healthy subjects. This study is an extension of earlier findings in fMRI to peripheral physiological parameters. Earlier work in fMRI has shown that similar brain regions were active during anticipation and perception of emotional stimuli (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Knutson, Adams, Fong, & Hommer, 2001; Koyama, McHaffie, Laurienti, & Coghill, 2005). In addition, an activity pattern resembling the anticipation of negative stimuli was found during the anticipation of stimuli of unknown valence, which was interpreted as a negativity bias in situations of uncertainty (Herwig, Kaffenberger, Baumgartner, & Jancke, 2007; Kaffenberger, Bruhl, Baumgartner, Jancke, & Herwig, 2010). Study 1 hypothesizes that these results can be transferred to peripheral physiological responses.

The second study investigates the influence of intranasally administered OXT on the startle response and its emotional modulation. Acoustic startle probes are first presented alone (baseline startle). Thereafter the startle response is measured during the presentation of emotional and neutral pictures of social and non-social content. The influence of OXT is tested versus placebo in a double-blind

crossover design in 44 healthy male subjects. The aim of this study is to test whether trait anxiety and social picture content might influence the effects of OXT on the emotional modulation of the startle reflex.

The third study investigates the association of startle reactivity and PTSD as well as trauma. The startle reactivity of remitted PTSD patients is compared to accident survivors who had never developed PTSD and subjects who had never experienced any traumatic events. The aim of study 3 is to investigate whether remitted PTSD patients show heightened startle reactions compared to trauma survivors who never developed PTSD and healthy controls. This would be in line with the notion of heightened startle reactivity being a trait characteristic of subjects who are vulnerable to develop PTSD.

The fourth study examines differences in emotional processing between patients with BPD and non-clinical controls. A total of 41 participants listen to acoustic emotional and neutral stimuli while peripheral physiological parameters are measured. This study investigates whether BPD patients show physiological hyperreactivity as often found with subjective self-reports (e.g. Henry et al., 2001; Koenigsberg et al., 2002; Stiglmayr, Shapiro, Stieglitz, Limberger, & Bohus, 2001) or hyporeactivity as earlier found for skin conductance responses to visual stimuli (Herpertz et al., 1999; Herpertz, Schwenger et al., 2000).

2. Study 1 - Psychophysiological responses during the anticipation of emotional pictures

In press in: Journal of Psychophysiology

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2.1. Abstract

The present study sought to investigate peripheral physiological responses to the anticipation of explicitly and ambiguously cued emotional pictures. Emotionally positive and negative as well as neutral pictures were presented to 32 healthy subjects. At the beginning of an anticipation period they were cued about the valence of the upcoming picture (neutral, positive, negative or ambiguous). Skin conductance, heart rate, and zygomaticus and corrugator electromyogram responses were measured during anticipation and perception. Responses specific to the emotional conditions were observed during anticipation as well as during perception. During the anticipation of ambiguously cued pictures, responses were similar to responses elicited by anticipating negative pictures. In line with results from

brain imaging studies, peripheral physiological responses could be interpreted to reflect a negative bias for ambiguous events.

2.2. Introduction

In everyday life, anticipation of and preparation for upcoming events are mostly automatic processes making it easier to handle the events (Gilbert & Wilson, 2007). Prior studies identified neural correlates reflecting the emotional preparation for upcoming events: an expectation period enhanced the subjective emotional intensity of pictures as well as the neural response to them (Bermpohl et al., 2006a) and was associated with brain activations comparable to the perception period in domains as pain (Koyama et al., 2005) and reward (Breiter et al., 2001; Knutson et al., 2001). In parallel, the startle reaction can be modulated by the mere anticipation of emotional pictures (Dichter, Tomarken, & Baucom, 2002; Sabatinelli, Bradley, & Lang, 2001). It is an open question, though, if valence specific reactions during the anticipation of emotional pictures can be directly measured in peripheral physiology.

Furthermore, some future events are known to be pleasant or unpleasant, others are uncertain. To know that something aversive is coming up can help to prepare for the event, while uncertainty might be harder to deal with and has even been associated with anxiety (Bach & Dolan, 2012; Grupe & Nitschke, 2013). From an evolutionary perspective it could be adaptive to prepare for the worse case in uncertain situations as this makes survival more likely (Darwin, 1872; Fridlund, 1991). In fMRI, anticipating announced events of unknown, possibly negative valence has been shown to activate similar brain regions as anticipating negative events, which supports the hypothesis of a pessimistic bias of anticipation in the face of uncertainty (Herwig et al., 2007; Kaffenberger et al., 2010). Uncertain cues were also found to enhance reactions to negative events and the relationship between uncertain cues and aversive events was shown to be overestimated by participants (Grupe & Nitschke, 2011; Sarinopoulos et al., 2010).

The presentation of emotional pictures is a widely used procedure to study emotional processes. Several peripheral physiological parameters, which closely correspond to behavioral measurements, can be used as objective measures for these processes (Bradley, Cuthbert, & Lang, 1990; Greenwald, Cook, & Lang, 1989; Lang, Greenwald, Bradley, & Hamm, 1993). Skin conductance (SC) is sensitive to arousal, therefore SC typically increases in response to positive as well as negative pictures (Bradley et al., 1990; Greenwald et al., 1989). Heart rate (HR) seems to show either valence or

arousal specific responses depending on the task: During the perception of negative pictures HR typically decelerates (Bradley et al., 1990; Hare, Wood, Britain, & Shadman, 1970; Libby, Lacey, & Lacey, 1973), whereas the recall of emotional (positive and negative) memories (Lang et al., 1993), highly pleasurable music (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011) or rewarding stimuli (Fowles, Fisher, & Tranel, 1982) can elicit HR acceleration. Corrugator and zygomaticus muscle activity are sensitive to valence. Corrugator muscle activity increases in response to negative, while activity of the zygomaticus muscle increases in response to positive pictures or videos (Bradley et al., 1990; Cacioppo, Petty, Losch, & Kim, 1986; Dimberg, 1982, 1986; Gomez, Zimmermann, Schar, & Danuser, 2009; Greenwald et al., 1989; Reynaud, El-Khoury-Malhame, Blin, & Khalfa, 2012).

The aim of the current study was to investigate peripheral physiological responses during the anticipation of emotional pictures using the same paradigm as in earlier fMRI studies (Herwig et al., 2007; Kaffenberger et al., 2010). We expected to find 1) valence specific responses during anticipation (reflected by stronger HR decelerations during the anticipation of negative pictures, HR accelerations during the anticipation of positive pictures, stronger electrodermal reactions during the anticipation of emotional compared to neutral pictures, increased zygomaticus activity during the anticipation of positive pictures, and increased corrugator activity during the anticipation of negative pictures) and 2) that the ambiguous anticipation condition would differ from the positive and the neutral anticipation condition in the same way as the negative anticipation condition (reflected by stronger HR decelerations, stronger electrodermal reactions and increased corrugator activity) . Furthermore, we expected to replicate prior studies on psychophysiological correlates during the perception of emotional stimuli (as described above).

2.3. Methods

2.3.1. Participants

Thirty-two healthy subjects were recruited through mailing lists and advertisements. Subjects were 20 to 42 years old (M=27, SD=6) and mostly female (81%, N=26). Mental and physical health was assessed by a semi-structured interview. Exclusion criteria assessed in the interview were known prior or current neurological or psychiatric illness, severe physical illness, current medication (except contraceptives), pregnancy, dermatological problems, excessive use of alcohol, nicotine or caffeine, impaired cognitive abilities (IQ known to be below 70 or inability to complete regular school) and insufficient command of German. Subjects were thoroughly informed about the procedures and gave

written informed consent according to the Declaration of Helsinki before participating. This study was approved by the ethics committee of the canton of Zurich, Switzerland. The whole run of one subject as well as the second half of another one had to be excluded from HR analysis because of poor data quality. Because of technical problems the second half of the whole experiment was missing for one subject. Twenty-seven subjects rated the pictures (rating data of five subjects were lost for technical reasons).

2.3.2. Physiological measures

Physiological recordings were performed using a BIOPAC MP150 System (Biopac Systems, Inc, Goleta, CA). Facial electromyographic (EMG) activity from the left corrugator and zygomaticus muscles was recorded using Ag/AgCl disposable snap connector electrodes filled with hydrogel jelly, which were cut to fit on the appropriate site. The EMG was 1-500Hz band-pass filtered online. SC electrodes were placed on the thenar and hypothenar eminence of the left palmar surface using Ag/AgCl electrodes filled with isotonic electrolyte gel. SC was 0.05-10Hz band-pass filtered online. The electrocardiogram (ECG) was recorded from three Ag/AgCl disposable snap connector electrodes filled with hydrogel jelly located below the left and right collarbone and on the left rib cage. The ECG was 0.05-35Hz band-pass filtered online. EMG and ECG were sampled at a 1000Hz rate, SC at a 62.5Hz rate.

2.3.3. Procedure and materials

The assessment took place at the psychophysiological laboratory of the Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland. Sensors were attached while the subjects reclined in a comfortable chair. Subjects were then asked to rest quietly for seven minutes in order to facilitate laboratory adaptation. A total of 56 trials were presented. The structure of a trial was as follows: A cue was presented for 1s followed by a blank screen with a fixation dot presented for 7s (anticipation period: 1s + 7s = 8s), followed by a positive, negative or neutral picture taken from the International Affective Picture System (IAPS; Lang et al., 2005) presented for 8s (perception period). The cue indicated the valence of the picture that would follow: “U” for a positive picture, “∩” for a negative picture, “–” for a neutral picture, and “I“ for either a positive or a negative picture (50/50 ratio, ambiguous condition). Each of the four conditions consisted of 14 trials. The inter-trial interval was 16s. The task was implemented in E-Prime 2.0 Professional (Psychology Software Tools Inc.,

Pittsburgh, PA., USA) and presented on a 19” computer screen placed approximately 80cm away from the subject. All participants performed a training session with 8 different, but comparable IAPS pictures before the experiment (2 trials per anticipation condition). Subjects were instructed to expect the emotional stimuli according to the cue and to watch the subsequent picture. Due to prior contact with the IAPS picture set because of participation in another study, five subjects were given a different, but comparable and matched set of IAPS pictures (Brühl, Kaffenberger, & Herwig, 2010). After the experiment each picture was presented again in order to collect subjective valence ratings on a 9-step visual analogue scale (1=negative, 5=neutral, 9=positive)[1]. Mean ratings of valence and arousal according to the IAPS manual are given in Table 1.

2.3.4. Data reduction

Autonomic Nervous System Laboratory 2.51 (ANSLAB; Wilhelm, F. H. & Peyk, P., 2005; available at the SPR Software Repository: http://www.sprweb.org) was used to filter the raw data offline and to extract mean and maximum scores for event and baseline intervals for each subject. Raw data were visually inspected to identify artifacts which were then manually excluded. ECG data were inspected for correct detection of R-waves, SC and EMG data were inspected for technical artifacts. The EMGs were 50Hz notch filtered, 20Hz high pass filtered, and the rectified signal was smoothed using a moving average width of 50ms. SC was 1Hz low-pass filtered. For the extraction of mean HR values Anslab uses the instantaneous HR which is sampled at 4Hz using linear interpolation. HR responses (HRR) and EMG responses were calculated by subtracting the mean value during the 2s baseline interval prior to the onset of the anticipation cue from the mean value during the 8s anticipation and from the mean value during the 8s perception interval (same baseline interval). For SC responses (SCR) the mean value during the 2s baseline interval prior to the onset of the anticipation cue was subtracted from the maximum value during the 8s event windows (anticipation and perception).

[1] IAPS picture numbers for training: neutral: 7224, 7490; negative: 1111, 3168, 9140; positive: 1750, 2310, 2340; main task: neutral: 2190, 2215, 2514, 2570, 2575, 2850, 5731, 7004, 7009, 7035, 7100, 7233, 7550, 7950; positive: 1603, 1710, 1920, 1999, 2057, 2091, 2311, 2341, 2352, 2550, 4599, 5600, 5830, 5831, 7230, 7580, 8190, 8350, 8461, 8496, 8497; negative: 1019, 1120, 2730, 2750, 3400, 3550, 6250, 7361, 8230, 8231, 9042, 9300, 9320, 9373, 9405, 9433, 9571, 9584, 9910, 9921, 2720; alternative set: neutral: 2200, 2214, 2495, 2518, 2870, 5900, 7002, 7006, 7080, 7090, 7235, 7491, 7496, 7560; positive: 1604, 1722, 1810, 2058, 2303, 2310, 2344, 2345, 2530, 2655, 4610, 5626, 5628, 5660, 5760, 5779, 7286, 7502, 8200, 8470, 8490; negative: 1040, 1051, 2490, 2710, 2749, 2900, 3010, 3053, 3150, 3530, 6244, 7380, 8232, 9045, 9253, 9340, 9500, 9570, 9582, 9611, 9911.

2.3.5. Data analysis

Statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). We used a linear mixed models design and applied restricted maximum likelihood estimation to compare the different emotional conditions. Linear mixed models are well suited for the analysis of repeated measures. In contrast to repeated measures ANOVA they preserve more information contained in the data, they account for correlations between the repeated measurements within each subject, and they can handle missing data (West, Welch, & Galecki, 2007). Full-factorial models were calculated for each measure (HR, SC, zygomaticus EMG and corrugator EMG responses) for anticipation as well as for the perception of explicitly cued pictures only (to compare valences), and for the perception of emotional pictures only (to compare cues). In all models picture valence was treated as a fixed effect and subjects as a random effect. There were four levels of picture valence during anticipation (neutral, positive, negative and ambiguous), three levels during perception of explicitly cued pictures (neutral, positive and negative), and two levels (positive and negative) for the perception of explicitly versus ambiguously cued pictures. In the latter model, cue (explicit and ambiguous) was treated as an additional fixed effect. In a second analysis, perception models were calculated with the IAPS arousal norm rating added as a covariate to control for the unequally distributed arousal between positive and negative pictures. Secondary analyses of the anticipation models were calculated with the STAI trait score added as a covariate to control for trait anxiety. To best account for correlations between repeated measurements, all models were optimized by the covariance type for the repeated observations which produced the lowest Akaike's Information Criterion (AIC; West et al., 2007).[2] Bonferroni corrected pairwise comparisons based on the estimated marginal means were used as post-hoc tests. Effect sizes were calculated according to Nakagawa & Schielzeth (2013). $R^2_{LMM(c)}$ indicates the variance explained by the full model (fixed and random factors).

2.4. Results

Estimated marginal means and standard errors per condition and pairwise comparisons for all four measures during anticipation and during perception of explicitly cued pictures can be seen in Figures 4

[2] The following covariance structures were fitted: anticipation: SC, zygomaticus, corrugator: first order ante-dependent structure; HR: heterogenous first order factor analytic structure; perception of explicitly cued pictures: SC: first order ante-dependent structure; HR: first order factor analytic structure; zygomaticus: diagonal structure; corrugator: first order autoregressive structure; perception of explicitly versus ambiguously cued pictures: SC, corrugator: heterogeneous first order autoregressive structure; HR: first order autoregressive structure; zygomaticus: scaled identity structure.

and 5. Effect sizes can be seen in Table 1. During anticipation, significant main effects of emotional valence were found for SCR ($F(3, 248) = 6.08$, $p = 0.001$), zygomaticus EMG responses ($F(3, 456) = 4.05$, $p = 0.007$) and corrugator EMG responses ($F(3, 470) = 7.19$, $p < 0.001$). For HRR there was no significant main effect of emotional valence ($p = 0.09$).

Pairwise comparisons showed that anticipation of negative pictures as well as of pictures with unknown valence elicited significantly higher SCR than anticipation of neutral pictures. Anticipation of positive pictures elicited significantly higher zygomaticus EMG responses than anticipation of neutral, negative or unknown pictures. Anticipation of negative and unknown pictures elicited higher corrugator EMG responses than anticipation of positive pictures. Anticipation of unknown pictures did not differ significantly from anticipation of neutral pictures in zygomaticus ($p = 1.0$) and corrugator responses ($p = 0.2$).

Adding the STAI trait score as a covariate to these anticipation models did not change the main effects of emotional valence for SC, zygomaticus and corrugator responses. For HRR, the main effect of emotional valence became significant when controlling for trait anxiety ($F(3, 547) = 3.49$, $p = 0.02$). The STAI trait score did not produce a significant main effect in any of our measures (p values > 0.4). In SCR, the pairwise comparison between anticipation of negative and neutral pictures was not significant anymore ($p = 0.09$) when controlling for trait anxiety. However, the comparison between positive and neutral became significant (anticipation of positive pictures elicited a higher SCR than anticipation of neutral pictures, $p = 0.04$) when controlling for trait anxiety. Pairwise comparisons for HRR showed that anticipation of positive pictures elicited a HR acceleration compared to negative pictures ($p = 0.008$) when controlling for trait anxiety. For zygomaticus responses pairwise comparisons remained unchanged when controlling for trait anxiety. For corrugator responses an additional significant pairwise comparison between negative and neutral was induced (anticipation of negative pictures elicited a higher response than anticipation of neutral pictures, $p = 0.05$) when controlling for trait anxiety.

During perception of explicitly cued pictures, significant main effects of emotional valence (neutral, positive, negative) were found for SCR ($F(2, 310) = 5.59$, $p = 0.004$), HRR ($F(2, 327) = 20.87$, $p < 0.001$), zygomaticus EMG responses ($F(2, 540) = 18.51$, $p < 0.001$) and corrugator EMG responses ($F(2, 1189) = 34.39$, $p < 0.001$). Pairwise comparisons showed that the perception of explicitly cued negative pictures elicited significantly higher SCR, stronger HR deceleration, and stronger corrugator EMG responses than neutral and positive pictures. Zygomaticus EMG responses were lowest for

neutral pictures, followed by negative and highest for positive pictures (all p values < 0.05). Adding the arousal values from the IAPS norm rating as a covariate to these perception models did not change the main effects of emotional valence. Only one previously significant pairwise comparison did not reach significance anymore: neutral versus negative picture in the zygomaticus (p = 0.5). Arousal norm ratings did not produce a significant main effect.

During perception, there was a significant interaction of picture valence (positive/negative) and prior cueing (explicit/ambiguous) in zygomaticus responses (F(1, 1277) = 3.84, p = 0.05). When comparing the perception of positive and negative pictures after an explicit cue, zygomaticus responses were significantly higher to positive pictures (M_{pos} = 0.62 µV, SE_{pos} = 0.14 µV vs. M_{neg} = 0.30 µV, SE_{neg} = 0.14 µV, p = 0.008). After an ambiguous cue, zygomaticus responses to the perception of positive and negative pictures did not differ significantly (p = 0.6). Comparing the perception of positive pictures after explicit versus ambiguous cueing resulted in higher zygomaticus responses associated with the explicit cue (M_{exp} = 0.62 µV, SE_{exp} = 0.14 µV vs. M_{amb} = 0.32 µV, SE_{amb} = 0.16 µV, p = 0.05). Explicit versus ambiguous cueing had no influence on zygomaticus responses during the perception of negative pictures (p = 0.4). There was no effect of cue on any of the other measures during perception. Adding the arousal values from the IAPS norm rating as a covariate to these perception models did not change the significant main effects of emotional valence or cue and arousal norm ratings did not produced a significant main effect (p values > 0.06).

