Westfälische
Wilhelms-Universität
Münster

Fachgebiet Psychologie

Anxiety, Inhibition and the Prefrontal Cortex

Inaugural-Dissertation
zur
Erlangung des Doktorgrades
der
Philosophischen Fakultät
der
Westfälischen Wilhelms-Universität
zu
Münster (Westf.)

vorgelegt von
Christina Sehlmeyer
aus Münster

2010

Tag der mündlichen Prüfung: 15.12.2010

Dekan: Herr Prof. Dr. Christian Pietsch

Referentin: Frau Prof. Dr. Pienie Zwitserlood

Korreferent: Herr Prof. Dr. Volker Arolt

Table of Content

List of Figures

List of Tables

1 General Introduction

The purpose of this introduction is to briefly present famous dispositional personality models, important anxiety-related personality traits and their relationship to anxiety disorders. Also, anxiety-related dysregulations of behavioural and emotional inhibition and neurobiological functions are outlined. The last part of the introduction provides the theoretical and neuroimaging background of the two experiments presented in chapter 3 and 4.

Personality is commonly defined as a psycho-physiological and dynamical construct. It displays and influences characteristic attitudes, feelings, thoughts and actions of a person (Carver and Scheier, 2000). Personality factors do not only play an important role in everyday life but also in the context of psychiatric disorders (Zinbarg et al., 2008). In contrast to categorical typologies of human personality, dimensional approaches assume that people differ on continuous personality variables, so called *traits* (dispositions). According to this trait perspective, each personality consists of an organized pattern of dispositional qualities. These dispositions are regarded as basically biological, enduring across changes in time and situation, and as inter-individually different.

The next paragraph shortly outlines three famous dispositional approaches that aimed to characterize the basic structure of human personality with a finite number of independent traits and that have contributed to a significantly better understanding of the structure of personality. Since the beginning of dispositional personality research in the 1950s, the *Five Factor Model of Personality*, often labelled as *Big Five,* has been of particular importance. It structures personality in terms of five stable and independent traits, such as *neuroticism* (emotionality, experience of anxiety) or *extraversion* (assertiveness, openness) (Digman, 1990). Other authors referred to the same five factors using a variety of different labels for each (McCrae and Costa, 1987). Eysenck postulated that inter-individual differences in neuroticism and extraversion may be due to different sensitivities of individual cortical arousal systems (Eysenck, 1967). Another theoretical approach important to describe the biological basis of personality is the *Reinforcement Sensitivity Theory* by Jeffrey Gray (Gray, 1970). It is based on the distinction between two systems of learning. The *behavioural approach system* (BAS)

responds to incentives, produces positive feelings and represents the biological basis of the personality traits impulsivity and extraversion. The *behavioural inhibition system* (BIS) responds to threat or danger, leads to the display of avoidance or inhibition behaviour and is regarded as the biological basis of introversion and anxiety (Gray, 1982). C. Robert Cloninger further extended the knowledge of the neurobiological basis of personality (Cloninger, 1986, Cloninger, 1987). He proposed three genetically independent but functionally interactive personality traits named *harm avoidance* (tendency to avoid intense, novel and aversive stimuli), *novelty seeking* (tendency to explore/seek novel and appetitive stimuli) and *reward dependence* (resistance to extinct rewarded behaviour). This *Tridimensional Theory* claims that traits are heritable and associated with neurobiological markers, for example with neurotransmitter systems and with variances in regional brain functions (Gardini et al., 2009).

In summary, the personality models describe human personality with a limited number of traits and propose a neurobiological basis of personality. Although number and labels of the traits differ between the models, the proposed personality dimensions are quite similar. For example, neuroticism, harm avoidance and behavioural inhibition focus on negative emotionality and anxiety. To conclude, the theoretical models exemplify that anxiety represents an important aspect of human personality. Other personality constructs, also closely related to anxiety, are *trait anxiety* and *anxiety sensitivity*. In the following, these anxiety traits will be described in more detail.

Trait anxiety is a stable personality trait reflecting an individual's general disposition to experience anxiety-relevant feelings or thoughts. It describes the tendency to respond fearfully to a wide variety of unspecific stressors (Spielberger, 1972, Spielberger, 1979) and the need for security and cognitive control (Fales et al., 2008). Highly trait-anxious subjects tend to perceive more situations as threatening and more frequently experience intense and sustained anxiety states compared to subjects with low trait anxiety (Spielberger, 1972, Spielberger, 1979, Spielberger, 1983, Mathews and MacLeod, 2005). Anxiety sensitivity represents the specific tendency to respond fearfully to one's own bodily sensations and anxiety-related symptoms, which is based on the cognitive misinterpretation that these symptoms are harmful (McNally, 2002, Domschke et al., 2010). People high in anxiety sensitivity may for example be frightened of heart palpitations because they believe that these sensations will lead to cardiac arrest. Therefore, anxiety sensitivity in particular is related to an increased risk

of panic disorders (Zvolensky and Schmidt, 2007, Domschke et al., 2010). The relationship between anxiety sensitivity and trait anxiety has been a matter of controversial debates (McWilliams and Cox, 2001). While some authors maintain that these personality traits represent a common personality factor, others are convinced that trait anxiety and anxiety sensitivity are distinct but related personality concepts. In this view, trait anxiety focuses on cognitive anxiety symptoms whereas anxiety sensitivity refers to the self-evaluation of both physical and psychological syndromes (McNally, 1996, McWilliams and Cox, 2001, Muris et al., 2001, Domschke et al., 2010). These anxiety-related traits are also regarded as stable and biological predispositions (Pujol et al., 2002, Omura et al., 2005, Rauch et al., 2005, Most et al., 2006).

The following paragraph describes the relationship between anxiety traits and anxiety disorders. According to the dimensional personality approach, both "normal" personality variations and the respective pathological states share one continuum. For example, pathological anxiety can be found in individuals that are positioned at the extreme high end of the "normal" trait-anxiety dimension. Thus, anxiety traits are closely related to anxiety disorders, such as phobias, posttraumatic stress disorders or panic disorders (Chambers et al., 2004, Zvolensky and Schmidt, 2007, Schmidt et al., 2008). As they may increase the risk of anxiety disorders (Hirschfeld et al., 1986, Hirschfeld et al., 1989, Bienvenu et al., 2001, Simon et al., 2003, Chambers et al., 2004), they should be taken into consideration when conducting psychotherapies (Zinbarg et al., 2008).

Moreover, anxiety traits and anxiety disorders share common anxiety-related attitudes and symptoms. In general, anxiety leads to enhanced feelings of threat, alertness, and altered cognitive functions. Particularly, both anxious subjects and anxiety patients can be characterized by increased fear, thoughts about suspected dangers, attentional biases to threatening cues and deficits in cognitive control. For example, they show enhanced behavioural avoidance of threatening situations, and reduced emotional control in response to originally innocuous stimuli. In summary, anxiety comes along with dysregulation of behavioural and emotional *inhibition*.