Mean subjective valence ratings were as follows: negative pictures: M = 2.80, SD = 0.94; neutral pictures: M = 5.20, SD = 0.58; positive pictures: M = 7.14, SD = 1.09. Subjective valence ratings did not differ from the IAPS valence norm ratings (paired t = -0.014, df = 111, p = 0.99).

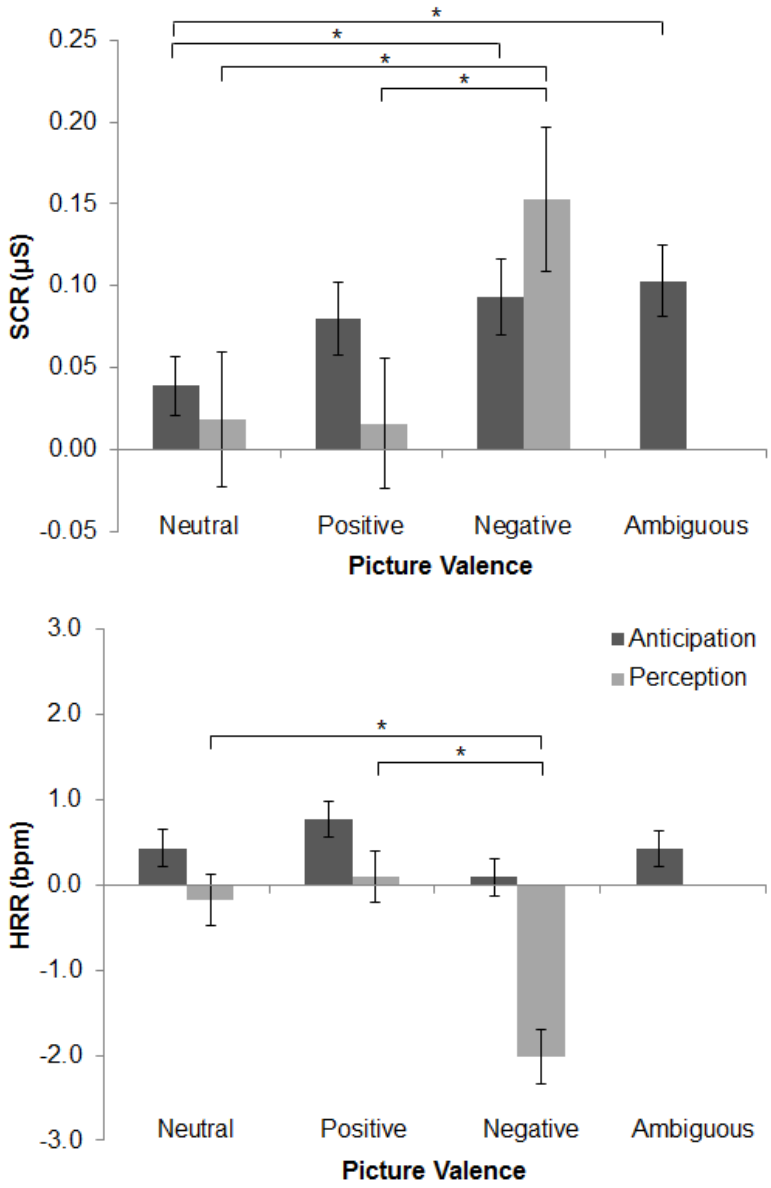

Figure 4. Estimated marginal means +/- 1 standard error of physiological responses during picture anticipation and perception of explicitly cued pictures. * Bonferroni corrected pairwise comparisons $p < 0.05$; SCR = skin conductance response, HRR = heart rate response, µS = microsiemens, bpm = beats per minute.

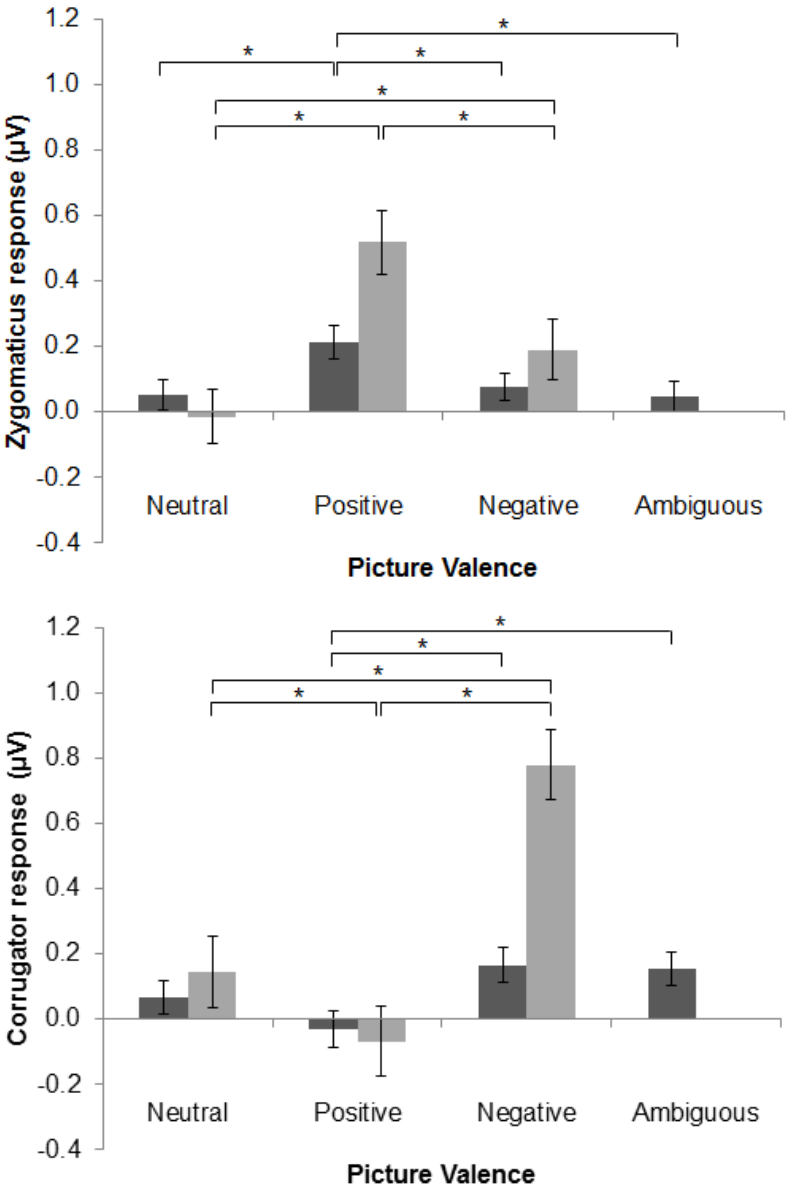

Figure 5. Estimated marginal means +/- 1 standard error of physiological responses during picture anticipation and perception of explicitly cued pictures. * Bonferroni corrected pairwise comparisons $p < 0.05$; µV = microvolt.

Table 1. Effect size for each model.

Model	Fixed factors	$R^2_{LMM(c)}$
Anticipation:		
SCR	$valence_1$	0.012
HRR	$valence_1$	0.011
Zygomaticus response	$valence_1$	0.027
Corrugator response	$valence_1$	0.044
Presentation of explicitly cued pictures:		
SCR	$valence_2$	0.021
HRR	$valence_2$	0.056
Zygomaticus response	$valence_2$	0.056
Corrugator response	$valence_2$	0.109
Picture presentation explicit vs. ambiguous:		
SCR	$valence_3$, cue	0.018
HRR	$valence_3$, cue	0.075
Zygomaticus response	$valence_3$, cue	0.093
Corrugator response	$valence_3$, cue	0.084

Note. SCR = skin conductance response, HRR = heart rate response; $R^2_{LMM(c)}$ indicates variance explained by the full model (fixed and random factors); $valence_1$: neutral, positive, negative, ambiguous; $valence_2$: neutral, positive, negative; $valence_3$: positive, negative; cue: explicit, ambiguous; all models included subject as a random factor.

2.5. Discussion

The current study investigated peripheral physiological responses to the cued anticipation of emotional visual stimuli. Within this framework, the study additionally examined the psychophysiological correlates of a previously reported pessimistic tendency during the anticipation of ambiguously cued stimuli in fMRI. We measured SC, HR, corrugator EMG and zygomaticus EMG responses and compared neutral, positive and negative conditions during a cued anticipation period as well as during the subsequent perception. In addition we investigated how these measures responded to anticipating ambiguously cued pictures.

In line with earlier studies (Bradley et al., 1990; Cacioppo et al., 1986; Dimberg, 1982, 1986; Greenwald et al., 1989; Hare et al., 1970; Libby et al., 1973) we found that compared to neutral and positive pictures the perception of negative pictures elicited higher SC and corrugator EMG responses and a decelerated HR, whereas the perception of positive pictures evoked a higher zygomaticus EMG response compared to neutral and negative pictures, which in principle confirmed the effectivity of our

study in eliciting and measuring emotional responses. We did not find a HR acceleration during the perception of positive pictures compared to neutral pictures as other studies found with rewarding stimuli (Fowles et al., 1982). This might indicate that the here used emotionally positive pictures do not evoke intensive reward-related reactions.

During the anticipation of these pictures we found valence specific responses similar to the perception period. SC showed higher responses for the anticipation of negative compared to neutral pictures (although this effect disappeared when controlling for trait anxiety); the zygomaticus muscle showed stronger responses to the anticipation of positive compared to negative or neutral pictures, and the corrugator muscle showed stronger responses to the anticipation of negative compared to positive pictures (and compared to neutral pictures when controlling for trait anxiety). These findings complement earlier fMRI results showing that emotional processes are evoked already during a cued anticipation period (Bermpohl et al., 2006b; Herwig et al., 2007; Kaffenberger et al., 2010). We found no significant effect of emotional condition for HR during the anticipation period. Only when controlling for trait anxiety, anticipation of positive pictures elicited HR acceleration compared to negative pictures. In the absence of explicit emotional stimuli, changes in HR have been primarily associated with imagery (Lang et al., 1993). Compared to imagery, the emotional activation during the anticipatory period as induced here is much shorter and less specific, which might explain the reduced differentiation on the HRR level.

Our data are in line with the hypothesis of a pessimistic bias, i.e. a tendency to anticipate a negative outcome in uncertain situations, as found in earlier studies on the neurofunctional level (Grupe & Nitschke, 2011; Herwig et al., 2007; Kaffenberger et al., 2010; Sarinopoulos et al., 2010). In zygomaticus and corrugators response, the ambiguous anticipation condition was not different from the negative condition, but significantly different from the positive condition. These findings disprove any optimistic tendency during the anticipation of ambiguous stimuli. However, possibly due to the generally rather weak emotional component during anticipation, the contrast between the ambiguous and the neutral condition was not significant in the EMG measures. Therefore, we cannot totally exclude a rather neutral tendency in our measures. However, the significantly elevated SC responses during the ambiguous anticipation condition, which differed from the neutral but not from the negative anticipation condition, contradict a neutral tendency during the ambiguous anticipation condition.

An influence of cueing on perception was only seen in zygomaticus responses. Positive pictures seemed to elicit an enhanced positive reaction if their valence had been known before their

presentation, and zygomaticus responses to positive and negative pictures differed only for explicitly cued pictures. Effect size calculations showed that valence explained more variance during picture presentation than during anticipation. Overall, the proportion of variance explained by our models is very small (between 1.1 and 10.9%). Therefore, although emotional valence information has a significant influence on physiological responding, a large proportion of variance in these reactions must be due to other factors.

A limitation of this study is that we did not assess subjective arousal ratings. According to the IAPS norm ratings, negative pictures in our dataset were more arousing than positive pictures, which is a common problem with picture sets, especially if erotic pictures are excluded because of unwanted additional qualities they would bring in (Bradley, Codispoti, Cuthbert, & Lang, 2001). However, as the focus of this study is on the anticipation period this should not affect our main conclusions as during anticipation the precise content of the picture is still unknown. In addition, inclusion of the IAPS arousal norm rating as a covariate in our perception models did not reduce the overall pattern of effects. Another limitation potentially affecting the picture perception period is that five subjects saw a different, but generally matched picture set. However, this picture set has been used before in an fMRI study and was comparable to the other picture set regarding relevant behavioral and neural effects (Brühl et al., 2010). A further limitation might be that our sample comprises mainly female participants. As gender differences in emotional reactivity are known (Bradley, Codispoti, Sabatinelli, & Lang, 2001) there might be a bias towards female reactivity in our data. Future studies should explicitly address gender-related differences of psychophysiological reactions during the anticipation and perception of emotional stimuli.

In conclusion, healthy subjects show similar valence specific reactions to the perception and anticipation of emotional pictures. Although a neutral attitude cannot be completely ruled out, there is at least some evidence that anticipating pictures of unknown valence elicits similar reactions as anticipating negative pictures. Furthermore, our data provide evidence against a positive tendency. The present study parallels, on the peripheral physiological level, results of previously conducted fMRI studies with the same paradigm (Herwig et al., 2007; Kaffenberger et al., 2010). Thus, our results support the conclusion that, on the physiological level, people prepare for a negative outcome in the sense of a pessimistic bias when faced with an upcoming event of unknown emotional valence.

3. Study 2 - Oxytocin, trait anxiety, and affective modulation of the startle reflex: a double-blind placebo-controlled crossover study

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3.1. Abstract

Previous research has demonstrated that the neuropeptide oxytocin (OXT) modulates social behaviors and reduces anxiety. However, effects of OXT on startle reactivity have been inconsistent. This paper presents our investigations into the influence of OXT on baseline startle and affective startle modulation with particular focus on the role of trait anxiety. Forty-four healthy male participants attended two experimental sessions. They received intranasal OXT (24 IU) in one session and placebo in the other (counterbalanced). Startle probes were presented separately (baseline startle) and in combination with emotionally neutral, positive, and negative pictures of social and non-social content (affective modulation). Eye-blink startle magnitude was measured by electromyography of the musculus orbicularis oculi. Additionally, picture valence and arousal ratings were obtained. Participants were assigned to groups of high vs. low trait anxiety based on questionnaire data. Across groups, baseline eye-blink startle magnitude was not affected by OXT, whereas OXT increased

arousal ratings of the pictures independent of emotional valence. For participants with low trait anxiety, OXT reduced startle magnitude across picture conditions and raised positivity of valence ratings for social pictures. In contrast, for participants with high trait anxiety OXT heightened startle magnitude across picture conditions and raised positivity of valence ratings for non-social pictures. Results indicate that the effect of OXT on affect-modulated startle reactivity is influenced by trait anxiety. Individual differences in trait anxiety may partially explain previous contradictory results found for the effects of OXT on startle reactivity.

3.2. Introduction

The effect of the neuropeptide oxytocin (OXT) on social behavior and stress reactivity has received increased attention in the last decade (Heinrichs, von Dawans, & Domes, 2009; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). OXT may play a key role in recognition of emotional facial expressions (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Guastella, Mitchell, & Dadds, 2008; Marsh, Yu, Pine, & Blair, 2010; Schulze et al., 2011) and in related memory (Guastella, Mitchell, & Mathews, 2008), interpersonal trust and cooperation (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and attachment (Buchheim et al., 2009) in humans. OXT also reduces behavioral and endocrine responses to social stress and mediates stress-protective effects of social support (Heinrichs et al., 2003). Moreover, recent studies suggest that the effect of OXT is dependent on social context (Bartz, Zaki, Bolger, & Ochsner, 2011). A review by Guastella & MacLeod (2012) suggested that OXT might enhance the early and rapid conceptual detection of affect from social stimuli and might improve the accurate appraisal of affect from socially relevant information. They mention that these effects of OXT are unique and cannot be explained as a result of simple effects, such as anxiety reduction, because medications and interventions that reduce anxiety fail to produce such effects on social cognition (Guastella & MacLeod, 2012).

The startle response is conceptualized as an involuntary reaction to an unexpected sudden intense stimulus that contracts several muscles in order to protect the body from harm (Koch, 1999; Landis & Hunt, 1939). Startle reactivity can be measured using the eye-blink reflex, which is part of the startle reaction and can easily be elicited by loud acoustic stimuli (Lang et al., 1990). High startle reactivity is characterized by high eye-blink amplitudes. The startle response is highly context-dependent and can be modulated by many factors. For example in fear potentiated startle, the startle response has significantly greater amplitude because the aversive motivational system is activated by a fear state

(Grillon, 2008; Lang, Bradley, & Cuthbert, 1998; Lang, Davis, & Ohman, 2000; Valls-Sole, Kumru, & Kofler, 2008). And in affective startle modulation, viewing unpleasant pictures potentiates the startle response compared to emotionally neutral pictures while eye-blinks evoked when viewing pleasant pictures are attenuated (Lang et al., 1998). Human startle potentiation is a reliable and specific index for fear learning (Hamm & Weike, 2005) and a valuable indicator for the analysis of neural systems associated with emotion, especially fear and anxiety, and emotion regulation (Grillon, 2008).

The investigation of the effect of OXT on the startle response has led to contradictory results. Results of animal studies include: increased startle response after OXT administration (King, Brown, & Kusnecov, 1985), no effects of OXT (Feifel & Reza, 1999; Missig, Ayers, Schulkin, & Rosen, 2010), and reduced startle response after central OXT administration (Ayers, Missig, Schulkin, & Rosen, 2011). In humans, a recent placebo-controlled double-blind study showed no significant difference between OXT and placebo on the baseline startle response. However, the startle eye-blink magnitude was significantly larger in the OXT group than in the placebo group during the viewing of negative (attacking humans, injured humans, mutilated bodies), but not neutral (household and kitchen objects) or positive (attractive women and erotic heterosexual couples) pictures (Striepens et al., 2012). Unfortunately, in this study valence categories were not matched for social vs. non-social content, which might be an additional important factor as social context may be particularly prone to OXY effects (Heinrichs et al., 2009). Another study tested how a single-nucleotide polymorphism of the OXT receptor gene relates to empathy and stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Individuals with a GG genotype of OXT receptor rs53576 displayed lower heart-rate reactivity than individuals with AA or AG genotypes during the anticipation of acoustic startle probes, which is in line with other studies showing that the GG genotype of rs53576 has a more efficient oxytocinergic function (for a review see Kumsta & Heinrichs, 2013). In summary, these findings suggest an association between the startle reflex and the oxytocinergic system. However, the exact nature of this association remains unclear. Trait anxiety was demonstrated to increase attention to threat (Calvo & Avero, 2005; Cisler & Koster, 2010; Pflugshaupt et al., 2005; Veljaca & Rapee, 1998). At the same time, endogenous OXT was shown to reduce anxiety and stress in the presence of fearful stimuli (I. D. Neumann, 2002; Viviani & Stoop, 2008). Therefore it could be hypothesized that the application of exogenous OXT might lower levels of anxiety specifically in high trait anxious men, which has already been reported in a study evaluating the perception of an impromptu speech performance (Alvares, Chen, Balleine, Hickie, & Guastella, 2012).

The aim of the present study was to investigate the effects of OXT on the startle response and its affective modulation by pictures (pleasant, neutral and unpleasant), using pictures in each valence category with both social and non-social content to control for this factor. We put particular focus on the effects of trait anxiety on affect-modulated startle reactivity. Under placebo, we expected the startle responses to be increased (higher startle eye-blink magnitude) during the presentation of negative pictures and to be reduced during the presentation of positive pictures, compared to neutral pictures (Lang et al., 1998). Based on the contradictory findings regarding the association of OXT and the startle reflex and the role of trait anxiety, we expected to find anxiety reducing effects in high trait anxious subjects and anxiety enhancing effects in low trait anxious subjects. We also expected OXT effects to be more pronounced with social compared to non-social stimuli.

3.3. Methods

3.3.1. Participants

Forty-four healthy non-smoking men were recruited through advertisements on pinboards and homepages. Exclusion criteria were neurological or psychiatric disorders, liver, kidney or heart diseases, allergy to preserving agents, use of medication including hormonal and herbal medication during the 4 weeks preceding the study, participation in other clinical trials during the 4 weeks preceding or during the study, impaired hearing (threshold over 30 dB), impaired cognitive abilities (IQ known to be below 70) and insufficient command of German. Physical and mental health was assessed by a structured screening interview (short medical history assessment) and by the German version (Ackenheil, Stotz, Dietz-Bauer, & Vossen, 1999) of the Mini-International Neuropsychiatric Interview (M.I.N.I.), a reliable and valid diagnostic structured interview (Lecrubier et al., 1997; Sheehan et al., 1998). For sample information on age and trait anxiety see Table 2. Participants were instructed not to consume alcohol or caffeine and not to exercise 24 hours, and not to eat or drink anything besides water 2 hours prior to the assessments. Seven subjects took part in only one of two sessions (see Table 2). Participants were thoroughly informed about the procedures and gave written informed consent according to the Declaration of Helsinki before participating. This study was approved by the local ethics committee and by the Swiss Regulatory Institute for drug trials (Swissmedic) and is registered as clinical trial at ClinicalTrials.gov, trial number NCT01066299. Monitoring of the study was performed by the Clinical Trial Center at the University Hospital Zurich.

Table 2. Sample description

	N	Range	Mean	SD	Median				
Both sessions	37								
Placebo session only	4								
OXT session only	3								
Age in years	44	18-51	27.2	8.6					
STAI trait scores	44	23-56	33.6	6.2	32.5				
	Low trait anxiety				High trait anxiety				
	N	Range	Mean	SD	N	Range	Mean	SD	p
Age in years	22	19-43	26.5	7.9	22	18-51	28.1	9.8	0.6
STAI trait scores	22	23-32	29.0	2.4	22	33-56	37.6	5.1	<0.001

Note. STAI = State Trait Anxiety Inventory.

3.3.2. Procedure

The study took place at the psychophysiology laboratory at the Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland. We used a double-blind placebo controlled crossover design. Assessments were made on 3 visits. During the first visit participants were screened for inclusion and exclusion criteria and received a URL website link to fill in the German version of the STAI trait form of the State Trait Anxiety Inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981) online. Psychophysiological assessments took place during the second and third visits, which were separated by 1-4 weeks. One week after the last visit participants were called for a follow-up check of their health status. Psychophysiological assessments took place at 2:00 p.m. in order to account for diurnal variation of OXT (Heinrichs et al., 2003) and were structured as follows: First, 24 IU of an intranasal spray was administered (3 puffs of 4 IU per nostril). Either OXT (Syntocinon, Novartis, Basel, Switzerland) or placebo (containing all ingredients except for the neuropeptide) was given at the first session and the other at the second session. The order was randomized across participants. After administration of the spray participants were left alone to read magazines for about 20 minutes. Then, sensors were attached while subjects sat in a comfortable chair and they were subsequently asked to rest quietly for seven minutes in order to facilitate adaptation to the laboratory setting. Forty-five minutes after spray application, subjects were given headphones and told that the session would start.

A background noise of 70 dB was running throughout the session to mask any environmental sounds. Two minutes of background noise only were followed by a block of 6 startle probes (bursts of

white noise, 95 dB, 40 ms) for baseline startle assessment. These 6 startle probes were separated by inter-trial intervals of 15-20 s. Then 38 pictures from the International Affective Picture System (IAPS; Lang et al., 2005) were shown for 6 s with inter-trial intervals of 15-20 s (M = 17 s). The first two trials were not included in the analysis. These two habituation trials each consisted of a neutral picture and a startle probe. During the presentation of 24 of the remaining 36 pictures a startle probe was given 3.5 s, 4 s or 4.5 s after picture onset. Time points for the startle probes were varied to make them less predictable. Another 6 startle probes were given between pictures and 12 pictures were shown without a startle probe. Figure 6 illustrates this sequence for a trial. At the end of the session each picture was shown again and rated for valence and arousal by the Self-Assessment Manikin (SAM; Bradley & Lang, 1994). Two separate sets of pictures, which were matched for valence and arousal, were used for the two sessions[3]. Each set consisted of 12 neutral, 12 positive and 12 negative pictures. For each valence half of the pictures were of social (showing people) and the other half of non-social content. In each condition 4 pictures were presented with and 2 without a startle probe. For each set three different serial presentation orders and combinations of pictures with or without startle were created. For the two habituation trials at the beginning the same two neutral pictures were used for all sets and versions. Subjects were randomly assigned to one of the two possible orders of set A and B and to one of the three versions of each set using the research randomizer on www.randomizer.org. Picture sets and substance sequences were approximately balanced between the two groups of high and low trait anxious subjects. Task presentation was done via E-Prime 2.0 Professional (Psychology Software Tools Inc., Pittsburgh, PA., USA). Pictures were shown on a 19'' computer screen and acoustic stimuli were presented binaurally via a Sony STR-DE197 amplifier and Novitronic sealed headphones. Noise volume level was calibrated using a Voltcraft SL-100 sound-level measuring device.

[3] IAPS picture numbers for set A: nonsocial neutral: 5532, 7037, 7095, 5395, 7042, 7211; nonsocial positive: 5551, 5200, 5780, 5611, 5814, 5910; nonsocial negative: 9301, 9470, 9830, 9373, 9090, 9000; social neutral: 9171, 2487, 3550.2, 2435, 2579, 7496; social positive: 2360, 5831, 2091, 2530, 2154, 2311; social negative: 9220, 2750, 2799, 6311, 9342, 2110.
IAPS picture numbers for set B: nonsocial neutral: 7484, 7560, 7920, 7242, 7058, 7057; nonsocial positive: 7545, 5779, 5594, 5631, 5300, 5600; nonsocial negative: 9320, 9471, 9101, 9290, 9340, 9280; social neutral: 2595, 2635, 2394, 2515, 2305, 2593; social positive: 8497, 2550, 2332, 2339, 5836, 2373; social negative: 3301, 2141, 2053, 9415, 9584, 2399.

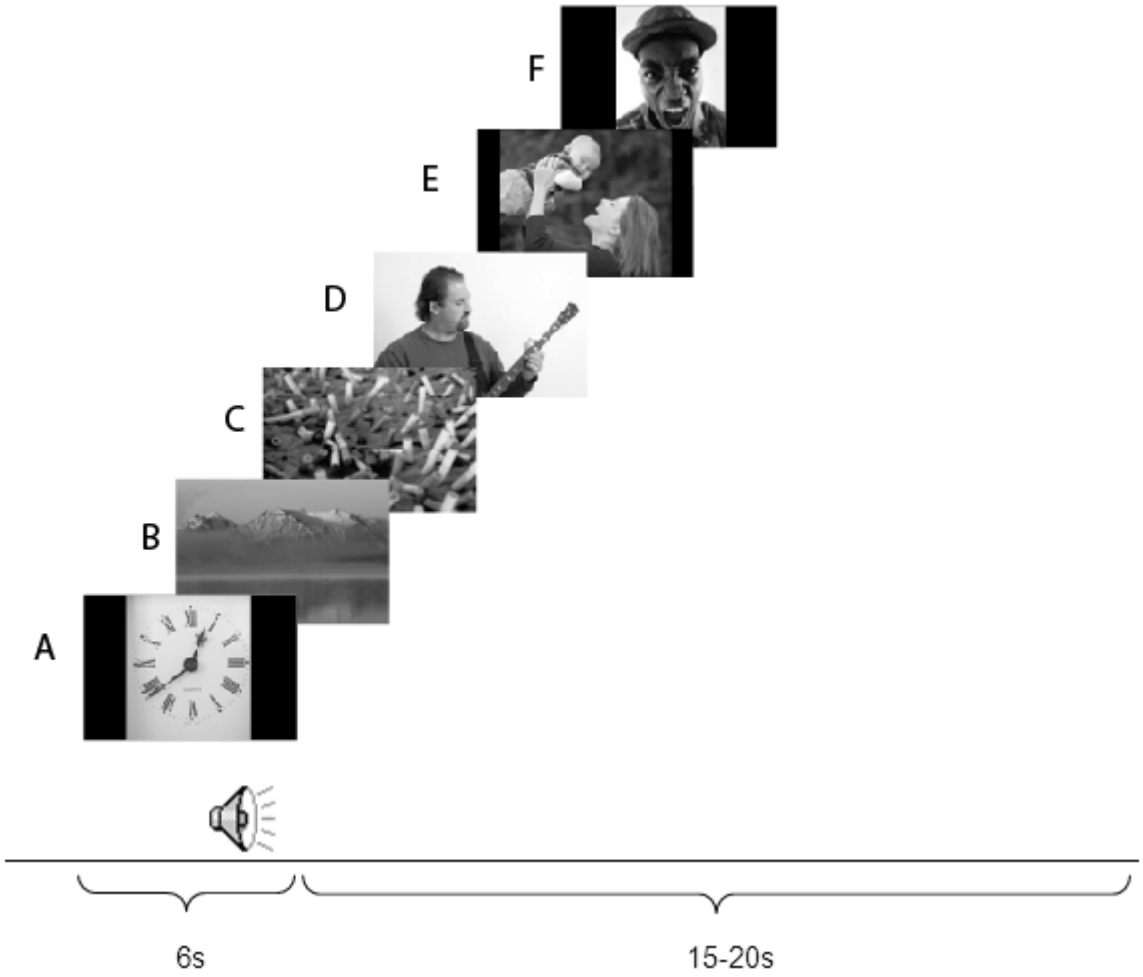

Figure 6. Illustration of a trial in the affective modulation task for the following contents: A) nonsocial neutral, B) nonsocial positive, C) nonsocial negative, D) social neutral, E) social positive, F) social negative. Startle probes were presented 3500ms, 4000ms, or 4500ms after picture onset. Because of copyright issues with IAPS pictures, alternative pictures with comparable content are shown in this illustration.

3.3.3. Physiological measurement and data reduction

Recording of the physiological signals was performed using a BIOPAC MP150 system (Biopac Systems, Inc, Goleta, CA). Facial electromyographic (EMG) activity from the left musculus orbicularis oculi was recorded using Ag/AgCl electrodes filled with electrolyte gel. EMG was sampled at a 1000Hz rate. Autonomic Nervous System Laboratory 2.51 (ANSLAB; Wilhelm, F. H. & Peyk, P., 2005; available at the SPR Software Repository: http://www.sprweb.org) was used to filter raw data and extract startle responses. The startle EMG was 50Hz notch filtered, rectified and startle eye-blink magnitude (baseline corrected peak amplitude for response trials) was computed. The 50ms before the startle probe onset were used as baseline. The 100ms startle response window started 20ms after probe onset. Due to insufficient data quality, 3.3 % of trials had to be excluded from analysis.

3.3.4. Data analysis

Statistical analyses were performed using IBM SPSS Statistics 21 (SPSS Inc., Chicago, Ill, USA). We used a linear mixed model design to compare conditions. The model for eye-blink magnitude during baseline startle was fitted with substance (OXT or placebo) and time (trials 1-6) treated as fixed effects. The model for eye-blink magnitude during picture viewing as well as the models for picture ratings (valence and arousal) contained substance (OXT or placebo), picture valence (neutral, positive or negative), and picture content (social or non-social) as fixed effects. STAI trait scores were median split to build two groups of subjects with low vs. high trait anxiety scores (see Table 2). In a further step, all models were calculated again with STAI group as an additional fixed factor. In all models subject was treated as a random effect. All models were optimized by the covariance type that produced the lowest Akaike's Information Criterion (AIC; Galecki, Welch, & West 2007)[4]. Bonferroni corrected pairwise comparisons based on the estimated marginal means were used as post-hoc tests.

3.4. Results

3.4.1. Baseline startle

A significant main effect of time was found for eye-blink magnitude ($F(5, 289) = 7.77$, $p < 0.001$). No effects were found for substance or the interaction of substance x time (p values > 0.1). Eye-blink magnitude habituated over time. Estimated marginal means and standard errors per trial can be seen in Figure 7. When adding STAI group as an additional factor to the baseline startle model the main effect of time stayed significant. No main effects of substance or STAI group appeared (p values > 0.1).

[4] A first-order factor analytic structure was fitted for baseline startle eye-blink and picture arousal ratings. A scaled identity structure was fitted for picture valence ratings and a first-order ante-dependent structure for affective modulation startle eye-blink.

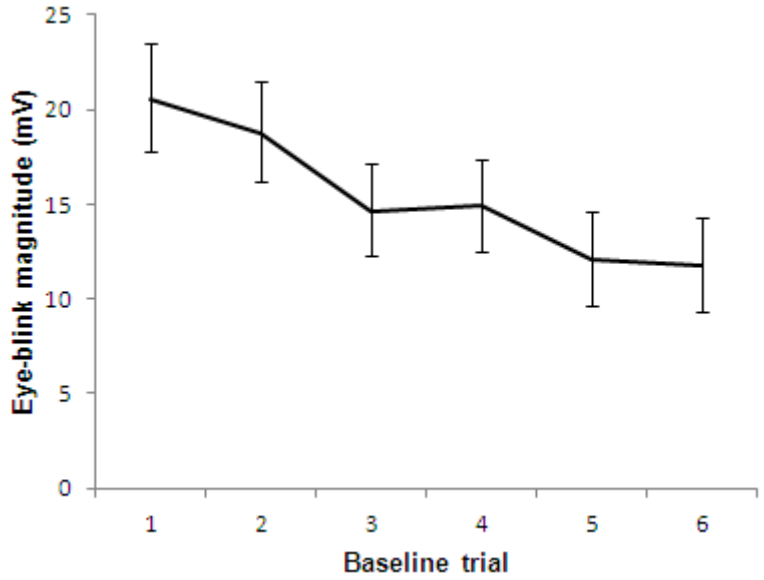

Figure 7. Estimated marginal means +/- 1 standard error for eye-blink magnitude in millivolt: habituation over the 6 trials of baseline startle (across conditions).

3.4.2. Affective modulation of startle

During picture viewing, no main effect of substance (p = 0.2) and no interactions of substance with picture valence or picture content (p values > 0.05) were found for eye-blink magnitude. Also, there was no main effect of picture valence (p=0.5). When adding STAI group as an additional factor to the model for eye-blink magnitude during picture viewing there were interactions of substance x STAI group (F(1, 423) = 28.34, p < 0.001), substance x picture valence x STAI group (F(2, 623) = 3.12, p = 0.045), and substance x picture valence x picture content (F(2, 594) = 3.06, p = 0.048). Individuals with lower STAI trait scores showed weaker eye-blinks under OXT (M = 7.43 mV, SE = 2.03 mV) than under placebo (M = 8.78 mV, SE = 2.04 mV; p = 0.009). Individuals with higher STAI trait scores showed stronger eye-blinks under OXT (M = 8.53 mV, SE = 2.04 mV) than under placebo (M = 5.92 mV, SE = 2.03 mV; p < 0.001). Decomposition of the interaction of substance x picture valence x STAI group showed that the difference between OXT and placebo was significant in both groups for positive and negative pictures (p values < 0.05). For neutral pictures it was only significant in the group with higher STAI trait scores (p = 0.02) but not in the group with lower STAI trait scores (p = 0.6). Estimated marginal means and standard errors are shown in Figure 8. Decomposition of the interaction of substance x picture valence x picture content revealed that under placebo, positive pictures with social content elicited stronger eye-blinks than neutral pictures with social content (p=0.04). Also under placebo, neutral pictures showed a trend towards stronger eye-blinks with non-social compared to

social content (p=0.056). Additionally, neutral pictures with social content showed a trend towards stronger eye-blinks under OXT (*M* = 8.00 mV, *SE* = 1.49 mV) than under placebo (*M* = 6.73 mV, *SE* = 1.48 mV; *p* = 0.053) while the difference between OXT and placebo was not significant for all other comparisons (*p* values > 0.1).

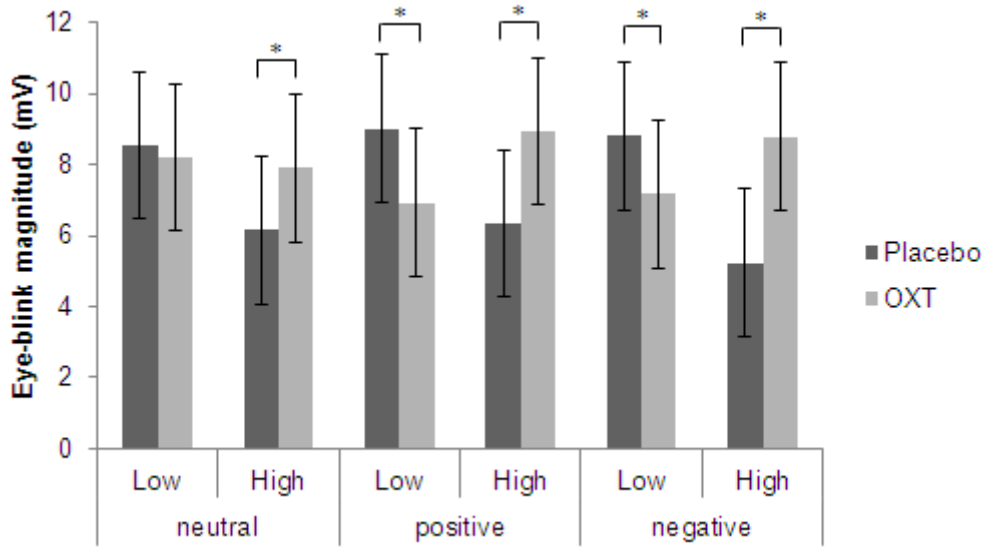

Figure 8. Estimated marginal means +/- 1 standard error for eye-blink magnitude in millivolt: substance x picture valence x STAI group interaction. Low = lower STAI trait scores, high = higher STAI trait scores, * p<0.05.