In modern psychology and cognitive neuroscience, "inhibition" has several different meanings. In different contexts, the term inhibition can refer to the inhibition either of motor/ behavioural responses, memories or emotions. In addition to different meanings related to *what* is inhibited, one can also make a distinction between *how* the inhibition

is made and distinguish between active/ willed inhibition and automatic/ latent inhibition (Aron, 2007) (see Figure 1).

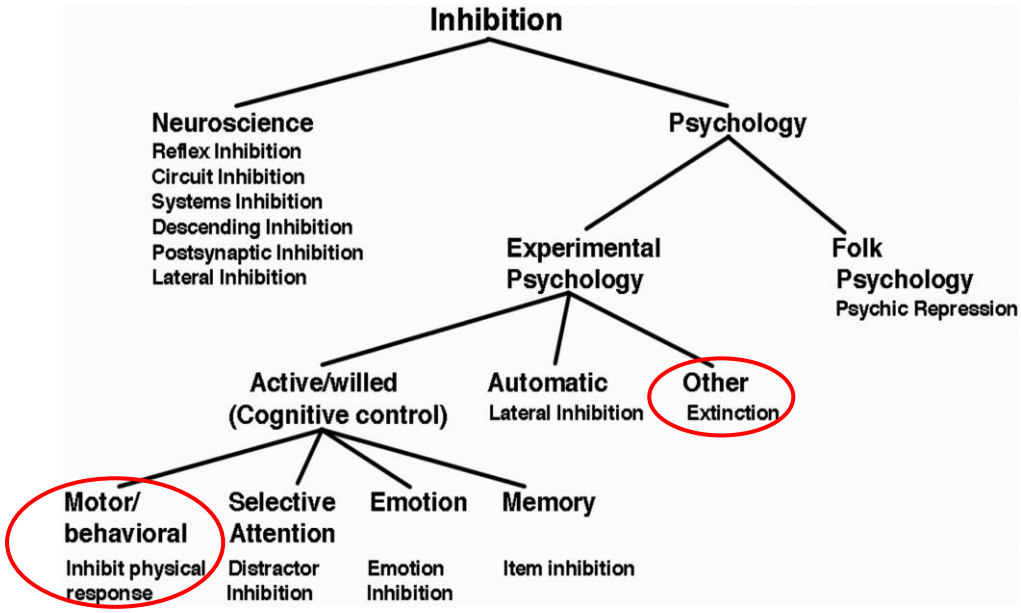


Figure 1 Types of inhibition in psychology and neuroscience (adapted from (Aron, 2007)). As motor/ behavioural inhibition and extinction are investigated in this thesis, they are marked in red.

An example of active/ willed inhibition is motor/ behavioural inhibition, also referred to as *response inhibition*. Response inhibition is described as the suppression of motor actions that are inappropriate in a given context. Furthermore, it represents an important component of the executive system (Norman and Shallice, 1986, Mostofsky and Simmonds, 2008), which is especially involved in planning, error correction, and the adaptation to novel situations (Norman and Shallice, 1986, Posner and Dehaene, 1994). An example of latent inhibition is *extinction*. Extinction refers to the process of *classical conditioning* (Pavlov, 1927). Classical conditioning was primarily examined by Ivan Pavlov in the early 1920s (Pavlov, 1927), and is most popular for the investigation of associative learning and implicit memory. In the context of conditioning, extinction occurs when the *conditioned stimulus* (CS) is no longer accompanied by the *unconditioned stimulus* (US) with which is was originally paired, resulting in the learned extinction of conditioned responses. In summary, response inhibition and extinction are essential types of the general inhibition concept and subject of this thesis.

The next paragraph shows how neuroscientific methods reveal significant findings about the neural basis of response inhibition and extinction, and anxiety-related dysfunctions of inhibitory processes. Since the 1990s, various brain imaging techniques, such as *functional Magnetic Resonance Imaging* (fMRI) and *Electroencephalography* (EEG), have been established in cognitive and behavioural neuroscience. FMRI is a non-invasive technique, which relies on the paramagnetic properties of oxygenated and desoxygenated haemoglobin. EEG is based on the measurement of neural activity along the scalp. While fMRI has the advantage of spatial precision of brain activation, EEG offers high temporal resolution (Friston, 2009).

In agreement, neuroimaging studies determine that the prefrontal cortex (PFC) plays a fundamental role in response inhibition and extinction (Konishi et al., 1999, Aron, 2007, Chambers et al., 2009, Herry et al., 2010, Huster et al., 2010, Walther et al., 2010). Another source of inhibition is the anterior cingulate cortex (ACC) (Huster et al., 2010), which is part of the medial PFC and may be divided into functionally different cognitive and emotional components (Bush et al., 2000, Banich et al., 2009). The PFC and the ACC are assumed to have extensive interconnections with the limbic system, basal ganglia or the motor cortex to exercise cognitive control (Aron, 2007, Banich et al., 2009). For example, neuroimaging and lesion studies have shown that during fear extinction fronto-amygdala circuits are involved. The medial PFC excites GABAergic cells which suppress amygdala-generated fear responses and thus decrease the expression of conditioned fear (Quirk et al., 2006). When behavioural responses must be controlled GABAergic mediated inhibitory circuits involving the PFC, ACC, basal ganglia and pre-supplementary motor area (SMA) are engaged (Nakamura et al., 1997, Banich et al., 2009).

Up to this point, the relationship between inhibition, the involvement of the PFC and anxiety has not been fully understood. It is assumed that anxiety disorders and anxiety traits are associated with structural and functional abnormalities in prefrontal and sub-cortical systems (Bishop, 2007, Etkin and Wager, 2007). For example, clinical and trait anxiety have been related to increased emotion-related activity and larger volume of the ACC, the amygdala or the insular cortex, and reduced prefrontal activity (Liotti et al., 2000, Pujol et al., 2002, Keightley et al., 2003, Omura et al., 2005, Most et al., 2006, Ferrari et al., 2008, Damsa et al., 2009, Shin and Liberzon, 2010). These dysregulations

may cause the anxiety-related deficits in behavioural and emotional inhibition described above.

This dissertation aims to clarify the influence of anxiety on the neurobiological aspects of behavioural and emotional inhibition using different neuroimaging techniques. The dissertation comprises three chapters. While chapters 2 and 3 focus on emotional inhibition, chapter 4 deals with behavioural inhibition. Chapter 2 provides an overview of the existing neuroimaging studies on fear conditioning and extinction in humans. The first experiment, described in chapter 3, examined the influence of trait anxiety on brain activation during fear conditioning and extinction using fMRI. The second experiment, described in chapter 4, investigated the impact of trait anxiety and anxiety sensitivity on *event-related potentials* (ERPs) of response inhibition using EEG.