3.4.3. Picture ratings

For valence ratings main effects of picture valence (*F*(2, 2896) = 2107.02, *p* < 0.001) and picture content (*F*(1, 2896) = 9.82, *p* = 0.002) as well as interactions of picture valence x picture content (*F*(2, 2896) = 3.15, *p* = 0.04) and substance x picture valence x picture content (*F*(2, 2896) = 3.16, *p* = 0.04) were found. There was no main effect of substance (*p* = 0.7). Pairwise comparisons showed that valence ratings were given according to picture categories with lowest values for negative pictures (*M* = 2.96, *SE* = 0.07) followed by neutral pictures (*M* = 5.59, *SE* = 0.07) and highest values for positive pictures (*M* = 7.27, *SE* = 0.07; all pairwise *p* values < 0.001). Social pictures were given higher valence ratings (*M* = 5.36, *SE* = 0.06) than non-social pictures (*M* = 5.19, *SE* = 0.06). Decomposition of the interaction of picture valence x picture content showed that only for neutral pictures were valence ratings higher for social content (*M* = 5.77, *SE* = 0.08) than non-social content (*M* = 5.41, *SE* = 0.08; *p* < 0.001), while this comparison was not significant for emotional pictures (*p* values > 0.3). Decomposition of the interaction of substance x picture valence x picture content showed that only under OXT were neutral pictures with social content given higher valence ratings

(*M* = 5.87, *SE* = 0.11) than neutral pictures with non-social content (*M* = 5.24, *SE* = 0.11; *p* < 0.001), while this comparison was not significant under placebo (*p* = 0.5). Also, neutral pictures with non-social content were given lower valence ratings under OXT (*M* = 5.24, *SE* = 0.11) than under placebo (*M* = 5.58, *SE* = 0.11; *p* = 0.01), while the comparison between placebo and OXT was not significant for emotional or social pictures (*p* values > 0.1).

For arousal ratings main effects of substance ($F(1, 139) = 17.30$, $p < 0.001$), picture valence ($F(2, 2828) = 308.71$, $p < 0.001$) and picture content ($F(1, 2833) = 10.66$, $p = 0.001$) were found as well as an interaction of picture valence x picture content ($F(2, 2848) = 3.36$, $p = 0.04$). Pairwise comparisons showed that under OXT arousal ratings were higher (*M* = 4.13, *SE* = 0.19) than under placebo (*M* = 3.83, *SE* = 0.19). Positive pictures were given the lowest arousal ratings (*M* = 3.22, *SE* = 0.19) followed by neutral pictures (*M* = 3.71, *SE* = 0.19) and negative pictures with the highest values (*M* = 5.00, *SE* = 0.19; all pairwise *p* values < 0.001). Social pictures were given higher arousal ratings (*M* = 4.07, *SE* = 0.19) than non-social pictures (*M* = 3.88, *SE* = 0.19). Decomposition of the interaction of picture valence x picture content showed that the difference between social and non-social content was only significant for positive pictures (social: *M* = 3.41, *SE* = 0.20; non-social: *M* = 3.03, *SE* = 0.20; *p* < 0.001).

When adding STAI group as an additional factor, the previously found effects for valence ratings remained significant. In addition, it induced a significant interaction of substance x picture valence x picture content x STAI group ($F(2, 2885) = 3.42$, $p = 0.03$). Participants with lower STAI trait scores assigned higher valence ratings to neutral pictures with social content under OXT than under placebo (*p* = 0.02). On the other hand, participants with higher STAI trait scores assigned lower valence ratings to neutral pictures with non-social content under OXT than under placebo (*p* = 0.03). Also, under placebo participants with higher STAI trait scores assigned higher valence ratings to positive pictures with social content than participants with lower STAI trait scores. Estimated marginal means and standard errors are shown in Figure 9. A significant interaction of picture valence x STAI group was also found ($F(2, 2885) = 4.16$, $p = 0.02$) but pairwise comparisons showed no differentiating effects (all group comparison *p* values > 0.1 and all valence comparison *p* values < 0.001).

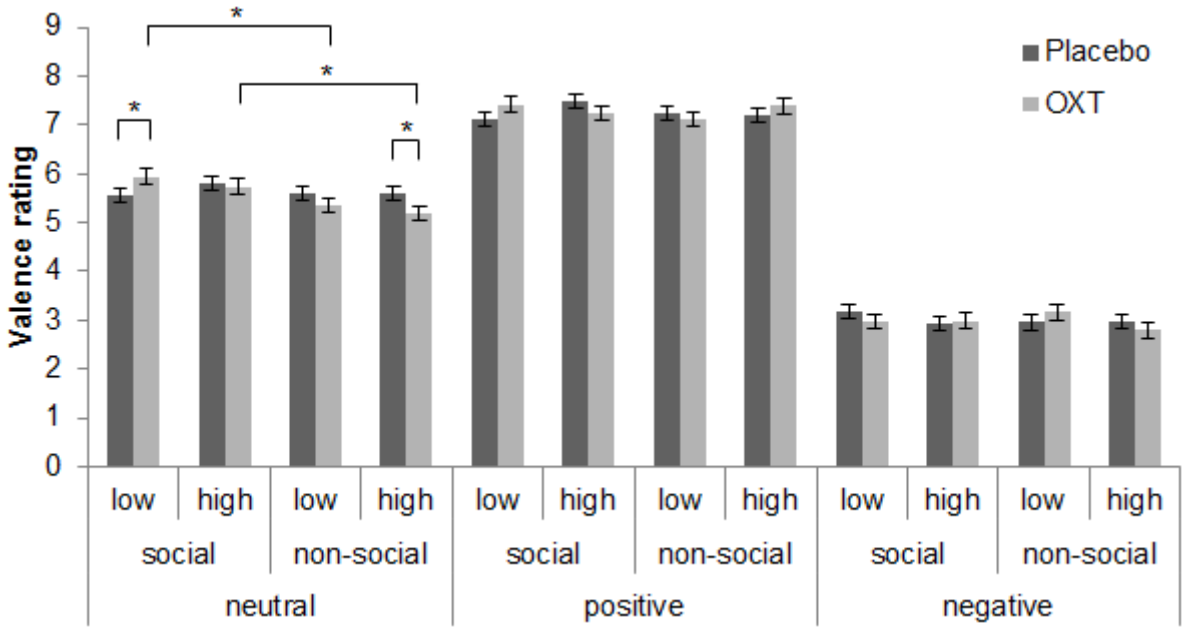

Figure 9. Estimated marginal means +/- 1 standard error for substance x picture valence x picture content x STAI group interaction in valence ratings. Low = lower STAI trait scores, high = higher STAI trait scores, * $p < 0.05$

Also the previously found effects for arousal ratings remained significant when adding STAI group as an additional factor. Additionally, an interaction of picture valence x STAI group ($F(2, 2824) = 10.00$, $p < 0.001$) was induced, but pairwise comparisons revealed no differentiating effects (all group comparison p values > 0.06 and all valence comparison p values < 0.001).

3.5. Discussion

The main aim of this study was to investigate the influence of OXT on the affective modulation of the startle reflex and how this modulation is related to social picture content and trait anxiety. Most remarkably, we found differential effects for eye-blink startle during picture viewing according to STAI trait scores. Specifically, subjects with lower STAI trait scores showed weaker startle responses under OXT than under placebo during picture viewing. And vice versa, subjects with higher STAI trait scores showed stronger startle responses under OXT than under placebo.

The startle reflex is a measure of defensive motivation (Lang et al., 1998) and in the context of negative emotional picture presentation it could be interpreted in terms of a fear potentiated startle. Our results therefore suggest that for people with lower trait anxiety OXT seems to have anxiety reducing effects, while for people with higher trait anxiety it might increase defensive reactions.

These results complement those found by Striepens et al. (2012) in contradicting an unspecific anxiety reducing effect of OXT. The differential effects of OXT on the startle reflex in relation to trait anxiety suggest that there are relevant interactions between individual trait characteristics and oxytocin. Anxiety reducing effects of OXT might be specific to certain personality traits in individuals under specific social-affective context conditions. However, the direction of the influence of trait anxiety was contrary to what we had expected. As Alvares et al. (2012) had found stress-reducing effects of OXT only in high trait-anxious participants, we also expected a startle-reducing effect in high trait-anxious subjects. Interestingly, our data show smaller startle responses under OXT compared to placebo for low trait anxiety. A result similar to ours was found with aggression in female rats (de Jong, Beiderbeck, & Neumann, 2014): Central infusion of OXT inhibited aggressive behavior against an intruder in rats selected for low anxiety, but not for those selected for high anxiety behavior. As the intruder in the rat study and the startle burst in our study can be viewed as stressors and aggression and the startle responses as different kinds of defensive reactions, there might be a common mechanism for the influence of OXT. Grillon et al. (2012) found anxiety-enhancing effects of OXT in response to unpredictable threat. In our study, startle bursts were not cued and occurred at different time points within the picture presentation. Unpredictability might therefore explain the discrepancy between our results and those of Alvares et al. (2012), where the stressor was continuous and therefore predictable.

OXT increased arousal ratings for pictures compared to placebo (across groups and picture categories). This is in line with the results of Lancel, Kromer, & Neumann (2003) who found centrally administered OXT to induce a state of arousal in rats. Induction of arousal might also explain the results of earlier studies showing anxiety-enhancing effects of OXT (Grillon et al., 2012; Guzman et al., 2013). For valence ratings we found differential effects for social and non-social picture content that were varied according to trait anxiety: for subjects with lower STAI trait scores, OXT raised valence ratings for neutral pictures with social content and for subjects with higher STAI trait scores, OXT reduced valence ratings for neutral pictures with non-social content. This could indicate that OXT raises the positive valence appraisal of social stimuli, as was concluded by Averbeck (2010) from the results of Gamer, Zurowski, & Buchel (2010), but only for subjects with low trait anxiety. At the same time, for subjects with high trait anxiety, social stimuli might appear more salient because OXT inhibits interest in non-social stimuli.

As expected, we found no general effect of OXT on baseline eye-blink startle or eye-blink startle during picture viewing, which is in line with results from Striepens et al. (2012). Also, we failed to find the expected affective modulation of the eye-blink (Lang et al., 1998) under placebo. In a study by Lyby, Forsberg, Asli, & Flaten (2012) a placebo manipulation caused a startle reducing effect. Therefore, the lack of differential valence effects in our data might also be due to an effect caused by the placebo. Another possible explanation could be the arousal level of our stimuli. Leite et al. (2012) found that only high arousing (but not low arousing) positive pictures attenuated the startle eye-blink. Therefore, our pictures might have been too low in arousal to elicit the typical startle modulation effect. But still, the presentation of pictures induced differential effects for the two groups which did not occur in the pure startle procedure.

Since the level of high trait anxiety in our sample was still within a subclinical range, our results cannot necessarily be generalized to individuals with psychological disorders associated with severe anxiety. It also should be kept in mind that pictures with social content are only a relatively mild social stimulus. Stronger behavioral social stress stimuli might have produced different results. A further limitation of our study is that we only investigated men in order to exclude endocrine influences of the female menstrual cycle.

In conclusion, this study is a further demonstration of the complex associations between OXT and anxiety. As the effect of OXT on the startle reflex seems to be dependent on trait anxiety, future studies should take individual characteristics into account as these might partially explain previous contradictory results. Further studies in clinical populations are needed to understand these effects in the framework of anxiety and stress related disorders.

4. Study 3 - Startle reactivity in the long-term after severe accidental injury: Preliminary data

Published in: Psychiatry Research 2013 Dec 15; 210(2):570-4

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4.1. Abstract

An exaggerated startle response is one of the core hyperarousal symptoms of posttraumatic stress disorder (PTSD). Heightened startle eye-blink magnitude and reduced habituation of this response in PTSD patients have been reported in several studies. However, it is unclear whether this is an enduring characteristic of individuals vulnerable for PTSD or to which degree trauma-exposed individuals who do not develop PTSD also show exaggerated startle. Thirteen accident survivors with remitted PTSD, 12 trauma controls, and 16 non-trauma controls were examined. Four measures of startle reactivity were analyzed in response to 15 bursts of white noise (95dB, 50ms): eye-blink magnitude, eye-blink onset latency, skin conductance response, and heart rate response. The eye-blink reflex was measured over the left musculus orbicularis oculi. Reactivity and habituation were analyzed using linear mixed models. Remitted PTSD subjects did not differ from non-trauma controls regarding any of the startle reactivity or habituation measures. Unexpectedly, trauma controls showed

larger eye-blink magnitude than non-trauma controls. These results suggest that the exaggerated startle response disappears after remission from PTSD. Further, they suggest that psychologically resilient trauma survivors might show a PTSD-like pattern of exaggerated physiological startle even many years after a traumatic event.

4.2. Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop after exposure to terrifying events in which grave physical harm occurred or was threatened (American Psychiatric Association, 1994). Resilience on the other hand is a personality characteristic that moderates the negative effects of stress and promotes adaptation. The rates of PTSD among accident survivors vary considerably between studies, some showing high rates of up to 46% (E.B. Blanchard, Hickling, Taylor, & Loos, 1995; E. B. Blanchard, Hickling, Taylor, Loos, & Gerardi, 1994; Ehlers, Mayou, & Bryant, 1998; Koren, Arnon, & Klein, 1999; Ursano et al., 1999). In contrast, in two studies in Switzerland less than 5% of severely injured accident survivors were found to suffer from PTSD (Schnyder, Moergeli, Klaghofer, & Buddeberg, 2001; Schnyder, Wittmann, Friedrich-Perez, Hepp, & Moergeli, 2008), indicating high psychological resilience in this population.

According to the DSM-IV(American Psychiatric Association, 1994), the diagnosis of PTSD includes persistent symptoms of increased arousal like exaggerated startle responses, difficulty falling or staying asleep, anger, or hypervigilance. The startle reaction is a physiologic response to a sudden unexpected stimulus that contracts several muscles in order to protect the body from harm (Landis & Hunt, 1939). Startle reactivity can be measured using the eye-blink reflex, which is part of the startle reaction and can easily be elicited by loud acoustic stimuli (Lang et al., 1990). High startle reactivity is characterized by high eye-blink amplitudes and short eye-blink onset latencies. The startle reaction can also be accompanied by a rise of the skin conductance level (Shalev et al., 1992) and an increased heart rate (Orr, Lasko et al., 1997; Orr et al., 1995; Orr, Solomon et al., 1997; Shalev et al., 1992).

Studies exploring the association between startle reactions and PTSD have found inconsistent results. In victims of single potentially traumatic events such as combat, rape, or accidents evidence for heightened startle reactions in PTSD has been found compared to traumatized subjects without PTSD (Butler et al., 1990; Grillon, Morgan, Davis, & Southwick, 1998; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Orr et al., 1995; Shalev et al., 1992; Shalev, Peri, Orr, Bonne, & Pitman,

1997) as well as compared to subjects without trauma history (Grillon et al., 1998; Morgan, Grillon, Lubin, & Southwick, 1997; Morgan et al., 1996; Shalev et al., 1992). Victims of prolonged or repeated traumatic exposure such as childhood sexual abuse, on the other hand, might reveal a reversed pattern of lower startle reactivity. For example Medina, Mejia, Schell, Dawson, & Margolin (2001) found that higher PTSD scores were associated with lower startle reactivity in women who had experienced childhood corporal punishment or intimate partner aggression. In a meta-analysis by Pole (2007) PTSD was reliably associated with larger responses to startling sounds. It is unclear, however, whether the exaggerated startle response is a stable trait characteristic of subjects vulnerable for PTSD (risk factor), or an acquired PTSD symptom that disappears after remission. In accordance with the former hypothesis, in a prospective investigation Guthrie & Bryant (2005) found a heightened startle reaction in firefighters prior to trauma to be a predictor for PTSD severity after traumatic events. On the other hand, Shalev et al. (2000) found that subjects who later developed PTSD showed elevated startle responses 1 month after trauma, while 1 week after trauma they did not differ from subjects who did not go on to develop PTSD. In a rat model of PTSD Nalloor, Bunting, & Vazdarjanova (2011) showed that higher acoustic startle reactions elicited by mild stress prior to a traumatic event were able to predict PTSD-like behavior after trauma. These results suggest a hidden risk factor for PTSD that can be seen under mildly stressing conditions. Additionally, studies investigating reactions to startle sounds in PTSD reported deficits in habituation, i.e. deficits in the decrease of physiological reaction after repeated exposure (Orr et al., 1995; Shalev et al., 1992; Shalev et al., 1997). These findings point to a possible learning deficit in PTSD patients that could partly explain the hyperarousal symptoms and might have implications for treatment. Also studies investigating fear-potentiated startle reactions point into this direction by showing that the ability to inhibit fear reactions under safe conditions is impaired in PTSD patients (Jovanovic et al., 2009; Jovanovic et al., 2012).

Taken together, these findings show that the relation between startle and PTSD is rather complex. The few studies that have compared startle reactions in remitted and current PTSD patients (Carson et al., 2007; Metzger et al., 1999) also found inconsistent results. While Carson et al. (2007) found that current PTSD patients showed higher heart rate responses than remitted PTSD patients and subjects who never had PTSD, Metzger et al. (1999) found higher heart rate responses and slower skin conductance habituation in current and remitted PTSD patients as compared to individuals who never had PTSD.

Further, it is unclear how subjects who are resilient against the development of PTSD after a traumatic event react physiologically compared to individuals who have never experienced any serious traumatic event. More specifically, it is not clear whether psychologically resilient subjects show a PTSD-like pattern at the physiological level or whether physiological changes only take place in association with psychological PTSD symptoms.

The aim of this study was to investigate whether remitted PTSD subjects still show heightened startle reactions. We examined the physiological startle reactivity of accident survivors, comparing remitted PTSD subjects with a group of accident survivors who did not develop PTSD (trauma controls) and a group of control subjects who had not experienced any trauma (non-trauma controls). On the assumption that heightened startle might be a pre-existing trait characteristic of subjects vulnerable for the development of PTSD, we expected the remitted PTSD subjects to have the largest startle response and slowest habituation. On the other hand, we expected the trauma control group to show the weakest startle response and fastest habituation as they seem to be resilient to stress. The non-trauma control subjects were expected to lie between the other two groups, because this group should comprise both resilient and susceptible individuals.

4.3. Methods

4.3.1. Participants

Twenty-two PTSD-remitted accident survivors and 16 resilient accident survivors who had not developed PTSD were recruited from two samples of physically injured subjects who had been hospitalized at the Department of Traumatology at the University Hospital Zurich 10 years ago and had taken part in earlier studies looking into the psychosocial consequences of accidental injuries (Schnyder et al., 2001; Schnyder et al., 2008). These patients had originally received a thorough psychiatric diagnostic assessment shortly after the accident and 6 and 12 months later. To recruit the subjects we called all the participants of the previous studies fulfilling our inclusion criteria, and informed them about our study. Additionally, 16 healthy controls were recruited from the general population through advertisements (non-trauma group). All subjects were over 18 years of age. To be included in the PTSD-remitted group subjects had to have been diagnosed with full or subsyndromal PTSD according to DSM-IV (American Psychiatric Association, 1994), as assessed by the German version (Schnyder & Moergeli, 2002) of the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) at least at one of the measurement points in the previous studies (full PTSD: fulfilling symptom

clusters B, C and D; subsyndromal PTSD: fulfilling symptom clusters B plus either C or D but not both) but not in the present study. For participants to be included in the trauma-control group, it was required that they never had a diagnosis of full or subsyndromal PTSD during the previous studies. Inclusion criteria for the non-trauma group were that the participants had never experienced a trauma according to DSM-IV criteria. Exclusion criteria for all three groups were current mental disorders, chronic somatic and neurological diseases and insufficient command of German. All subjects were tested for normal hearing function. Groups were matched for age and gender (see Table 3). Participants were thoroughly informed about the procedures and gave written informed consent according to the Declaration of Helsinki before participating. This study was approved by the local ethics committee.

Table 3. Sample description.

	PTSD-remitted		Trauma controls		Non-trauma controls				
	N	%	*N*	%	*N*	%	Chi^2	*df*	*p*
Men	5	38.5	5	41.7	6	37.5	0.05	2	0.9
Women	8	61.5	7	58.3	10	62.5			
	M	SD	M	SD	M	SD	*F*	*df*	*p*
Age	53.2	9.3	58.5	7.2	54.1	10.3	1.22	2/38	0.3
Years of education	13.5	2.9	13.8	2.3	15.1	3.9	1.09	2/38	0.3
STAI - trait anxiety	34.5	4.3	32.4	4.2	35.5	6.6	1.17	2/38	0.3
BDI - depression	7.5	3.4	6.2	4.0	5.2	4.5	1.23	2/38	0.3
	M	SD	M	SD	M	SD	*t*	*df*	*p*
CAPS – current total score	6.5*	8.2*	2.6	4.2			-1.47	22	0.2
Years since trauma exposure	11.5	1.8	9.9	0.3			3.30	12.9	0.006
Years without symptoms	7.3	5.2							

Note: STAI= State Trait Anxiety Inventory, BDI= Beck Depression Inventory, CAPS= Clinician-Administered PTSD Scale. * Missing CAPS data in one subject.

Six participants were excluded from the study due to current major depression or anxiety disorders. Two participants were excluded because of non-normal hearing, and three because of technical problems. One subject canceled the assessment, and one did not tolerate the face electrodes for the startle measurement. From the remaining 13 subjects in the PTSD-remitted group, one subject was excluded from skin conductance analysis and two from heart rate analysis because of poor data quality. Also, one of the remaining 12 subjects in the trauma-control group and two of the 16 subjects in the non-trauma group were excluded from skin conductance analysis for the same reason. The

sample description is given in Table 3. Two subjects in the remitted PTSD group were taking psychotropic medication, one was taking antidepressants and one anticonvulsants. Analyses were performed both including and excluding these subjects (results without these two subjects are provided in the supplemental material in Appendix A). Two subjects of the remitted PTSD group had received psychotherapy.

4.3.2. Psychometrics

Current PTSD symptoms were assessed using the German version (Schnyder & Moergeli, 2002) of the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). Axis I comorbidity was established by the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Symptoms of depression were measured by the German version (Hautzinger, Bailer, Worall, & Keller, 1995) of the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and trait anxiety by the German version of the State Trait Anxiety Inventory (STAI; Laux et al., 1981). The absence of traumatic events in the non-trauma group was checked by the German version of the first part of the Posttraumatic Stress Diagnostic Scale (PDS; Foa, 1995).

4.3.3. Physiological measures

Recording of the physiological data was performed using a BIOPAC MP150 System (Biopac Systems, Inc., Goleta, CA). The eye-blink reflex was measured by electromyographic (EMG) recordings of activity in the left musculus orbicularis oculi (Fridlund & Cacioppo, 1986) using Ag/AgCl disposable snap connector electrodes filled with hydrogel jelly. Skin conductance electrodes were placed on the thenar and hypothenar eminence of the left palmar surface using Ag/AgCl electrodes filled with isotonic electrolyte gel. Electrocardiograms (ECG) were recorded from three Ag/AgCl disposable snap connector electrodes filled with hydrogel jelly located below the left and right collarbone and on the left rib cage. EMG and ECG were sampled at a 1000Hz rate, skin conductance level at a 62.5Hz rate.

4.3.4. Procedure

The study took place at the psychophysiological laboratory of the Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland. Sensors were attached while the subjects reclined in a comfortable chair. Subjects were then asked to rest quietly for 7 min in order to facilitate laboratory adaptation. Then 15 startle probes (bursts of white noise, 95 dB, 50 ms) were presented binaurally via Novitronic sealed headphones with variable inter-trial intervals ranging from 27 s to 52 s.

The presentation of the startle probes was done via E-Prime 2.0 Professional (Psychology Software Tools Inc., Pittsburgh, PA., USA) and a Sony STR-DE197 amplifier. Loudness was calibrated using a Voltcraft SL-100 sound-level measuring device.

4.3.5. Data reduction

Autonomic Nervous System Laboratory 2.51 (ANSLAB; Wilhelm, F. H. & Peyk, P., 2005; available at the SPR Software Repository: http://www.sprweb.org) was used to filter the raw data, to correct for artefacts and to extract mean and maximum scores for event and baseline windows.

The startle EMG was 50 Hz notch filtered and rectified and rated for eye-blink magnitude (baseline corrected amplitude) and onset latency. The 50 ms before probe onset were used as baseline. The 100ms response window started 20ms after probe onset. The onset of the eye-blink was defined as the time point when the signal reached a value higher than five standard deviations of baseline variance above the baseline mean.

The ECG signal was band-pass filtered (0.5 – 40 Hz); skin conductance level was low-pass filtered (1 Hz). Heart rate was extracted using the interval between successive R waves. Heart rate and skin conductance level were rated for a 6s event window beginning at the startle probe onset and corrected for a baseline window of 2s before startle probe onset. The baseline mean was subtracted from the event mean for the heart rate and from the event maximum for skin conductance level. For the skin conductance level a response was defined as a baseline corrected event maximum of at least 0.05 µS. Non-responses were not included in the analysis. Skin conductance responses were log transformed (Ln(SCR+1)) in order to normalize the distribution.

4.3.6. Data analysis

Statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc., Chicago, Ill, USA). We used a linear mixed model design and applied restricted maximum likelihood estimation to analyze time effects (habituation) and to compare the three groups of subjects. Full-factorial models were built with group and time (trial) treated as fixed effects and subjects as a random effect. All models were run using all possible covariance types for the repeatedly measured outcomes. The models were optimized by the covariance type which produced the lowest Akaike's Information Criterion (AIC; West et al., 2007). A first order ante-dependent covariance structure was accommodated for eye-blink magnitude. For eye-blink onset latency the best fit was obtained with a first order auto-regressive covariance structure. For skin conductance response and heart rate response the best fit was

obtained with a first order factor analytic structure. Bonferroni corrected pairwise comparisons based on the estimated marginal means were used as post-hoc tests.

4.4. Results

There was a significant main effect of group on eye-blink magnitude ($F(2, 41.1) = 3.56$, $p = 0.04$). The trauma-controls showed significantly higher eye-blink magnitude (M = 11.94 mV, SE = 2.09 mV) than the non-trauma controls (M = 4.60 mV, SE = 1.80 mV; mean difference = 7.33 mV, SE = 2.75 mV, 95%-CI 0.46 mV to 14.21 mV, $p = 0.03$). There was neither a significant difference in eye-blink magnitude between remitted PTSD subjects (M = 8.19 mV, SE = 2.00 mV) and trauma-controls (mean difference = -3.74 mV, SE = 2.89 mV, 95%-CI -10.95 mV to 3.47 mV, p=0.6), nor between the remitted PTSD subjects and non-trauma controls (mean difference = 3.59 mV, SE = 2.69 mV, 95%-CI -3.11 mV to 10.30 mV, $p = 0.6$). There was a significant main effect of time on eye-blink magnitude ($F(14, 64.2) = 6.49$, $p < 0.001$) with magnitude decreasing over time across all groups of subjects. Skin conductance response showed a significant main effect of time ($F(14, 91.3) = 6.85$, $p < 0.001$), decreasing over time across all groups of subjects. There was no significant main effect of group for skin conductance response ($p = 0.3$). No significant main effects were found for eye-blink onset latency and heart rate response (p values > 0.1). No significant time x group interaction was found in any of the measures (p values > 0.1). Figure 10 illustrates the time course of all four measures by group. Analyses without the two subjects taking antidepressants and anticonvulsants revealed the same pattern of significant effects (see supplemental material).

Descriptively, a reversal of the habituation can be seen in Figure 10 for skin conductance response in the remitted PTSD group. Pairwise comparisons showed that for the remitted PTSD group trials 6 and 8 to 11 differed from trial 1 (p values ≤ 0.03) but trials 12 to 15 did not anymore (p values = 1.0). For trauma controls only trial 11 differed significantly from trial 1 ($p = 0.05$) while for non-trauma controls significant differences to trial 1 could be seen for trials 8, 10, 12, 14 and 15 (p values ≤ 0.05). Separate models for trials 1 to 6 and 7 to 15 revealed that the group effect in eye-blink magnitude only reached significance in the later part of the experiment. All other effects showed the same pattern as in the model for the whole experiment including both parts (see supplemental material). Remitted PTSD subjects and trauma controls did not differ in CAPS scores. We did not find any group differences in BDI or STAI scores, either (see Table 3).

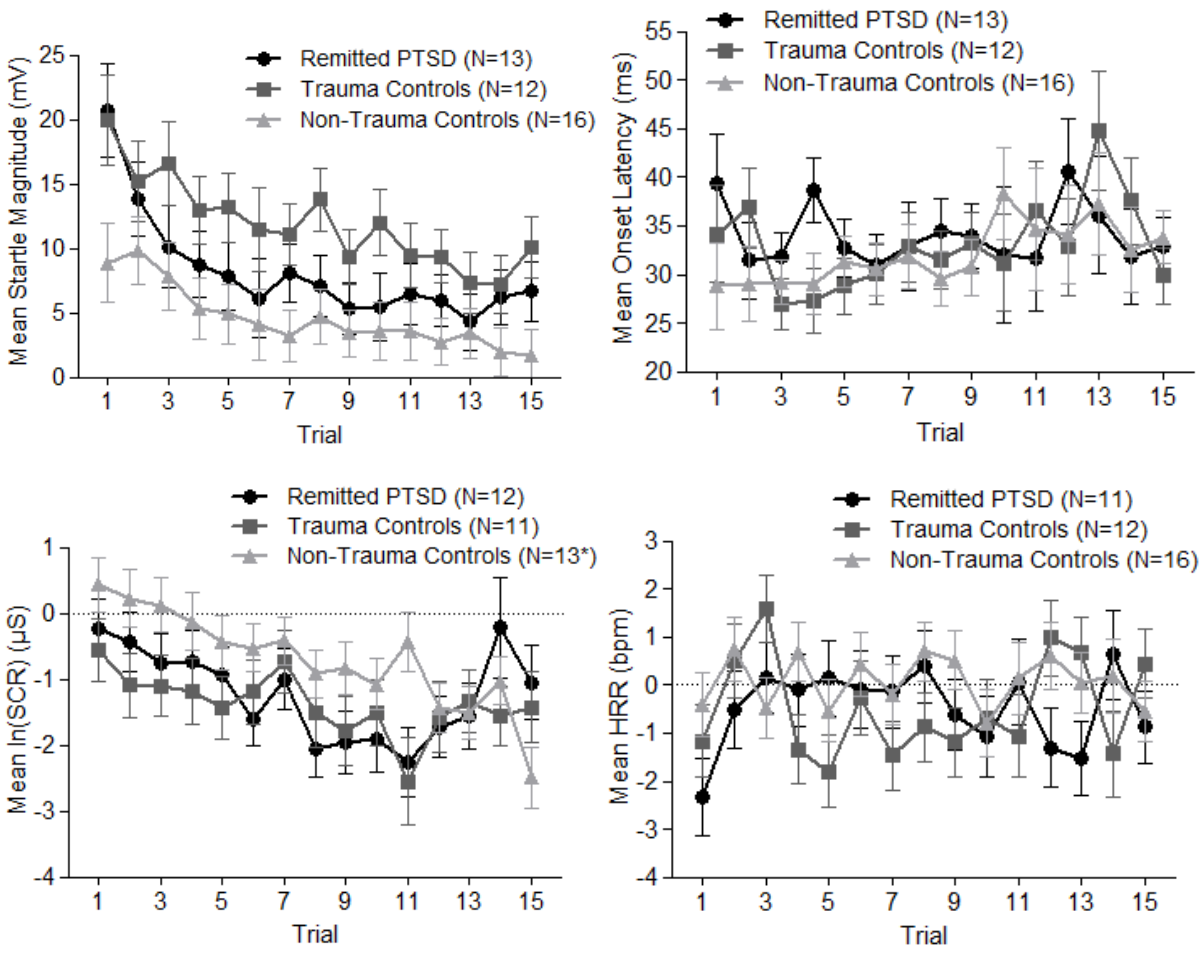

Figure 10. Estimated marginal means and standard errors for the time course of eye-blink magnitude in millivolt (top left), eye-blink onset latency in milliseconds (top right), natural logarithm of skin conductance response in micro Siemens (bottom left) and heart rate response in beats per minute (bottom right). * One of 14 subjects dropped out of skin conductance analysis because none of the responses reached the threshold of 0.05 µS.

4.5. Discussion

The aim of this exploratory study was to provide further insight into the origin of exaggerated startle responses in PTSD. We compared the startle reactivity of PTSD-remitted accident survivors with accident survivors who had not developed PTSD (trauma controls) and healthy controls who had never experienced any serious traumatic event (non-trauma controls). We found no difference between remitted PTSD subjects and non-trauma control subjects in any of the physiological measures of startle reactivity. Unexpectedly, even 10 years after the accident the trauma control group showed, in the absence of psychopathological symptoms, higher startle eye-blink magnitude than the non-trauma controls.

Our data indirectly support the hypothesis that heightened startle reactions observed in PTSD subjects (Butler et al., 1990; Grillon et al., 1998; Morgan et al., 1997; Morgan et al., 1996; Orr et al., 1995; Shalev et al., 1992; Shalev et al., 1997) might be an acquired PTSD symptom (Shalev et al., 2000) that disappears after remission. On the other hand they are not in line with the results of earlier studies suggesting the heightened startle reaction to be a trait characteristic of subjects that develop PTSD (Guthrie & Bryant, 2005; Metzger et al., 1999). A possible explanation for this discrepancy might be that we investigated a different type of trauma. Only two subjects of the remitted PTSD group had received psychotherapy, which makes it unlikely that the missing difference between the remitted PTSD group and the non-trauma controls is a therapy effect. It neither seems that psychotropic drugs are accountable for our results, as the pattern of significant effects stayed the same with and without the two subjects taking psychotropic medication.

One possible explanation for the unexpected heightened startle eye-blink magnitude we found in trauma-controls is that the experience of trauma, even if not related to psychopathological symptoms, might elicit physiological changes. This means that psychological resilience could still be associated with physiological symptoms of PTSD. It is unclear, however, why the heightened eye-blink magnitude had not recovered in trauma controls, despite similar traumatic events as had been experienced by the remitted PTSD subjects. It could also be speculated that dealing with and recovering from psychological problems restores normal learning functions while in people who do not develop psychological problems in the first place dysfunctional learning might persist on the physiological level. On the other hand, though not significant, our data might also indicate instable learning in skin conductance responses in remitted PTSD patients.

Important limitations of this study are its small sample size and the rather broad confidence intervals we found for mean differences, raising questions regarding the reliability of our findings. We wish to emphasize that these preliminary results do not necessarily reflect a generalizable feature for the majority of remitted PTSD patients and resilient people. Another shortcoming is that we have no information about the subjects' startle reactivity before the accident or during the PTSD episode in the remitted PTSD group. Therefore, we cannot rule out the possibility that the startle reactivity of the trauma controls differed from the non-trauma controls already before the traumatic event or that our sample of remitted PTSD subjects did not show heightened startle reactions while they suffered PTSD symptoms. A group of current PTSD patients would have allowed a direct comparison with the

reactivity in symptomatic subjects but unfortunately it was not possible to recruit a comparable group from the previous studies. Furthermore, we investigated only participants that had experienced accidental physical injuries, while earlier research on trauma and startle was often performed on subjects with war-related traumatic experiences. As war and accidental injury are completely different sorts of potentially traumatic events it might well be that different processes underlie their startle reactivity. Due to these limitations these initial results in an underexplored area clearly need to be replicated. Ideally, a longitudinal design should be used to disentangle the exact time course of startle reactivity in trauma survivors over the time span of several years. It might also be informative to include a measure of subjective resilience into a longitudinal design to see how subjective attitudes change over time and if they are associated with physiological measures.

In conclusion, this study provides a first and preliminary indication of heightened startle in trauma survivors who had not developed PTSD. The fact that remitted PTSD subjects did not differ from non-trauma controls indirectly supports the idea of heightened startle reactions being a symptom of PTSD rather than a trait of individuals who develop PTSD. The difference between trauma survivors who had not developed PTSD and non-trauma controls indicates that trauma survivors might show a PTSD-like physiological pattern while they are psychologically resilient. One could hypothesize that trauma survivors who do not develop PTSD might be less involved in dealing with the traumatic experience, and that this in turn might lead to long lasting symptom-like physiological patterns. Long-term prospective studies are needed to find out more about the relationship of psychological and physiological symptoms after traumatic experiences.

5. Study 4 - Acoustic emotional processing in patients with borderline personality disorder: hyper- or hypoarousal?

In press in: Journal of Personality Disorders

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5.1 Abstract

Earlier studies demonstrated emotional overreactions to affective visual stimuli in borderline personality disorder (BPD) patients. However, contradictory findings regarding hyper- versus hyporeactivity have been reported for peripheral physiological measures. In order to extend previous results we investigated emotional reactivity and long-term habituation in the acoustic modality. Twenty-two female BPD patients and 19 female non-clinical controls listened to emotionally negative, neutral, and positive sounds in two identical sessions. Heart rate, skin conductance, zygomaticus/corrugator muscle, and self-reported valence/arousal responses were measured. BPD patients showed weaker skin conductance responses to negative sounds than controls. The elevated zygomaticus activity in response to positive sounds observed in controls was absent in BPD patients and BPD patients assigned lower valence ratings to positive sounds than controls. In session two, patients recognized fewer positive sounds than controls. Across both groups, physiological measures habituated between sessions. Our findings add to growing evidence towards partial affective hyporeactivity in BPD.

5.2 Introduction

Emotional instability is a core diagnostic feature of borderline personality disorder (BPD; American Psychiatric Association, 2013; World Health Organization (WHO), 1989). According to Linehan (1993), emotional instability in BPD is largely due to high sensitivity to emotional stimuli, high levels of emotional arousal, and a slow return to baseline. Within Linehan's theory, other characteristics of BPD, such as self-mutilation and suicidal behavior, are considered sequelae of the core feature of emotional instability (Shearin & Linehan, 1994).