In the first experiment, brain activation of healthy subjects was investigated during a classical fear conditioning and extinction task using fMRI. In a typical fear conditioning design, a previously neutral stimulus is associated with an aversive and fear-inducing unconditioned stimulus and becomes intrinsically aversive. During the last decades, neuroimaging research has provided valuable insights in the neurobiology of classical fear conditioning and extinction. These studies have revealed that the amygdala, the ACC and the insular cortex are central brain structures for fear conditioning (Sehlmeyer et al., 2009), and that the PFC plays a major role during the extinction of learned fear responses (Herry et al., 2010) (see chapter 2). Furthermore, studies have reported ambiguous findings about the influence of certain personality factors and pathological states on the ability to learn or extinguish fear responses (Blechert et al., 2007, Michael et al., 2007, Hooker et al., 2008, Barrett and Armony, 2009, Pineles et al., 2009). For this reason, the first experiment was aimed to investigate the influence of trait anxiety on brain activation during the acquisition and extinction of fear in healthy subjects.

In the second experiment, the neural basis of response inhibition was explored in healthy subjects using EEG. The Go/ Nogo-task is a popular paradigm to study response inhibition (Aron, 2009, Chambers et al., 2009). In this task, subjects were instructed to respond to one target stimulus in the *Go-condition* and withhold responses to the target stimulus in the *Nogo-condition*. Neuroimaging studies have yielded that the ACC and the PFC are mainly activated during the inhibition of responses to Nogo-stimuli (Aron, 2007, Swick et al., 2008, Huster et al., 2010). Deficits in response inhibition have been

discussed controversially with respect to the influence of psychopathology (Weisbrod et al., 2000, Herrmann et al., 2003, Kaiser et al., 2003, Kim et al., 2007). Only few studies emphasized the importance of investigating personality traits of healthy subjects in Go/ Nogo-tasks (Righi et al., 2009). Hence, the second experiment examined response inhibition in a Go/ Nogo-paradigm with regard to the influences of trait anxiety and anxiety sensitivity in healthy subjects.

2 Literature Review[1]

2.1 Introduction

Fear conditioning is an ability that is vital for the detection of danger, initiation of self-protection mechanisms, and for survival of a species. Disorders in humans associated with increased anxiety and fear levels, such as posttraumatic stress disorder, phobias, or panic disorder, exemplify how misguided fear conditioning might render originally innocuous stimuli fear-inducing and threatening. In addition, extinction of these associations is also hampered in these disorders. A life time prevalence of anxiety disorders of about 16,6 % (Somers et al., 2006) highlights the substantial clinical and socioeconomic relevance of fear conditioning and extinction.

The term *conditioning* refers to the process of learning the association between two previously unrelated stimuli (Pavlov, 1927). In a typical differential fear conditioning design, a previously neutral conditioned stimulus (CS+) is associated with an aversive and fear-inducing US and becomes intrinsically aversive, while another neutral stimulus remains unpaired (CS-) (Maren, 2001). Two main types of conditioning designs can be distinguished, which differ in the temporal relationship between CS+ and US, hence in the temporal *contiguity*. In *trace conditioning*, a time interval ranging from for example 500 milliseconds (Cheng et al., 2008) to 10 seconds (Knight et al., 2004a) separates the presentation of the CS+ from presentation of the US. The expression “trace conditioning” stems from the idea that a memory trace needs to bridge the gap between CS+ and the delayed US to form an association, therefore working-memory processes are more strongly involved in trace conditioning. In contrast, in *delay conditioning* the CS+ overlaps or is immediately followed by the US. A repeated exposure of the originally neutral stimulus without presenting the aversive stimulus gradually eliminates the fear reaction and is defined as *extinction*. In the past, extinction was regarded as a process of forgetting this association. However, the phenomena of *spontaneous recovery*, *renewal*, *rapid acquisition*, and *reinstatement* after extinction, suggest that

[1] Sehlmeyer C, Schöning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V and Konrad C (2009) Human Fear Conditioning and Extinction in Neuroimaging: A Systematic Review. PLoS ONE 4(6): e5865.doi: 10.1371/journal.pone.0005865

fear extinction is “an active learning process that is distinct from acquisition and requires additional training to develop” (Myers and Davis, 2002).

Fear conditioning has proven to be an extremely robust, rapid, and precise experimental approach for studying the neurobiological substrates of fear (Pavlov, 1927, Rachman, 1977, Pape et al., 1998, Pape et al., 2001, Pape and Stork, 2003, Pape et al., 2004, Lissek et al., 2005, Pape, 2005, Pape et al., 2005, Anderson and Insel, 2006), while fear extinction most probably represents the main therapeutic ingredient of exposure-based psychotherapies. Numerous studies have investigated fear conditioning and extinction in animals and humans, resulting in a core neural network involved in conditioning and extinction (see e.g. (Fendt and Fanselow, 1999, LeDoux, 2000, Stoppel et al., 2006)).

While the literature on animals has been summarized in several review articles (see e.g. (Maren, 2001, Myers and Davis, 2002)), there has been no such approach in the current functional neuroimaging literature on human fear conditioning. So far, only a few reviews have been published and they focus on special topics such as extinction of conditioned fear (Barad et al., 2006, Sotres-Bayon et al., 2007), or socio-cultural and cognitive influences on learning (Delgado et al., 2006). Büchel et al.’s (2000) review compared event-related fear conditioning studies to block-design studies and PET studies. This important review was one of the first to identify a common core network for human aversive conditioning, including the amygdala and ACC (Buchel and Dolan, 2000). Other reviews concentrated on cellular and synaptic mechanisms, or on plasticity within this neuroanatomical circuitry (Maren, 2001, Kim and Jung, 2006).

Even though a core network for fear conditioning has consistently been reported in most imaging studies, results obtained from modern neuroimaging techniques differ in many respects, for example, in the number or the type of activated areas.

Therefore, the main aim of this review is to identify consistent and common findings on aversive conditioning and extinction in humans, as assessed by PET and fMRI, and to present them in a structured manner. The second aim is to look at the differences between neuroimaging studies with respect to neuroimaging results and design parameters. We therefore identify and evaluate typical experimental factors that may influence brain activation patterns and may thereby contribute to the heterogeneity of neuroimaging results. Overall, this review is intended to facilitate the interpretation of seemingly contradictory neuroimaging findings, as well as the selection of an

appropriate conditioning design for specific research purposes. Therefore, this review is relevant both to clinicians seeking for a state-of-the-art overview and to researchers investigating fear conditioning or extinction by means of neuroimaging.

The main results of the reviewed studies will be briefly summarized first, followed by an evaluation of specific consequences on activation patterns of critical factors concerning conditioning paradigms, measures of conditioning success, stimuli, and their timing. The review concludes with a critical discussion of these factors and an evaluation of their impact on past and future research.

2.2 Methods

2.2.1 Literature Search

To identify relevant neuroimaging studies on human fear conditioning and extinction, a computerized database search of journal articles via Pubmed was conducted for the years 1994 - 2008. This Pubmed search, as of December 2008, used combinations of the keywords “conditioning”, “extinction”, “aversive”, “fear”, “fMRI”, “neuroimaging”, “PET” and “humans”. No truncations and language restrictions were applied. We screened the abstracts for relevant literature based on the literature search criteria and additionally examined the references sections of articles and reviews for potentially useful studies.