Emotional instability in BPD is well documented. Measured by self-report questionnaires, BPD patients were found to show higher levels of affective intensity and lability in comparison to patients with other personality disorders (Henry et al., 2001; Koenigsberg et al., 2002). In a further study, BPD patients rated their states of aversive tension as significantly more intense and longer lasting in comparison to healthy controls (Stiglmayr et al., 2001). In a 24-hour ambulatory monitoring study BPD patients reported more negative and fewer positive emotions as well as higher intensity of negative emotions (Ebner-Priemer et al., 2007). As affective instability may also be seen as impulsivity, Herpertz et al. (Herpertz et al., 1997) investigated a group of patients with a variety of personality disorders characterized by impulsive behaviors, including BPD patients. They found that impulsive personality disorder types reported intense affective responses and frequent emotional alterations while listening to a short story alluding to borderline specific problems with interpersonal relations. Compared to healthy controls, their self-reported emotional reactions were more intense in response to both aversive and pleasant parts of the story but not qualitatively different (i.e., they experienced the same specific emotions). In addition, a study by Ebner-Priemer et al. (Ebner-Priemer et al., 2005) showed larger startle responses and slower startle habituation in BPD patients compared to healthy controls. Also, in functional magnetic resonance imaging studies, BPD patients showed stronger activation of the amygdala than healthy controls in response to facial expressions of emotions (Donegan et al., 2003), emotional pictures (Hazlett et al., 2012; Herpertz, Dietrich et al., 2001), and emotional distractors in working memory tasks (Krause-Utz et al., 2012; Prehn et al., 2013).

On the other hand, several studies failed to demonstrate stronger emotion-related physiological responses. Herpertz et al. (1999) found comparable startle responses and affective startle potentiation for BPD patients and healthy controls. Also, Vitale & Newman (2012) could not find heightened startle reactions to unpleasant pictures in BPD patients showing high compared to those showing low levels of BPD symptoms. Some studies even found emotional pictures to elicit lower skin conductance

responses (SCR) in BPD patients than in healthy controls (Herpertz et al., 1999; Herpertz, Schwenger et al., 2000).

An explanation for these partly contradictory findings is that emotional dysfunction in BPD may be limited to borderline specific stimuli (Suvak et al., 2012; Vitale & Newman, 2012). Another possibility is that hyporeactivity is associated with depressive mood in BPD patients. While many studies have shown hyporeactivity in depressed patients (Bylsma, Morris, & Rottenberg, 2008), studies that found hyperreactivity in BPD patients have often excluded patients with comorbid affective disorders (Hazlett et al., 2012; Herpertz, Dietrich et al., 2001; Krause-Utz et al., 2012; Prehn et al., 2013). At the same time, sensory modalities other than the visual domain have largely been neglected in experimental studies in BPD. In a questionnaire study by Rosenthal, Ahn, & Geiger (2011) assessing emotional reactivity across several sensory modalities, BPD patients reported to be more reactive than healthy controls across all assessed domains, with the group difference being most pronounced in the acoustic domain. To our knowledge, psychophysiological responses to acoustic stimuli other than startle have not yet been tested in BPD.

The main aim of the present study was to test whether BPD patients show a different intensity in responses than controls to emotionally evocative, acoustic stimuli in self-reported and psychophysiological measures. We investigated two physiological systems: autonomic responses, measured by heart rate (HR) and skin conductance (SC), as well as facial expressions, measured by musculus zygomaticus major and musculus corrugator supercilii responses. Facial expressions are particularly important for effective social interaction, a context where BPD patients exhibit emotional difficulties (American Psychiatric Association, 2013). BPD patients and non-clinical controls listened to negative, neutral and positive emotional sounds during two sessions that were one week apart. The procedure was adapted from a previous study with healthy participants using the same acoustic stimuli (Martin-Soelch, Stocklin, Dammann, Opwis, & Seifritz, 2006). In addition to altered emotional responding to the different sound categories, we aimed at assessing if (and to what degree) BPD patients' ratings and physiological responses habituate between sessions or if they may even show sensitization. According to Linehan (1993), short-term habituation to emotional stimuli is deficient in BPD patients, but to our knowledge, long-term habituation has not yet been investigated in these patients. Long-term habituation may be particularly important, though, as emotional hyperreactivity might result from deficient habituation to reoccurring emotional situations in daily life.

Analogous to the finding that BPD patients' subjective emotional experiences are not qualitatively different from those of healthy controls (Herpertz et al., 1997), we hypothesize that BPD patients overall show the same pattern of affective modulation of psychophysiological reactions as non-clinical controls. Expected patterns include HR deceleration in response to unpleasant sounds, stronger SCR to emotional (i.e., both negative and positive) than neutral sounds, increased zygomaticus responses to pleasant sounds, and increased corrugator responses to unpleasant sounds. These are typical patterns of peripheral reactions to emotional stimuli (visual as well as acoustic) that have been described in several studies (Bradley et al., 1990; Bradley & Lang, 2000; Cacioppo et al., 1986; Dimberg, 1982; Greenwald et al., 1989; Lang et al., 1990; Martin-Soelch et al., 2006; Verona, Patrick, Curtin, Bradley, & Lang, 2004). Yet, based on the contradictory findings in earlier studies, we expect that psychophysiological as well as self-reported reactions to both negative and positive emotional sound stimuli are either more pronounced or weaker in BPD patients than in controls. Based on Linehan's assumption that emotional reactions in BPD patients are long lasting (Linehan, 1993), between-session habituation of the above described responses is expected to be weaker in BPD patients than in controls. As memory is facilitated for emotional content (D'Argembeau & Van der Linden, 2004) the expected physiological difference in emotional reactivity between BPD patients and controls should also be reflected in recognition of sound stimuli in the second session (i.e. the group with higher emotional reactivity is expected to show better recognition for emotional sounds). Additionally, we would expect emotional reactivity to be negatively associated with depressive symptoms.

5.3. Methods

5.3.1. Participants

Twenty-two female inpatients with BPD and a comparison group of 19 female non-clinical controls participated in this study. Sample characteristics are described in Table 4. The BPD sample was recruited from patients attending an inpatient disorder-specific treatment program. As inpatient populations of BPD tend to be mostly female, we included only female subjects. Exclusion criteria were neurological diseases, paranoid schizophrenia, schizo-affective psychosis and bipolar I disorders. Thirteen BPD patients were diagnosed with comorbid affective disorders, 13 showed substance abuse or dependence, 5 had eating disorders, 5 had comorbid personality disorders other than BPD, one had a somatoform disorder, one had a post-traumatic stress disorder, one a

depersonalization/derealization syndrome and two had other disorders. Twenty BPD patients were taking antidepressant medication (SSRI and/or SSNRI), 9 were taking neuroleptics, 6 were taking anti-epileptics, 4 were taking sedatives, 2 were taking hypnotics, and 3 took medication against alcohol dependence. Non-clinical controls were university students participating for course credit. Fifteen participants of the BPD group and 18 controls completed a second session one week after the first. One BPD patient was excluded from SC analyses due to insufficient data quality. The study was explained to participants and written informed consent was obtained prior to participation. The study was approved by the local ethics committee for medical research in accordance with the declaration of Helsinki.

Table 4. Sample description.

	Controls		BPD			
	M	SD	M	SD	t	p
Age (in years)	31.42	9.55	26.73	6.94	1.82	0.07
BDI scores (0-63)	5.58	6.54	27.44	12.37	-7.20	<0.001
STAI trait scores (20-80)	35.37	10.98	59.65	10.58	-7.03	<0.001
STAI state scores (20-80) session 1	30.84	6.14	54.57	11.78	-8.24	<0.001
STAI state scores (20-80) session 2	32.28	8.88	54.73	13.65	-5.69	<0.001

Note. BDI = Beck Depression Inventory score, STAI = State-Trait Anxiety Inventory, BPD = borderline personality disorder.

5.3.2. Psychometrics

Patients were diagnosed with BPD according to DSM-IV (American Psychiatric Association, 1994) by means of the German version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID II; Wittchen, Zaudig, & Fydrich, 1997). Comorbidity was assessed by the German version of the SCID I. Symptoms of depression and anxiety were measured by the German version (Hautzinger et al., 1995) of the Beck Depression Inventory (BDI; Beck et al., 1961) and the German version of the State-Trait Anxiety Inventory (STAI; Laux et al., 1981).

5.3.3. Physiological Measures

Physiological data were recorded using a BIOPAC MP150 system (Biopac Systems, Inc, Goleta, CA). SC was recorded from Ag/AgCl electrodes filled with isotonic electrolyte gel and placed on the volar surfaces of the medial index and middle fingers. Except for one BPD patient whose left hand was

injured, SC was measured from the non-dominant hand. Electrocardiograms (ECG) were recorded from the manubrium sterni, the processus xiphoideus, and the left costal arch, using Ag/AgCl electrodes filled with hydrogel jelly. Electromyographic (EMG) facial activity was recorded over the left corrugator and zygomaticus muscle regions as recommended by Fridlund and Cacioppo (1986), using Ag/AgCl miniature electrodes filled with electrolyte gel. Physiological data were sampled at 1000Hz throughout the whole experiment.

5.3.4. Procedure

Participants were assessed individually in a temperature-controlled room. They were seated in a comfortable chair placed in front of a computer screen. After completing informed consent and psychometric questionnaires, physiological sensors were attached and the light was dimmed. Participants were then asked to rest quietly for 5 minutes to facilitate laboratory adaptation. After three test trials, comprising one unpleasant, one neutral, and one pleasant sound, 45 sounds from the International Affective Digitized Sounds (IADS; (Bradley & Lang, 2000) were presented for 6 s each in a randomized order. Fifteen sounds were neutral (e.g. footsteps), 15 were positive (e.g. music), and 15 were negative (e.g. a crying baby)[5]. Sound stimuli were presented via E-Prime (Psychology Software Tools Inc., Pittsburgh, PA., USA) and subjects listened to them via stereophonic headphones (Pioneer SE 205). A similar procedure with the same stimuli was used in a previous study, which demonstrated that this design reliably provokes self-report as well as physiological responses (Martin-Soelch et al., 2006).

Each trial consisted of a six-second sound during which a white screen was displayed and participants were instructed to simply focus on the sound. Each stimulus was followed by a 2.5 second break during which participants focused on the white display. Thereafter, participants were instructed to rate the valence and arousal each sound elicited on a Likert-type rating scale from 1 (negative valence/low arousal) to 9 (positive valence/high arousal) on screen. During the second session participants were additionally asked after each sound if they remembered it from the first session. Participants were instructed to answer as fast as possible although time was not limited. Ratings were followed by a variable inter-stimulus interval of 14 to 22 seconds. During this interval a white screen was presented and participants were instructed to relax until they heard the next sound.

[5] IADS numbers for the sounds were 100, 251, 310, 319, 322, 325, 358, 410, 425, 602, 701, 708, 710, 720, 722 (neutral), 111, 151, 206, 220, 221, 226, 352, 601, 721, 802, 810, 811, 815, 816, 820 (positive), 106, 116, 261, 277, 278, 279, 286, 287, 424, 502, 600, 625, 627, 709, 712 (negative).

5.3.5. Data reduction

Autonomic Nervous System Laboratory 2.51 (ANSLAB; Wilhelm, F. H. & Peyk, P., 2005; available at the SPR Software Repository: http://www.sprweb.org) was used to filter the raw data, to correct for artefacts, and to extract mean and maximum scores for event and baseline windows. The ECG signal was band-pass filtered (0.5 – 40 Hz), R waves detected, and HR was extracted using instantaneous heart rate sampled at 4 Hz. SC level was low-pass filtered (1 Hz). EMG signals were 50 Hz notch filtered, 28 Hz high pass filtered, and the rectified signal was smoothed using a moving average width of 50 ms. Heart rate responses (HRR) and EMG responses were calculated by subtracting the mean value during the 2 s baseline interval prior to the onset of the stimulus from the mean value during the 6 s sound presentation. For SCR the mean value during the 2 s baseline interval was subtracted from the maximum value during the 6 s sound presentation.

5.3.6. Data analysis

Statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). We used linear mixed models to compare the different emotional conditions. For each measure (HRR, SCR, zygomaticus response, corrugator response, valence rating, and arousal rating) a model was calculated with group (BPD and controls), sound valence (neutral, positive, and negative), and session (1 and 2) treated as fixed effects. For valence and arousal ratings a second model was calculated only including the data from the second session with group, sound valence, and recognition (yes or no) treated as fixed effects. For all models, subject was treated as a random effect. All models were optimized by the covariance type for the repeated observations which produced the lowest Akaike's Information Criterion (AIC). If AICs were less than 3 points apart, the model which produced the lowest Schwartz's Bayesian Criterion (BIC) was chosen. A first-order ante-dependent structure was fitted for physiological responses and a scaled identity structure for ratings. Bonferroni corrected pairwise comparisons based on the estimated marginal means were used as post-hoc tests. For psychometric measures and recognition performance, unpaired and paired t-tests were used to compare groups and sessions. To test whether depressive mood influenced emotional reactivity, Pearson correlations were used to examine the association between BDI scores and mean physiological and rating responses for each sound valence category across groups and sessions.

5.4 Results

5.4.1. Psychometric measures

Means, standard deviations, and group comparison statistics are shown in Table 4. BPD patients showed higher BDI scores than controls. Also STAI trait and STAI state scores were higher for BPD patients than for controls. STAI state scores did not differ between sessions (p = 0.8). SCR was negatively correlated with BDI scores across groups and sessions. All other measures (physiological and self-report) were unrelated to BDI scores (see Table 5).

Table 5.

Correlations of BDI scores with physiological and self-report measures across groups and sessions.

Sound valence	Negative		Neutral		Positive	
	r	p	r	p	r	p
BDI - SCR	-0.39	0.01	-0.34	0.03	-0.35	0.03
BDI - HRR	0.03	0.84	0.03	0.87	-0.19	0.24
BDI - zygomaticus response	-0.19	0.24	-0.18	0.25	-0.26	0.10
BDI - corrugator response	0.00	0.98	0.09	0.56	0.25	0.11
BDI - valence rating	-0.10	0.54	-0.13	0.41	-0.28	0.07
BDI - arousal rating	0.11	0.50	0.28	0.08	0.08	0.61

Note. BDI = Beck Depression Inventory score, SCR = skin conductance response, HRR = heart rate response.

5.4.2. Physiological measures

Estimated marginal means, standard errors, and pairwise comparisons for physiological effects are shown in Figures 11 (habituation) and 12 (valence modulation). There were main effects of group ($F(1, 35) = 4.36$, $p = 0.044$), sound valence ($F(2, 1227) = 38.60$, $p < 0.001$) and session ($F(1, 524) = 18.17$, $p < 0.001$) as well as interactions of group x sound valence ($F(2, 1227) = 4.93$, $p = 0.007$) and session x sound valence ($F(2, 1218) = 3.42$, $p = 0.033$) in SCR. Across sessions and sound valences, controls showed higher SCR (M = 0.12 µS, SE = 0.02 µS) than BPD patients (M = 0.05 µS, SE = 0.02 µS). Across groups and sessions, the lowest SCRs were elicited by neutral sounds (M = 0.04 µS, SE = 0.02 µS), followed by positive (M = 0.08 µS, SE = 0.02 µS), and negative sounds (M = 0.13 µS, SE = 0.02 µS; all p values ≤ 0.001). Across groups and sound valences, SCRs during the first session (M = 0.11 µS, SE = 0.02 µS) were higher than during the second session (M = 0.06 µS, SE = 0.02 µS). Decomposing the group x sound valence interaction showed that negative sounds elicited higher

SCR in controls than in BPD patients (p = 0.006) while positive sounds just missed significance in the group difference (p = 0.054). Decomposition of the session x sound valence interaction revealed that neutral sounds did not differ between sessions (p = 0.3), while responses to positive and negative sounds were smaller during the second session (p values < 0.003). HRR showed a main effect of session (F(1, 909) = 4.45, p = 0.035), with stronger HR deceleration during the first (M = -0.65 bpm, SE = 0.18 bpm) than during the second session (M = -0.35 bpm, SE = 0.19 bpm). No other main effects or interactions were found for HRR (p values > 0.1).

For zygomaticus responses there were main effects of sound valence (F(2, 1145) = 11.14, p < 0.001) and session (F(1, 754) = 4.71, p = 0.030) as well as a group x sound valence interaction (F(2, 1145) = 5.58, p = 0.004). Across groups and sessions, positive sounds elicited higher zygomaticus responses (M = 0.87 μV, SE = 0.48 μV) than negative (M = 0.70 μV, SE = 0.48 μV; p = 0.007) and neutral sounds (M = 0.61 μV, SE = 0.48 μV; p < 0.001). Across groups and valences, zygomaticus responses were higher during the first session (M = 0.78 μV, SE = 0.48 μV) than during the second session (M = 0.67 μV, SE = 0.48 μV). However, decomposition of the group x sound valence interaction revealed that only controls showed heightened zygomaticus responses to positive sounds (p values < 0.001) while BPD patients did not distinguish between valences in this measure (p values > 0.6). The main effect of group was not significant for zygomaticus responses (p = 0.2) and no interaction with session was found either (p values > 0.1). Corrugator responses showed main effects of sound valence (F(2, 1501) = 62.32, p < 0.001) and session (F(1, 753) = 4.13, p = 0.042). Negative sounds elicited the strongest corrugator responses (M = 0.63 μV, SE = 0.13 μV) followed by neutral (M = 0.32 μV, SE = 0.13 μV) and positive sounds (M = -0.07 μV, SE = 0.13 μV; p values < 0.001). Corrugator responses were stronger during the first session (M = 0.35 μV, SE = 0.12 μV) than during the second (M = 0.24 μV, SE = 0.13 μV). No main effect of group (p = 0.5) and no interactions were found in this measure (p values > 0.1).