2.2.2 Selection criteria

Studies were included if they were: (1) PET or fMRI studies, (2) performed on healthy volunteers, (3) focused on cued fear conditioning and/ or extinction. Furthermore, exclusion criteria were: (1) pharmacological modulation, (2) subliminal or masked presentation, (3) context conditioning, (4) combination of fear conditioning with other experimental tasks, such as cognitive-demanding working-memory tasks. Inclusion criteria were applied independently by two reviewers. Specific experimental designs for fear conditioning in fMRI and PET were compared, focusing on the impact of critical experimental variables, such as timing parameters, the contingency rate, or characteristics of the stimuli, on neuroimaging results.

2.2.3 Data Extraction

Data were extracted by the first author (CS) and double-checked independently by the second author (SS). The discrepancies were resolved by consensus and the senior author (CK) was consulted if needed. The following variables were extracted and presented in Table 1: 1) demographic characteristics (number of participants, gender, and age), 2) study design (delay, trace, and extinction), 3) neuroimaging technique (fMRI, PET), 4) characteristics of the stimuli (modality of CS and US), 5) independent assessments of the conditioning process (e.g. heart rate), and 6) neuroimaging results. In the data analysis, the outcomes of interest were brain areas activated during conditioning and extinction. Therefore, we extracted the neuroimaging data presented by each study as the main results. Finally, we extracted those contrasts of interest that represent the conditioning or extinction effect (e.g. CS+>CS-).

2.2.4 Data Analysis

The review provides a qualitative summary of neuroimaging findings on fear conditioning and extinction of the included empirical studies. These studies were classified according to the type of study design (delay, trace, and extinction), the modality of the CS and US, the contingency rate, and the independent assessment of the conditioned response. For each category, we extracted the absolute frequency of activated brain areas for the contrasts of interest. Moreover, we attempted to identify common and divergent activations across individual study results. Studies, reporting additional or different activation from those described in the core fear network, were examined for the following variables to shed light on reasons for the discrepant findings: conditioning design (delay, trace, and extinction), contingency rate, and characteristics of the CS and US. We refrained from statistically combining results from the studies due to the differences in their design.

2.3 Results

2.3.1 Included studies

Based on the literature search strategies, 147 citations were retrieved from the Pubmed database. Among these, we identified 33 relevant studies. Additionally, we examined the references of relevant articles and reviews. Thirteen citations met the selection criteria. As a whole, we reviewed 46 articles on human fear conditioning and/or extinction. Figure 2 shows the search and selection process. Forty studies exclusively used a delay conditioning paradigm during the acquisition phase (Table 1; No. 1-3, 5, 7, 9, 11-18, 20-23, 26, 28-29, 31-33, 35-36, 38-40, 42-45). Only two studies investigated solely trace conditioning during acquisition (Table 1; No. 4, 34), whereas four other studies used both delay and trace conditioning protocols (Table 1; No. 6, 8, 10, 25). Extinction of learned fear was additionally reported by seven of the 40 delay conditioning studies (Table 1; No. 19, 24, 27, 30, 37, 41, 46). Thirty-two of the 46 studies are fMRI studies, 14 are PET studies. Table 1 contains information on empirical study characteristics and corresponding neuroimaging results.

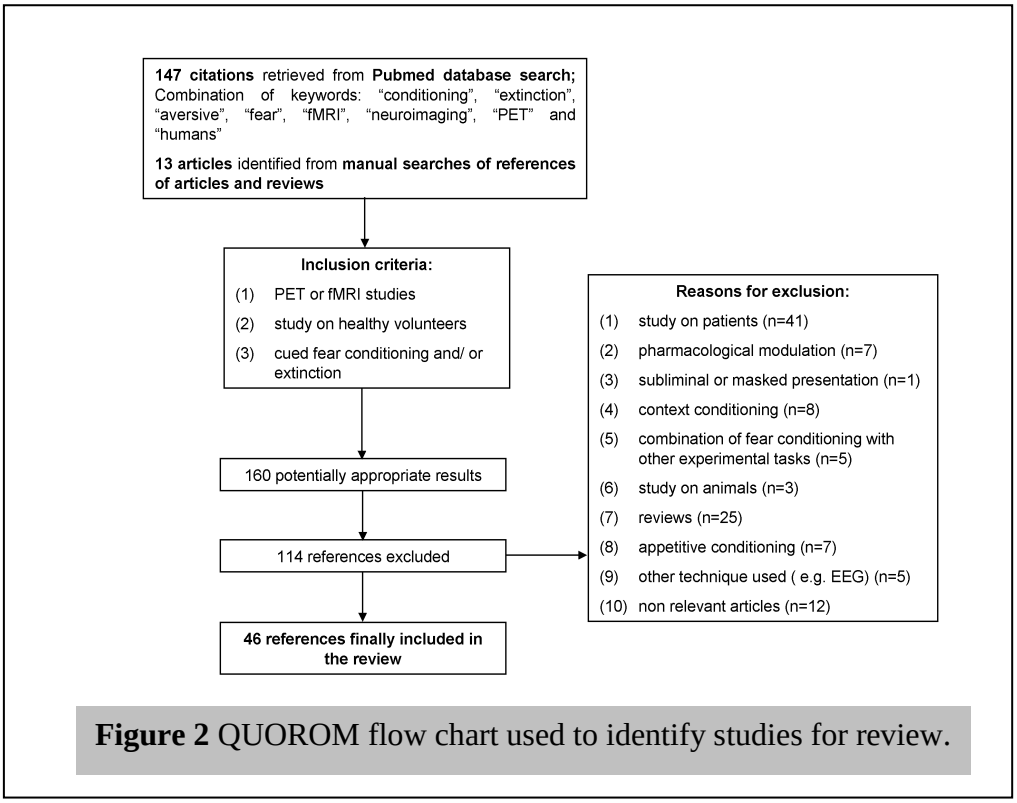


Figure 2 QUOROM flow chart used to identify studies for review.

2.4 Summary of Findings

2.4.1 Brain regions involved in delay fear conditioning

As a major and stable result, the amygdala, the ACC and the insular cortex turned out to be crucial structures in the acquisition of aversive delay conditioning, independent of general design characteristics. Twenty-five of the 44 delay conditioning studies reported amygdala activation, with results varying with respect to the laterality of activation. While nine studies reported bilateral amygdala activation (e.g.(Morris et al., 1997, Dunsmoor et al., 2007, Petrovic et al., 2008)), eight studies detected left-lateralized (e.g. (Carlsson et al., 2006, Carter et al., 2006, Schiller et al., 2008)), and eight right-lateralized activations (e.g.(Pine et al., 2001, Cheng et al., 2007)). Methodologically, nineteen of the 25 studies additionally tested for temporal interactions of amygdala activation or split up the acquisition phase into an early and late phase, in order to assess the temporal gradation in the signal intensity of the amygdala. Seventeen of these studies reported learning-related responses of the amygdala (e.g. (Buchel et al., 1999, Morris and Dolan, 2004, Straube et al., 2007, Li et al., 2008)): fourteen studies found initial increase and rapid decrease of activation during repeated exposure to unpleasant stimuli (e.g. (LaBar et al., 1998, Fischer et al., 2000)), whereas three studies only reported increases of amygdala activation during the acquisition phase (Phelps et al., 2004, Tabbert et al., 2005, Klucken et al., 2008). The remaining 19 delay conditioning studies did not report activation of the amygdala. Seventeen of them did not test for temporal aspects of amygdala activation (e.g. (Jensen et al., 2003)). Sixteen delay conditioning studies found activation of the ACC (e.g. (Blaxton et al., 1996, Buchel et al., 1998)), five of the posterior cingulate cortex (PCC) (e.g. (Doronbekov et al., 2005)), and two reported activation of the cingulate cortex (Fischer et al., 2000, Straube et al., 2007). Sixteen studies detected insular activities (e.g (Ploghaus et al., 1999, Jensen et al., 2003, Schiller et al., 2008)). These areas are all part of the classical key fear network as described previously (Buchel and Dolan, 2000, Kim and Jung, 2006).

Activation of brain areas such as the hippocampus, the cerebellum, the thalamus, the striatum or the sensory cortices has been reported by fewer delay conditioning studies, underlining the considerable variability in neuroimaging findings. Hippocampal activity, mostly lateralized, was found for example by ten studies (e.g. (Fischer et al., 2002)). Twelve studies showed activation of the striatum (including putamen,

accumbens nucleus, caudate nucleus) (e.g. (Jensen et al., 2003, Carlsson et al., 2006)), whereas thalamic activity (including pulvinar, geniculate nucleus) was reported by twelve delay conditioning studies (e.g. (Morris and Dolan, 2004)) (for details, see Figure 3). As argued below, we believe such differences in results to be methodological in origin (Lissek et al., 2005).

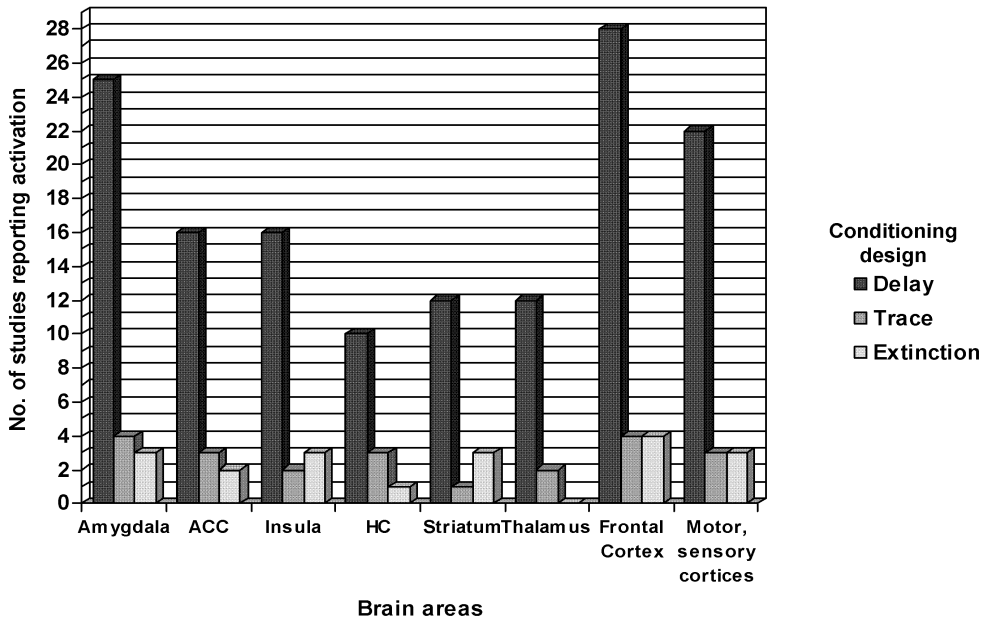


Figure 3 Brain areas involved in aversive conditioning and/ or extinction. Different brain areas (with at least unilateral activation during aversive conditioning and/ or extinction) are plotted against the x-axis. The number of studies out of 46 studies per brain region is plotted against the y-axis, taking into account the conditioning design which is delay conditioning in 40, trace conditioning in two, delay and trace conditioning in four, and extinction in seven studies.

2.4.2 Brain regions involved in trace fear conditioning

So far, only two fMRI studies have employed solely trace conditioning (Buchel et al., 1999, Nitschke et al., 2006) and four fMRI studies were conducted on both delay and trace conditioning (Knight et al., 2004a, Carter et al., 2006, Cheng et al., 2006, Cheng et al., 2008) (for details, see Table 1), all with either auditory, visual or tactile aversive stimulation. Again, the amygdala and the medial temporal lobe (MTL) were predominantly activated during the acquisition of trace conditioning in five studies (e.g. (Buchel et al., 1999, Carter et al., 2006, Cheng et al., 2008)). Activation of the ACC was apparent in three studies (Buchel et al., 1999, Knight et al., 2004a, Nitschke et al., 2006)

and of the PCC in one study (Knight et al., 2004a). The hippocampus was bilaterally activated in three trace conditioning studies (Buchel et al., 1999, Knight et al., 2004a, Carter et al., 2006), and two studies showed additional activation of the insula (Buchel et al., 1999, Nitschke et al., 2006). These fear-related structures such as the amygdala, the hippocampus, the ACC, the insula and the MTL were active independently of US-modality. Furthermore, activation was observed in different areas of the frontal cortex such as the dorsolateral prefrontal cortex (DLPFC) (e.g. (Buchel et al., 1999)) or the middle frontal gyrus (Knight et al., 2004a, Carter et al., 2006) in four trace conditioning studies. Activation of other brain areas, such as the cerebellum, was reported in one study, of the motor cortices in three studies (e.g. (Knight et al., 2004a, Cheng et al., 2008)) (for details, see Figure 3). Again, this variability in study results may be due to critical design characteristics, which will be discussed below.

2.4.3 Brain areas involved in fear extinction

Although extinction is very relevant in therapeutic settings, only seven studies with focus on extinction met criteria for our review (Molchan et al., 1994, Schreurs et al., 1997, LaBar et al., 1998, Gottfried and Dolan, 2004, Knight et al., 2004, Phelps et al., 2004, Yaguez et al., 2005). All seven used a classical delay conditioning design during acquisition. Six studies used a tactile US (e.g. (Phelps et al., 2004)), and one an olfactory US (Gottfried and Dolan, 2004). Three of the seven studies reported major activation foci in the amygdala (LaBar et al., 1998, Gottfried and Dolan, 2004, Knight et al., 2004), two in the ACC (Phelps et al., 2004, Yaguez et al., 2005), one study in the PCC (Molchan et al., 1994) and three in the insula (e.g. (Molchan et al., 1994, Gottfried and Dolan, 2004)), whereas four studies observed activation in frontal regions such as the PFC, and the ventromedial prefrontal cortex (VMPFC) (e.g. (Yaguez et al., 2005)). Activation of the hippocampus was found in only one study (Knight et al., 2004) (for details, see Figure 3).