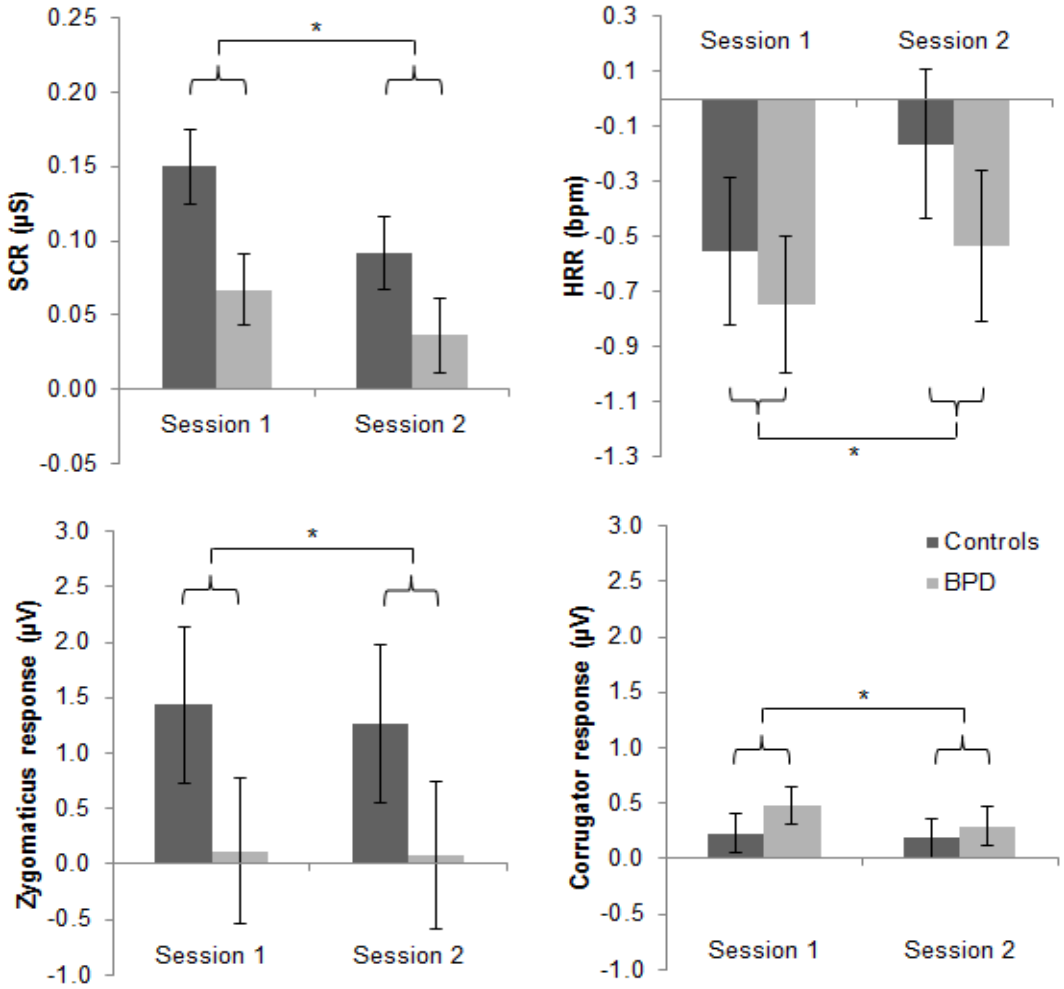

Figure 11. Estimated marginal means +/- 1 standard error for between-session habituation effects across groups for skin conductance response (SCR, top left) in microsiemens (µS), heart rate response (HRR, top right) in beats per minute (bpm), zygomaticus response (bottom left) and corrugator response (bottom right) in microvolt (µV); * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder.

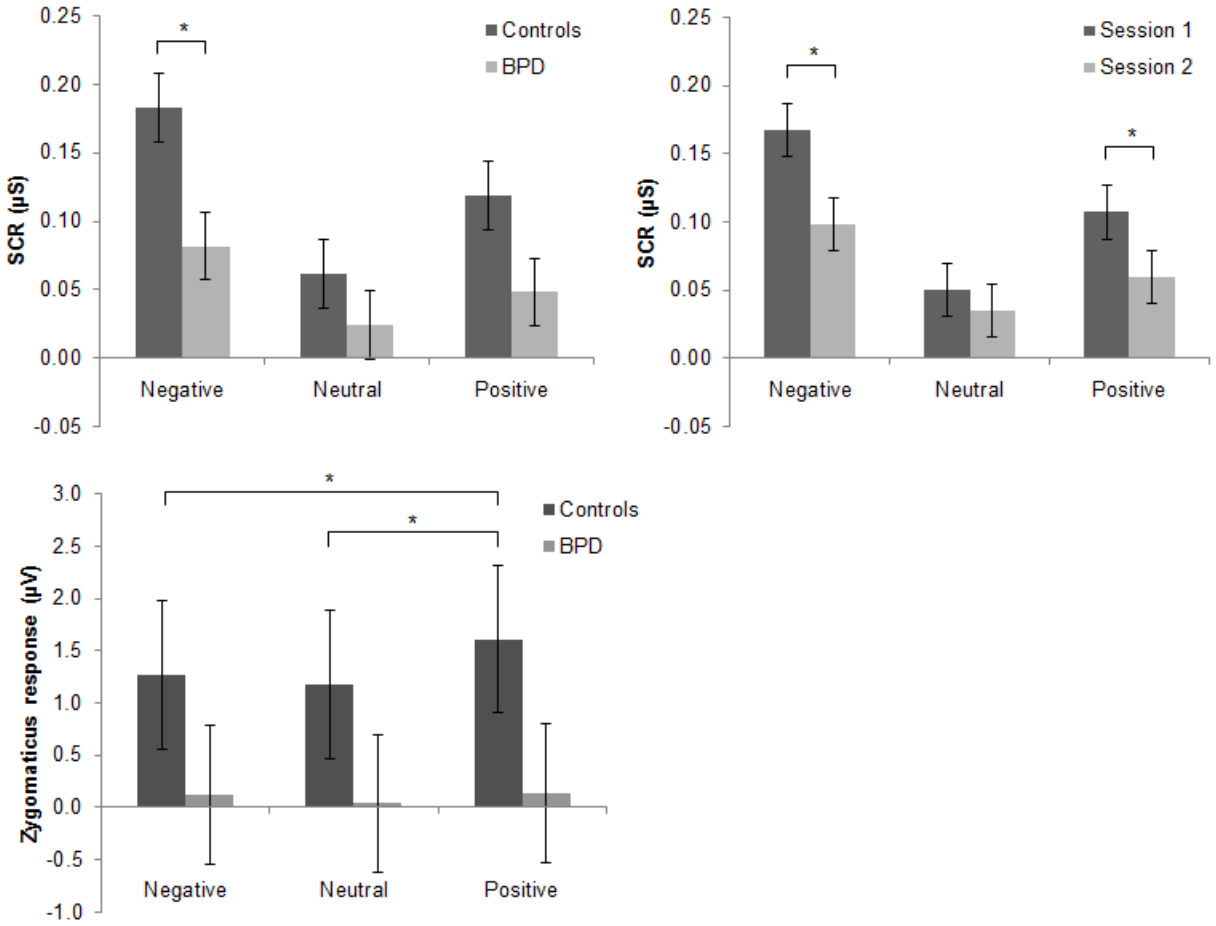

Figure 12. Estimated marginal means +/- 1 standard error for sound valence modulated effects. SCR = skin conductance response; * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder, µS = microsiemens, µV = microvolt.

5.4.3. Ratings

Estimated marginal means, standard errors, and pairwise comparisons for group effects in valence and arousal ratings are shown in Figure 13. Valence ratings showed a main effect of sound valence ($F(2, 3275) = 1095.37$, $p < 0.001$) as well as a group x sound valence interaction ($F(2, 3275) = 9.31$, $p < 0.001$). Across groups, negative sounds were given the lowest valence ratings ($M = 2.5$, $SE = 0.09$) followed by neutral ($M = 4.4$, $SE = 0.09$) and positive sounds ($M = 6.0$, $SE = 0.09$; p values < 0.001). Decomposing the interaction revealed that controls rated positive sounds more positively than BPD patients ($p = 0.019$). There were no main effect or interactions involving session in valence ratings (p values > 0.1).

For arousal ratings there were main effects of sound valence ($F(2, 3272) = 264.77$, $p < 0.001$) and session ($F(1, 3311) = 14.43$, $p < 0.001$) as well as a group x sound valence interaction ($F(2, 3272) = 5.86$, $p = 0.003$). The interaction of session x sound valence just missed significance ($F(2, 3272) =$

2.97, p = 0.052). Across groups and sessions, neutral sounds were given the lowest arousal ratings (M = 3.9, SE = 0.14) followed by positive (M = 4.2, SE = 0.14) and negative sounds (M = 5.8, SE = 0.14; p values < 0.001). Across groups and sound valences, arousal ratings were lower during the first session (M = 4.5, SE = 0.13) than during the second session (M = 4.8, SE = 0.14). Decomposition of the group x sound valence interaction showed that in contrast to controls, BPD patients did not distinguish between arousal ratings for neutral and positive sounds (p = 0.5). The tendency for BPD patients to assign higher arousal ratings to neutral sounds than controls just missed significance (p = 0.052).

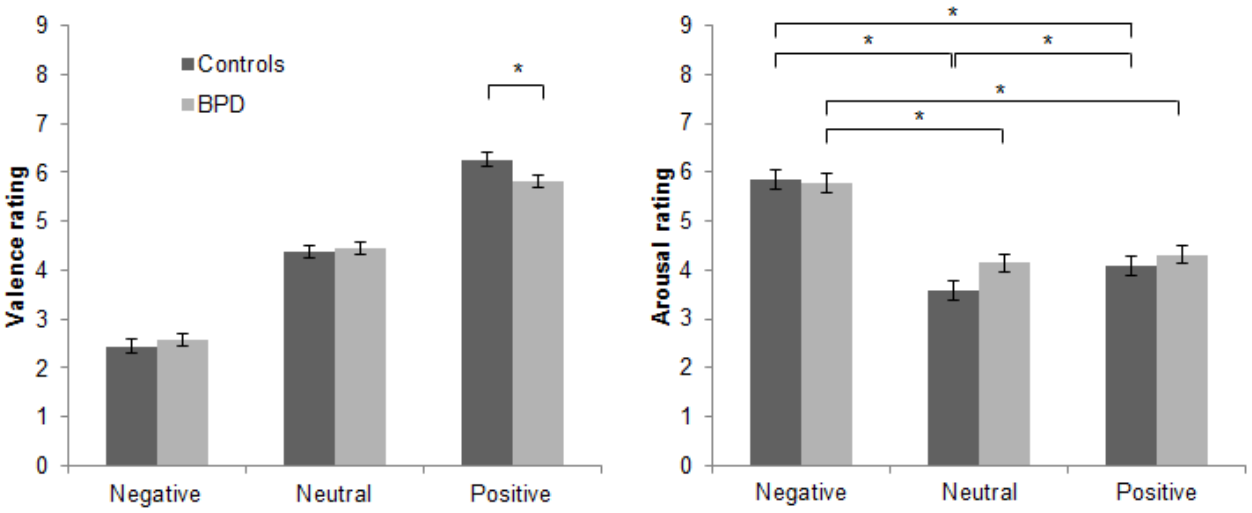

Figure 13. Estimated marginal means +/- 1 standard error for rating effects. * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder.

5.4.4. Sound recognition

Percentages of recognized items per valence category and group comparisons are shown in Figure 14. BPD patients recognized fewer positive sounds than controls (p = 0.021). When sound recognition was entered as an additional factor into the statistical model for the second session, the only significant effect for valence ratings involving the factor recognition was an interaction of sound valence x recognition (F(2, 1451) = 6.63, p = 0.001). Recognized positive sounds were rated more positively (M = 6.2, SE = 0.1) than positive sounds which were not recognized (M = 5.5, SE = 0.2; p < 0.001). No recognition effects were found for arousal ratings.

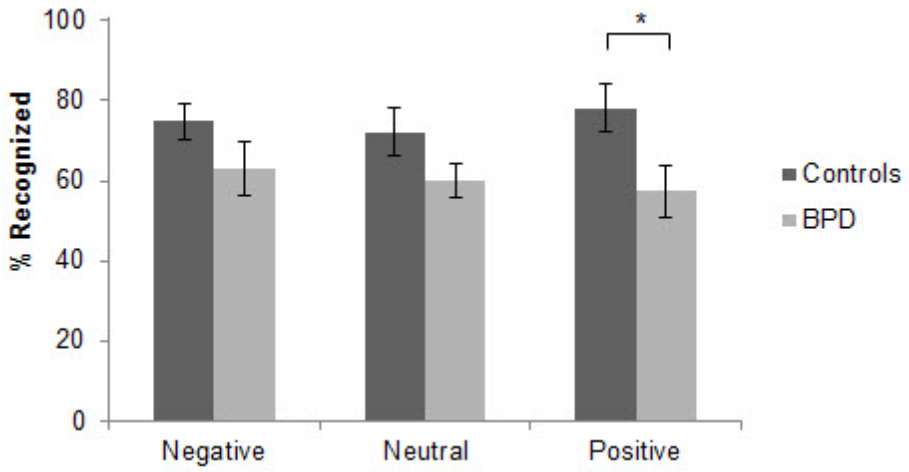

Figure 14. Means +/- 1 standard error for % recognized sounds. * significant t-test (p = 0.021); BPD = borderline personality disorder.

5.5 Discussion

The main aim of this study was to investigate whether BPD patients show stronger or weaker reactions to emotional acoustic stimuli than non-clinical controls. In consideration of contradictory results in earlier studies, this extension to the acoustic modality was expected to provide further insight into the existence of affective hyper- versus hyporeactivity in BPD. An affect-related acoustic hypersensitivity would not only be of theoretical but also of clinical relevance, given that this might contribute to the frequent, highly aversive emotional states and corresponding physiological hyperarousal which BPD patients seem to experience in daily life (Ebner-Priemer et al., 2008) and which may contribute to self-harming behaviors (Linehan, 1993). Weaker responses on the other hand might be associated with depressive mood which has been associated with hyporeactivity (Bylsma et al., 2008) and is common in BPD patients. In addition to the intensity of responses, we were interested in whether BPD patients show alterations in long-term habituation patterns compared to controls, because deficient habituation to repeated emotional stimuli might partly explain the hyperreactivity to emotional stimuli in BPD patients postulated by Linehan (1993). We measured HR, SC, zygomaticus and corrugator responses as well as valence, arousal and recognition ratings of the sounds.

Our results indicate partial hyporeactivity to affective acoustic stimuli in autonomic as well as facial-muscular measures. For negative sounds we found lower SCR in BPD patients than in controls. Moreover, while controls showed heightened zygomaticus responses to positive sounds compared to negative and neutral sounds, as would be expected, BPD patients did not show this differentiation. In addition, BPD patients assigned lower valence to positive sounds than controls. They also recognized

fewer positive sounds than controls in the second session. Our finding of reduced SCR to negative sounds in BPD patients is in line with the findings of Herpertz and colleagues (Herpertz et al., 1999; Herpertz, Schwenger et al., 2000) demonstrating weaker SCRs to visual, non-borderline specific emotional stimuli in borderline patients. Our data thus extend this finding of hyporeactivity to non-borderline specific stimuli to the acoustic domain.

BPD patients typically have a history of cumulative traumatic experiences (Fiedler, 2001; Guzder, Paris, Zelkowitz, & Marchessault, 1996; Holm & Severinsson, 2008; Zanarini et al., 1997). According to Herpertz, Kunert et al. (2000), these cumulative stressors might initiate a down-regulation of BPD patients' autonomic responsiveness to protect patients from an overflow of sensations. Consistent with this theory, a study by Dixon-Gordon, Gratz & Tull (2013) showed that heightened physiological reactivity in BPD patients was only present in individuals with low levels of PTSD symptoms. Also, a study by D'Andrea, Pole, DePierro, Freed, & Wallace (2013) showed that in trauma-exposed college students moderate trauma exposure was associated with heightened autonomic responding, while extreme trauma exposure was associated with blunted reactivity. Though we do not have systematic information about traumatic experiences and related symptoms in our BPD sample, descriptively these patients often reported traumatic childhood experiences during therapy. This might at least partially explain the lower affective SCRs we found compared to non-clinical controls.

Herpertz, Werth et al. (Herpertz, Werth et al., 2001) measured corrugator but not zygomaticus EMG responses to visual, emotional stimuli and found reduced affective modulation of corrugator activity in male criminal offenders with BPD. While we were unable to replicate this finding for corrugator responses to acoustic emotional stimuli, our finding of reduced zygomaticus EMG responses is in line with a reduced modulation of facial expressions in BPD. Also, in a study by Renneberg, Heyn, Gebhard, & Bachmann (2005) a sample of BPD patients more comparable to ours, showed reduced facial expressions to emotional films. On the other hand, our results contradict earlier studies indicating generally stronger responses to emotional stimuli in BPD. More specifically, they contradict the findings of a questionnaire study by Rosenthal et al. (2011) that indicate that BPD patients may be particularly overreactive to auditory stimuli. Our experiment directly addressed this issue by presenting auditory stimuli and did not substantiate these questionnaire data. This may be due to memory biases or the fact that questionnaires often better relate to attitudes rather than to directly measured responses. Our results are furthermore in contrast to the results of Herpertz et al. (1997) who found more intense self-reported emotional reactions to both pleasant and aversive situations in an affect-

inducing short story. This discrepancy might be explained by the suggestion that patients only react more intensely to borderline specific stimuli that were used in the Herpertz et al. (1997) study but not in ours.

An interesting finding of the present study is that hyporeactivity effects in the BPD group seem to predominantly appear in response to positive sounds, expressed by zygomaticus responses, valence ratings, and memory. Lower recognition of positive sounds in the second session by BPD patients compared to controls might be explained by the lower valence patients assigned to these sounds during the first session. As memory is enhanced for emotional content (D'Argembeau & Van der Linden, 2004), less emotionality could explain the lower recognition rate.

Interestingly, in contrast to this finding in declarative memory, the more basic implicit memory processes involved in long-term habituation (Rankin et al., 2009) seem unaffected in our BPD patients. Our results do not show different between-session habituation patterns for BPD patients compared to controls. The habituation pattern we found across groups is in line with that reported for healthy subjects by Martin-Soelch et al. (2006) who found between-session habituation in SC and zygomaticus responses. In our study, SCR as well as zygomaticus and corrugator responses habituated from the first to the second session across both groups. In contrast to Martin-Soelch et al. (2006) who found no between-session change in heart rate responses, in our study HR showed less deceleration during the second session across both groups.

The depressive mood which BPD patients often experience (Gunderson et al., 2004; Koenigsberg et al., 1999; Zanarini et al., 1998) was confirmed by higher BDI scores compared to controls, which may relate to the hyporeactivity in the BPD group. However, our data support this explanation only for SCR as all other measures were not correlated with BDI scores. Therefore, BDI scores do not explain why BPD patients assigned less positive valence ratings and showed hyporeactivity in zygomaticus responses to positive sounds compared to controls. Still, the lower SCR in BPD patients to negative sounds might be explained by depressive mood. Therefore, future studies should further evaluate the influence of comorbid affective disorders, which are common in BPD.

Limitations of this study are the relatively small sample size and that we only investigated women. Furthermore, all our patients were using psychotropic medication. As unmedicated BPD patients are rare and may represent a healthier subgroup (Ebner-Priemer et al., 2007), investigating medicated BPD patients allows for a more clinically representative sample. On the other hand, medication may affect patients' physiological reactions. Selective serotonin reuptake inhibitors (SSRIs) for example

were found to reduce general baseline levels of SC and HR in healthy volunteers (Siepmann, Grossmann, Muck-Weymann, & Kirch, 2003), but we are not aware of any documented picture or sound reactivity effects of such medications. In addition, Herpertz, Schwenger et al. (2000) assessed only unmedicated BPD patients and also found reduced psychophysiological reactivity, suggesting that our results are not simply attributable to effects of psychotropic medication.