Although consensus exists that the amygdala again plays an important role in extinction, a closer look reveals that the details about amygdala activation vary. As with acquisition, four of the seven studies reported habituation of the amygdala response during extinction (LaBar et al., 1998, Gottfried and Dolan, 2004, Knight et al., 2004, Phelps et al., 2004). To assess the temporal gradation in signal intensity of the

amygdala, two of them split up the extinction phase into an early and late phase (LaBar et al., 1998, Phelps et al., 2004), and one study tested for time x condition interaction (Gottfried and Dolan, 2004). Knight and co-workers (2004) reported an increase of right amygdala and a decrease of left amygdala activation during extinction, by t-test comparison (Knight et al., 2004). Three other studies that did not analyse temporal activation patterns failed to find amygdala activation (Molchan et al., 1994, Schreurs et al., 1997, Yaguez et al., 2005).

2.4.4 The influence of CS-US-contingency

Contingency describes the rate of pairing between the previously neutral CS+ and the aversive US, and therefore the predictability of the US in relation to the CS. In some cases, the CS is paired with the US on every trial (continuous pairing), whereas in other conditioning designs, CS and US are paired intermittently.

Contingency rates in neuroimaging studies cited here are quite heterogeneous. Twenty-five studies used 100 % contingency (e.g. (LaBar et al., 1998, Knight et al., 1999, Cheng et al., 2003, Dimitrova et al., 2004)), two employed an 80 % or a 90 % pairing rate (Logan and Grafton, 1995, Knight et al., 2005), six included a 50 % partial reinforcement procedure (e.g. (Gottfried and Dolan, 2004)), and eight described lower contingencies of 40 %, 33 %, 25 % or 0 % (e.g. (Fischer et al., 2000, Phelps et al., 2001, Morris and Dolan, 2004, Phelps et al., 2004, Schiller et al., 2008)). Three studies used 100 % and 50 % contingency rates during different phases of the experiment (Yaguez et al., 2005, Dunsmoor et al., 2007, Dunsmoor et al., 2008). Another study employed a continuous pairing design during trace conditioning and a 50 % pairing rate during delay conditioning (Carter et al., 2006). One study did not report any contingency rates (Doronbekov et al., 2005). Results of the studies cited here indicate that activation of the amygdala seems to be independent of contingency rate: While thirteen studies employing continuous (100 %) pairing, eight studies using 50 % reinforcement and six studies with 0 %, 25 %, 33 % , 40 % and 80 % all reported amygdala activation, (e.g. (Morris et al., 1997, Buchel et al., 1998, Buchel et al., 1999, Cheng et al., 2003, Gottfried and Dolan, 2004)), others with the same pairing rates did not (e.g. (Blaxton et al., 1996, Yaguez et al., 2005)).

Awareness about this CS-US-contingency, mediated by conscious US-expectancies or by explicit instruction about the CS-US-contingency, also influences brain activation. Participants were explicitly informed about the CS-US pairing before the experiment in some studies (e.g. (Fischer et al., 2000)), but not in others (e.g. (LaBar et al., 1998)).

Finally, the choice of contingency rates is related to a problem specific to neuroimaging studies: the choice of contrasts between conditions. In a continuous pairing paradigm where the CS+ is always presented with the US, contrasts may be calculated between CS+ and CS- (e.g. (Tabbert et al., 2005)), between paired und unpaired subjects (e.g. (Knight et al., 2004)), or between conditioned and pseudo-conditioned phases - in which CS and US are not correlated in time (e.g. (Blaxton et al., 1996)). In a partial-reinforcement design, CS+ may be paired or unpaired with the US. Here, contrasts are mainly calculated between CS+unpaired and CS- (e.g. (Buchel et al., 1998)) .

2.4.5 Characteristics of the CS and US

Neuroimaging studies on fear conditioning have used different types of conditioned and unconditioned stimuli. Conditioned stimuli were presented visually, acoustically or olfactory. Thirty-one studies used a visual cue as CS: five studies used coloured lights (e.g. (Pine et al., 2001, Knight et al., 2004, Cheng et al., 2006)), one study photographs (Doronbekov et al., 2005), and four videotapes (e.g. (Fredrikson et al., 1995, Fischer et al., 2002)). Seven studies, however, employed photographs of human faces (e.g. (Morris et al., 1997, Buchel et al., 1998, Gottfried and Dolan, 2004, Anders et al., 2005, Petrovic et al., 2008)), and 14 used geometrical figures (e.g. (Phelps et al., 2004, Tabbert et al., 2005)). Fourteen investigations used auditory conditioned stimuli (e.g. (Logan and Grafton, 1995, Buchel et al., 1999, Knight et al., 2005, Dunsmoor et al., 2007)), whereas only one study employed odours (Li et al., 2008). Again, activation of the amygdala was independent of CS-modality: five studies with auditory CS (e.g. (Buchel et al., 1999)), 21 using a visual CS (e.g. (Straube et al., 2007)) and one study which employed an olfactory CS (Li et al., 2008) reported amygdala activation.

Unconditioned stimuli differ in modality (auditory, olfactory, tactile, and visual), in salience, as well as in unpleasantness, factors that may all influence the neurobiology of fear learning. Twenty-four studies used electric shocks (e.g. (LaBar et al., 1998, Fischer

et al., 2000, Cheng et al., 2003, Knight et al., 2004a, Carter et al., 2006, Cheng et al., 2006)). The intensity of the shock is often assessed and adjusted to an individual level described as "unpleasant but not painful", such that voltage varied from 40 V to 70 V between participants (e.g. (LaBar et al., 1998, Knight et al., 1999, Gottfried and Dolan, 2004, Doronbekov et al., 2005, Carlsson et al., 2006, Neumann and Waters, 2006)). Electrical stimuli were administered to different areas, such as the wrist (e.g. (LaBar et al., 1998, Phelps et al., 2001, Phelps et al., 2004)), shin (e.g. (Tabbert et al., 2005)), foot (e.g. (Carter et al., 2006)), or finger (e.g. (Fischer et al., 2000, Jensen et al., 2003)). Further tactile stimulations, such as air blasts are reported in eight studies (Logan and Grafton, 1995, Blaxton et al., 1996, Schreurs et al., 1997, Pine et al., 2001, Yaguez et al., 2005, Cheng et al., 2008), thermal stimulation with hot water in one study (Ploghaus et al., 1999), and painful phasic esphageal distention in another study (Yaguez et al., 2005). Nine studies cited here included auditory US, such as loud unpleasant tones (Buchel et al., 1998, Buchel et al., 1999), or loud white noises (e.g. (Morris et al., 1997, Morris and Dolan, 2004, Knight et al., 2005, Dunsmoor et al., 2007)) at intensities of 95dB to 100dB, for 500-1000ms. A verbal stimulus, a human scream, was presented as unconditioned stimulus in one study (Anders et al., 2005). Another study used an olfactory unconditioned stimulus in human fear conditioning, such as "rotten eggs" and "sweaty socks" (Gottfried and Dolan, 2004). Finally, pictures (IAPS; International Affective Picture System (Lang et al., 1990)) or aversive videotapes were presented as aversive stimuli in three studies (Doronbekov et al., 2005, Nitschke et al., 2006, Klucken et al., 2008).

Again, activation of the fear network was observed to be independent of US-modality. In spite of different USs, activations of the amygdala, ACC and insula were reported for every stimulus type. Of the 33 studies with tactile stimulation, fifteen found activation of the amygdala (e.g. (Cheng et al., 2003)), ten of the ACC (e.g. (Fredrikson et al., 1995)), and ten of the insular cortex (e.g. (Jensen et al., 2003)). Other main activation foci for tactile stimuli concern the thalamus in seven (e.g. (Logan and Grafton, 1995)), and the striatum in ten studies (e.g. (Phelps et al., 2001)). Other regions such as the occipital cortex, motor or somatosensory cortices are also activated during tactile conditioning in 16 studies (e.g. (Fredrikson et al., 1995, Carter et al., 2006)). By contrast, the nine studies on auditory fear conditioning mainly report activation of the fear network, with emphasis on amygdala in seven (e.g. (Dunsmoor et al., 2007)), on

ACC in five (e.g. (Morris and Dolan, 2004)), and on insula in five studies (e.g. (Knight et al., 2005)). Moreover, activations of the motor or sensory cortices (e.g. auditory, occipital) are also apparent in five studies (e.g. (Buchel et al., 1998)). The one study on olfactory conditioning mainly reports activations in amygdala, insula and orbitofrontal cortex (OFC) (Gottfried and Dolan, 2004), areas that are also associated with the perception of disgust (Schienle et al., 2002, Stark et al., 2007). All three studies on visual aversive conditioning reported activation of key fear areas such as the amygdala and ACC or the PCC (Doronbekov et al., 2005, Nitschke et al., 2006, Klucken et al., 2008). Activation of the insula was found in two of the studies (e.g. (Nitschke et al., 2006)). Furthermore, activations of the DLPFC, OFC, thalamus, nucleus accumbens and the occipital cortex are apparent in these visual conditioning studies (e.g. (Klucken et al., 2008)) (for details, see Figure 4).

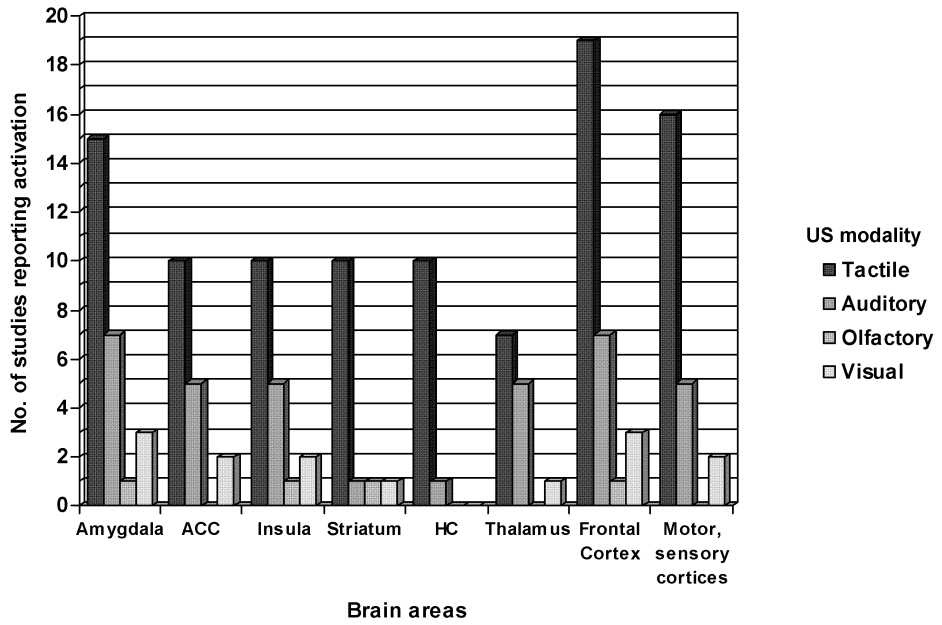


Figure 4 Brain areas involved in aversive conditioning according to the modality of the US. Different brain areas (with at least unilateral activation during aversive conditioning) are plotted against the x-axis. The number of studies out of 46 studies per brain region is plotted against the y-axis, taking into account US modality, which is tactile in 33 studies (such as electrical shocks), auditory in nine studies (such as noise), olfactory in one study (such as odors), or visual in three studies (such as aversive pictures).

Our review reveals that 38 of the reviewed studies employed different modalities of US and CS. Only five studies chose an auditory CS paired with an auditory US (e.g. (Buchel et al., 1999, Knight et al., 2005, Dunsmoor et al., 2007)), and three were conducted on visual CS and US (e.g. (Klucken et al., 2008)). Again, research is needed to quantify this effect of common CS-US-modality on neuroimaging results.

2.4.6 Independent assessment of the conditioning process

A control procedure to ensure that a physiological response towards the CS+ has actually occurred, with data from dependent variables other than brain activation, was used in 41 of the 46 studies cited here (for details, see Table 1, Figure 5). Autonomous, endocrine, or behavioural responses, such as skin-conductance responses, heart rate, verbal responses (ratings of the CS, US-expectancy ratings, or CS-US-contingency assessment), reaction times, or eye-blink reflex qualify as parameters of successful conditioning. The majority of the studies employed independent measures online during scanning.