In conclusion, the findings of this study contribute to growing evidence towards partial hyporeactivity to affective stimuli in BPD in psychophysiological measures, reflected in the autonomic nervous system as well as facial expression. Our findings support earlier studies (Elices et al., 2012; Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2010) suggesting that hyperreactivity might be specific to self-reported responses to borderline related stressors. In addition, the current study provides first evidence towards normal physiological long-term habituation to affective stimuli in BPD. These findings put the theory of Linehan (1993) for explaining emotional instability in BPD into perspective and thus make an important contribution to a better understanding of the symptoms observed in BPD, which in turn could yield new behavioral intervention approaches by discerning general affective vs. borderline-relevant stimuli.

6. General discussion

6.1. Studies results

This thesis reported four studies looking at different aspects of psychophysiological responses in the context of emotions and stress with the aim to improve the understanding of the interplay of psychological processing and somatic reactions. In Study 1 we investigated physiological responses of healthy subjects to the anticipation and perception of emotional pictures. Our results showed that valence specific physiological as well as self-reported responses to emotional stimuli already take place in an anticipation period. These results demonstrate that emotional responses during anticipation can be directly measured at the peripheral physiological level. Our results are also in line with the hypothesis of a negative bias in uncertain situations. However, further studies are needed to better differentiate between a negative and a neutral attitude towards ambiguous conditions.

In Study 2 we investigated how nasally administered OXT modulates the startle response during the perception of emotional pictures. Results showed that OXT can have differential effects on emotional processing depending on trait anxiety. For subjects with low trait anxiety OXT reduced the startle eye-blink while for subjects with high trait anxiety OXT increased the eye-blink response during picture modulation. As our results emphasize complex interactions of OXT with subject features, they are not conclusive with regard to the therapeutic potential of OXT. Also, high trait anxiety within a normal range might not be comparable to that of subjects with anxiety disorders. But our results indicate that the effect of administered OXT is probably very specific and not generally stress reducing. We did not find differential physiological effects of social versus non-social stimulus content. But subjects with lower trait anxiety under OXT assigned more positive valence ratings to neutral pictures with social versus non-social content while subjects with higher trait anxiety under OXT assigned less positive valence ratings for neutral pictures with non-social versus social content.

In Study 3, we compared the startle response to loud tones in traumatized subjects with and without a history of PTSD as well as non-traumatized subjects. Results showed that traumatized subjects who had never developed PTSD showed higher startle responses to loud tones than non-trauma controls. This may indicate that traumatic experiences per se can lead to long lasting alterations of the startle response even in subjects who never develop PTSD. But as we had no information about startle reactivity of our subjects before trauma or during acute PTSD, long-term studies are clearly needed to support this conclusion.

In Study 4 we compared physiological responses to emotional sounds in BPD patients and non-clinical controls. We found lower skin conductance responses to negative sounds in BPD patients than in controls. In addition borderline patients rated positive stimuli less positive and they recognized fewer positive items than controls. This speaks against a general overreactivity in these patients as it is postulated by Linehan's theory (Linehan, 1993). Further studies are needed to find out more about the specific features of conditions which cause hyper- or hyporeactivity.

6.2. Interpretation

The results of study 1 emphasize the importance of cognitions in emotional processes as postulated by cognitive theories of emotion and stress (Gross, 2014; Lazarus & Folkman, 1984; Schachter & Singer, 1962; Scherer, 2001). The fact that emotional responses can be measured directly in peripheral physiology already during anticipation demonstrates that mere cognitions are able to activate physiological emotional processes. In addition, our results are in line with a negative bias in uncertain situations. Therefore, these measures might also be sensitive to the investigation of cognitive biases in patient groups.

Study 2 demonstrates the impact of individual characteristics on physiological emotional responding. We found that trait anxiety might determine the influence of OXT on the emotional modulation of the startle reflex. This indicates that inter-individual differences might, at least in part, account for contradictory findings of earlier studies on OXT effects. Our results indicate that anxiety reducing effects of OXT might be specific to certain personality characteristics and specific social-affective conditions. Therefore, possible therapeutic applications require a better understanding of the complex interactions of hormones with other factors. As differential effects for social versus non-social stimuli were only found for ratings, pictures might be too weak to induce physiological responses specific to social context. This factor could be further addressed by using stronger stimuli like, for example, videos of social interactions versus non-social content.

In study 3 we found no evidence for heightened physiological reactivity to be a trait characteristic of people at risk for the development of PTSD. At the contrary, we found higher startle responses in individuals who were able to maintain psychological health in the face of extreme stress. Therefore, our findings do not support the notion of heightened reactivity as a symptom of PTSD either. It seems that in some cases psychological health and physiological symptoms might diverge. Successful emotion regulation has been shown to lower health risks (Kubzansky et al., 2011). But Gross (2013)

also mentions that emotion regulation is prone to failure. It might be interesting to investigate whether such failure could lead to an uncoupling of psychological and physiological phenomena. The phenomenon that self-report and psychophysiological measures of emotion can disagree is known as discordance (Wilhelm & Roth, 2001). Therefore, the subjective experience of an emotion and physiological responses can diverge. Maybe in some cases psychological health can be maintained at the cost of physiological symptoms in this way.

In study 4 we found further evidence for partial hypoarousal in BPD. Our finding extends physiological hypoarousal phenomena in BPD patients to acoustic stimuli. The lower skin conductance we found might be associated with depressive symptoms, which again emphasizes the importance of individual differences within a disorder. Therefore, the discussion around hyper- versus hypoarousal might be resolved by investigating patient subgroups.

A possible confounding factor in all four studies, which we have not yet looked at, might be dissociation. A study by Oathes & Ray (2008) investigated valence ratings of high and low dissociaters and showed that high dissociaters were more sensitive to emotional stimuli. They concluded that their results support the theory that more sensitive subjects tend to dissociate to protect themselves from overwhelming emotions. As dissociation is closely related to BPD as well as PTSD it might have played a role in studies 3 and 4. Ebner-Primer et al. (2005) showed that dissociation can reduce startle responses in BPD patients and Lanius et al. (2010) present data supporting a dissociative subtype of PTSD. Should a tendency to dissociate be a risk factor for PTSD, it might be that remitted PTSD subjects like in our study 3 tend to dissociate more than traumatized subjects who never developed PTSD when confronted with stress inducing material. Moreover, as dissociation is not only a pathological phenomenon but also exists in milder forms in healthy people, it could also influence emotional processing in healthy subjects like in our studies 1 and 2. As study 2 points to the importance of trait characteristics, future studies of emotional processing in healthy subjects should also take dissociation into account.

6.3. Outlook

Future research will hopefully further improve the understanding of the mechanisms behind emotional processing and yield interventions to help patients who suffer from too high or too low emotional reactivity. Some studies have already investigated the therapeutic potential of hormones like cortisol and oxytocin in psychiatric disorders. As PTSD is regarded as an inability to learn that the

traumatic stressor is no longer present (Milad et al., 2008) and cortisol is associated with learning (Roozendaal, 2002) and was found to be lowered in PTSD patients (Meewisse et al., 2007; Yehuda et al., 1990), cortisol has been investigated as a therapeutic agent in the treatment of PTSD (de Quervain & Margraf, 2008). Interestingly, there have also been attempts with OXT to treat PTSD (Pitman et al., 1993). As OXT reduces HPA axis reactivity and therefore the release of cortisol (Cardoso et al., 2013), this further points to the complexity of physiological processes in response to stress. Maybe even a combination of cortisol and OXT might be most effective in treating PTSD and other stress-related disorders. Further studies are needed to more precisely investigate the interplay of these two hormones and other factors that influence their effects. Long-term studies investigating the time course of startle reactivity as well as cortisol and OXT concentrations after traumatic events and during the development of and remission from PTSD might help to develop hormonal treatment approaches for trauma-related disorders. As BPD patients seem to have problems with social cognition (Roepke, Vater, Preissler, Heekeren, & Dziobek, 2012) and OXT enhances the retention of social cognition (Hollander et al., 2007) OXT might also have potential in the treatment of BPD. In the summary of a symposium on effects of OXT on mental health Olff et al. (2013) also draw the conclusion that contextual as well as individual factors need to be taken into account.

Habituation, as investigated in Studies 3 and 4, might also be a target for therapeutic interventions for emotional overreactions. Studies have shown that BPD patients show slower short-term habituation to emotional stimuli than healthy subjects (Koenigsberg et al., 2014). Our results in study 4, on the other hand, suggest normal long-term habituation in these patients. Future studies should take a closer look at habituation patterns in emotionally overreactive patients in order to investigate whether interventions could be able to train normal short-term habituation to novel stimuli. In PTSD, habituation trainings have already been investigated in the context of self-reports (Vaughan & Tarrier, 1992). The influence of similar procedures on physiological responses could be tested.

6.4. Concluding remarks

As a general conclusion it can be said that psychophysiological responses can be influenced by visual and acoustic emotional or stress inducing stimuli as well as the mere anticipation of emotional pictures. In addition, the responses to these stimuli can be modulated by the content of additional stimuli as well as subjects' individual characteristics. Therefore, to better understand these responses and their alterations in mental disorders studies need to take situational and personal characteristics

into account. Study 1 demonstrates that anticipatory emotional responses can directly be measured in peripheral physiological parameters. But a possible negativity bias of healthy subjects in uncertain situations still needs to be better distinguished from a neutral attitude in these measures. Study 2 indicates the importance of trait anxiety when the effect of oxytocin on indirectly measured emotional responses is investigated. Study 3 points to possible physiological symptoms in mentally healthy subjects with a history of traumatic experiences. Finally, Study 4 confirmed partial hyporeactivity in BPD patients. Taken together these studies show that psychophysiological measures are a useful tool in research about emotions and stress and that future studies should investigate subgroups based on personal characteristics.

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Appendix A

Supplemental material to study 3 - Startle reactivity in the long-term after severe accidental injury: Preliminary data

Results without subjects taking psychotropic medication

There was a significant main effect of group on eye-blink magnitude ($F(2, 52.8) = 3.62$, $p = 0.03$). The trauma-controls showed significantly higher eye-blink magnitude (M = 11.90, SE = 2.06) than the non-trauma controls (M = 4.61, SE = 1.77; mean difference = 7.30, SE = 2.72, 95%-CI 0.58 to 14.01, p=0.03). There was neither a significant difference in eye-blink magnitude between remitted PTSD subjects (M = 7.35, SE = 2.14) and the trauma-controls (mean difference = -4.55, SE = 2.97, 95%-CI -11.89 to 2.80, $p = 0.4$) nor between the remitted PTSD subjects and the non-trauma controls (mean difference = 2.75, SE = 2.78, 95%-CI -4.13 to 9.62, $p = 1.0$). There was a significant main effect of time on eye-blink magnitude ($F(14, 54.6) = 3.99$, $p < 0.001$) with magnitude decreasing over time across all groups of subjects. Skin conductance response showed a significant main effect of time ($F(14, 89.8) = 6.83$, $p < 0.001$), decreasing over time across all groups of subjects. There was no significant main effect of group for skin conductance response ($p = 0.4$). No significant main effects were found for eye-blink onset latency and heart rate response (p values > 0.07). No significant time by group interaction was found in any of the measures (p values > 0.1).

Separate model for trials 1 to 6 (all subjects)

There was no significant main effect of group on eye-blink magnitude ($p = 0.1$). There was a significant main effect of time on eye-blink magnitude ($F(5, 49.0) = 6.83$, $p < 0.001$) with magnitude decreasing over time across all groups of subjects. Skin conductance response showed a significant main effect of time ($F(5, 68.5) = 6.22$, $p < 0.001$), decreasing over time across all groups of subjects. There was no significant main effect of group for skin conductance response ($p = 0.1$). No significant main effects were found for eye-blink onset latency and heart rate response (p values ≥ 0.06). No significant time by group interaction was found in any of the measures (p values > 0.08).

Separate model for trials 7 to 15 (all subjects)

There was a significant main effect of group on eye-blink magnitude ($F(2, 39.2) = 3.33$, $p = 0.05$). The trauma-controls showed significantly higher eye-blink magnitude (M = 9.90, SE = 1.99) than the non-trauma controls (M = 3.12, SE = 1.71; mean difference = 6.77, SE = 2.63, 95%-CI 0.21 to 13.34,

p = 0.04). There was neither a significant difference in eye-blink magnitude between remitted PTSD subjects (M = 6.09, SE = 1.90) and the trauma-controls (mean difference = -3.80, SE = 2.75, 95%-CI -10.69 to 3.08, *p* = 0.5) nor between the remitted PTSD subjects and the non-trauma controls (mean difference = 2.97, SE = 2.56, 95%-CI -3.42 to 9.36, *p* = 0.8). There was a significant main effect of time on eye-blink magnitude (*F*(8, 50.1) = 2.75, *p* = 0.01) with magnitude decreasing over time across all groups of subjects. Skin conductance response showed a significant main effect of time (*F*(8, 103.6) = 2.16, *p* = 0.04), decreasing over time across all groups of subjects. There was no significant main effect of group for skin conductance response (*p* = 0.9). No significant main effects were found for eye-blink onset latency and heart rate response (p values > 0.2). No significant time by group interaction was found in any of the measures (p values > 0.2).

Record of achievement

In study 1 my contribution consisted in supporting the adaptation of the MRI-task for psychophysiological measurement, instructing the experimenter in laboratory use, preparation of the data for analysis in Anslab and analysis of the data in SPSS. I further created the figures, wrote the paper, and edited it according to co-authors' comments. Finally, I handled the review process with important assistance and advice from Annette Brühl.

I assisted in the design setup and preparation of study 2 and I programmed the task in E-Prime. I coordinated the collaboration with the pharmacy for the production and delivery of oxytocin, and I instructed the experimenters in laboratory use. I prepared the data for analysis in Anslab and analyzed them in SPSS. I drafted the paper together with Misari Oe as co first authors, created the data figures and edited the paper according to co-authors' comments.

In study 3 I assisted with the literature research. Further, I instructed the experimenters in laboratory use and coordinated the laboratory measurements. I prepared the data for analysis in Anslab and analyzed them in SPSS. I created the figures, drafted the paper, and edited it according to co-authors' comments. I handled the review process with important assistance from Chantal Martin Sölch, Ulrich Schnyder, and Hanspeter Mörgeli.

In study 4 I prepared the data for analysis in Anslab and I analyzed them in SPSS. I created the figures and wrote the paper together with Monique Pfaltz as co first authors and edited it according to co-authors' comments.

Table Index

Study 1

Table 1 Effect size for each model.
Note. SCR = skin conductance response, HRR = heart rate response; $R^2_{LMM(c)}$ indicates variance explained by the full model (fixed and random factors); $valence_1$: neutral, positive, negative, ambiguous; $valence_2$: neutral, positive, negative; $valence_3$: positive, negative; cue: explicit, ambiguous; all models included subject as a random factor.

Study 2

Table 2 Sample description
Note. STAI = State Trait Anxiety Inventory.

Study 3

Table 3 Sample description.
Note: STAI= State Trait Anxiety Inventory, BDI= Beck Depression Inventory, CAPS = Clinician-Administered PTSD Scale. * Missing CAPS data in one subject.

Study 4

Table 4 Sample description.
Note. BDI = Beck Depression Inventory score, STAI = State-Trait Anxiety Inventory, BPD = borderline personality disorder.

Table 5 Correlations of BDI scores with physiological and self-report measures across groups and sessions. Note. BDI = Beck Depression Inventory score, SCR = skin conductance response, HRR = heart rate response.

Figure Index

General introduction

Figure 1 Illustration of the modal model of emotions with *situation*, *attention*, *appraisal* and *response* as stages in emotional processing and the response looping back at the situation (Gross, 2014). Five points are illustrated at which emotions can be regulated (Gross, 2013).

Figure 2 Illustration of the three stages of the general adaptation syndrome (Selye, 1974). In the alarm stage the individual prepares for action. In the resistance stage the organism tries to restore homeostasis through recovery. If this is not possible the organism falls into the third stage of exhaustion.

Figure 3 Illustration of the hypothalamus-pituitary-adrenal (HPA) axis. The release of corticotropin releasing hormone from the hypothalamus leads to the release of adrenocorticotropic hormone from the pituitary, which in turn leads to the release of cortisol from the adrenal cortex. The release of cortisol leads to negative feedback to build a regulatory circuit (Gauggel & Hermann, 2008).

Study 1

Figure 4 Estimated marginal means +/- 1 standard error of physiological responses during picture anticipation and perception of explicitly cued pictures. * Bonferroni corrected pairwise comparisons $p < 0.05$; SCR = skin conductance response, HRR = heart rate response, µS = microsiemens, bpm = beats per minute.

Figure 5 Estimated marginal means +/- 1 standard error of physiological responses during picture anticipation and perception of explicitly cued pictures. * Bonferroni corrected pairwise comparisons $p < 0.05$; SCR = skin conductance response, mV = millivolt.

Study 2

Figure 6 Illustration of a trial in the affective modulation task for the following contents: A) nonsocial neutral, B) nonsocial positive, C) non-social negative, D) social neutral, E) social positive, F) social negative. Startle probes were presented 3500ms, 4000ms, or 4500ms after picture onset. Because of copyright issues with IAPS pictures, alternative pictures with comparable content are shown in this illustration.

Figure 7 Estimated marginal means +/- 1 standard error for eye-blink magnitude in millivolt: habituation over the 6 trials of baseline startle (across conditions).

Figure 8 Estimated marginal means +/- 1 standard error for eye-blink magnitude in millivolt: substance x picture valence x STAI group interaction. Low = lower STAI trait scores, high = higher STAI trait scores, * $p<0.05$.

Figure 9 Estimated marginal means +/- 1 standard error for substance x picture valence x STAI group interaction in valence ratings. Low = lower STAI trait scores, high = higher STAI trait scores, * $p < 0.05$

Study 3

Figure 10 Estimated marginal means and standard errors for the time course of eye-blink magnitude in millivolt (top left), eye-blink onset latency in milliseconds (top right), natural logarithm of skin conductance response in micro Siemens (bottom left) and heart rate response in beats per minute (bottom right). * One of 14 subjects dropped out of skin conductance analysis because none of the responses reached the threshold of 0.05 µS.

Study 4

Figure 11 Estimated marginal means +/- 1 standard error for between-session habituation effects across groups for skin conductance response (SCR, top left) in microsiemens (µS), heart rate response (HRR, top right) in beats per minute (bpm), zygomaticus response (bottom left) and corrugator response (bottom right) in microvolt (µV); * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder.

Figure 12 Estimated marginal means +/- 1 standard error for sound valence modulated effects. SCR = skin conductance response; * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder, µS = microsiemens, µV = microvolt.

Figure 13 Estimated marginal means +/- 1 standard error for rating effects. * significant pairwise comparisons at $p \leq 0.05$; BPD = borderline personality disorder.

Figure 14 Means +/- 1 standard error for % recognized sounds. * significant t-test ($p = 0.021$); BPD = borderline personality disorder.