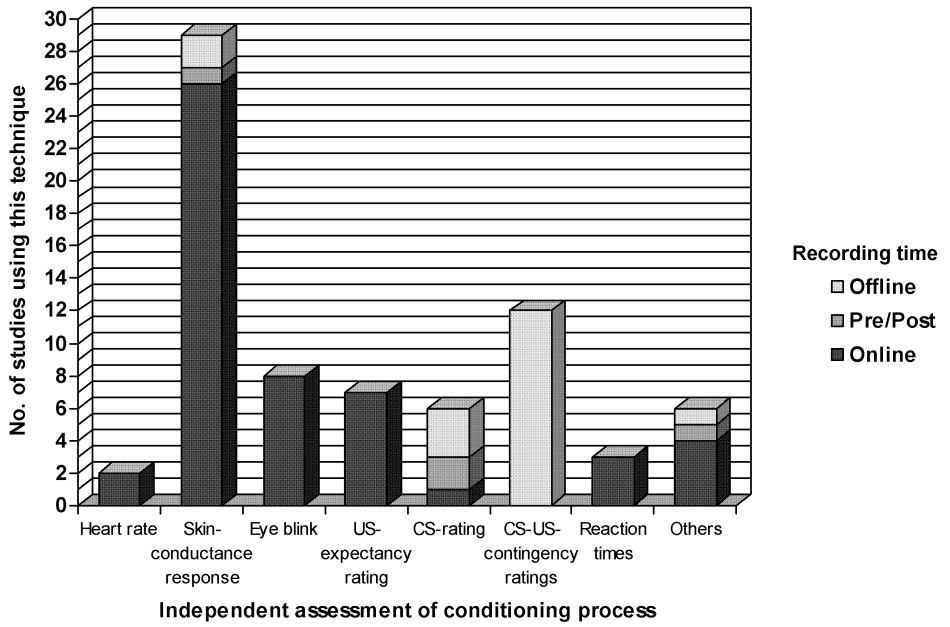


Figure 5: Number of studies employing an independent assessment of the conditioning process. Different independent assessments of the conditioning process which may be autonomous (such as skin-conductance responses), or behavioural (such as verbal ratings), are plotted against the x-axis. The number of studies out of 46 studies per technique is plotted against the y-axis taking into account if the technique is applied online during scanning, offline after scanning or offline before and after scanning (pre/post).

Autonomous measures, such as heart rate, were applied in two (Fredrikson et al., 1995, Dimitrova et al., 2004), skin-conductance responses in 26 (e.g. (Morris et al., 1998, Cheng et al., 2007, Cheng et al., 2008, Dunsmoor et al., 2008, Petrovic et al., 2008, Schiller et al., 2008)), and eye-blink startle response in eight studies (e.g. (Logan and Grafton, 1995, Blaxton et al., 1996, Schreurs et al., 1997, Anders et al., 2005)). Only three studies used SCR outside the scanner: before and after conditioning (Hugdahl et al., 1995) or in an additional experiment (LaBar et al., 1998, Straube et al., 2007). Online assessments of verbal responses, such as CS-ratings, were used in one study (Doronbekov et al., 2005), and US-expectancy ratings in seven studies (e.g. (Cheng et al., 2006, Cheng et al., 2007, Dunsmoor et al., 2007)). Two studies compared ratings of the CS before and after scanning (Straube et al., 2007, Petrovic et al., 2008). Twelve studies employed CS-US-contingency ratings and three studies CS-ratings post experimentally (e.g. (Carter et al., 2006, Klucken et al., 2008)). To conclude, twenty-three studies combined different measurements of the conditioned response (e.g. (LaBar et al., 1998, Carter et al., 2006)). To summarize, objective measurements are necessary when studying conditioning, to verify that conditioned learning has indeed occurred.

2.5 Discussion

This review deals with the neural correlates of human fear conditioning in current fMRI and PET studies. Our analysis indicates that neuroimaging studies on human fear conditioning and extinction activate a common core fear network which is in accordance with evidence from other sources (e.g. (Stoppel et al., 2006)). Some neuroimaging studies do not find these activations. This heterogeneity is not surprising taking into account the large methodological variety in imaging and design parameters. Methodological differences were found a) in the conditioning protocol (delay, trace), b) in the contingency rate (100 %, 80 %, 50 % or less) and awareness, c) in the modality of CS and US (tactile, auditory, visual, olfactory), and d) with respect to the further assessment of the conditioned response (e.g. psycho-physiological measurements, verbal ratings).

Neuroimaging studies have substantially extended our understanding of fear conditioning and extinction, adding in vivo evidence from humans to previous electrophysiological and lesion studies from animals (Maren, 2001, Blair et al., 2005).

Consistent with comparative animal data, neuroimaging investigations have corroborated the finding of a neural fear network activated during fear conditioning. Within this core fear network, key structures for the acquisition and the extinction of conditioned fear have been identified, although there is considerable methodological heterogeneity between studies, with some of them not reporting these activations. Furthermore, it turned out that anatomical regions relevant in fear conditioning are also involved in the extinction of fear memories. In conformity with animal and lesion data, our review indicates that the amygdala, as one principal structure of the limbic system, is one of the key regions involved in fear conditioning and extinction. Amygdala activation occurs in response to emotional stimuli and is therefore regarded as the gate keeper funnelling emotionally relevant information into different processing channels. This region is activated during conditioned-fear acquisition as well as during the expression of learned fear (see for an overview (Kim and Jung, 2006)). Furthermore, amygdala activation undergoes rapid habituation during acquisition and extinction that should be taken into account in neuroimaging studies (e.g. (Buchel et al., 1998)). This typical response profile of the amygdala may not be detected by categorical comparisons of e.g. CS+ and CS-, as this contrast reflects time-invariant neural responses. Consequently, some studies carried out an analysis that tested for this type of time-dependent response profile. They set up a statistical model that allows characterizing the activation of the amygdala by a time by condition interaction. Therefore, we suppose that testing for interactions between conditions and time may reveal conditioning results that otherwise remain hidden, such as amygdala activation.

Furthermore, some brain regions, especially the MTL, are difficult to assess using echo-planar imaging (EPI) because they are highly vulnerable to susceptibility artifacts (Morawetz et al., 2008). These differences may cause image distortion and signal dropout (Bellgowan et al., 2006, Stocker et al., 2006, Morawetz et al., 2008). This might be another reason why some studies did not find amygdala activation during conditioning. Activation of the insula, another central structure for emotion processing, was also shown in 40% of the neuroimaging studies. Phelps and co-workers (2001) assume that the insula cortex conveys a cortical representation of fear to the amygdala (Phelps et al., 2001), and that uncertainty about the advent of the aversive stimulus during intermittent pairing is reflected by insula and dorsal prefrontal cortex activation (Volz et al., 2003, Dunsmoor et al., 2007, Dunsmoor et al., 2008). Another region

belonging to the core fear conditioning and extinction network described by the majority of the cited neuroimaging studies is the ACC (for an overview, see (Buchel et al., 1998, Stoppel et al., 2006)). The ACC plays an important role in approach and avoidance learning (Freeman et al., 1996) as well as in fear learning (Buchanan and Powell, 1982). The frontal cortex is particularly crucial for emotional regulation and therefore for the extinction of conditioned fear. Although extinction is the essential process in therapeutic settings, only seven studies have so far focused on extinction. From both animal data and theoretical considerations, it is evident that fear extinction involves mainly interactions between cortical and subcortical structures, such as the PFC and the amygdala or the hippocampus (see for an overview (Sotres-Bayon et al., 2006)). As one of the principal structures of the brain's extinction circuitry, the PFC regulates the expression of fear by inhibiting the amygdala, such that the fear-conditioned stimulus is prevented from causing a conditioned fear response (Quirk et al., 2003, Quirk et al., 2006, Sotres-Bayon et al., 2006). In this review, only one study reported hippocampal activation during extinction. This is surprising, because from other studies is known that the hippocampus and the VMPFC seem specifically important during late phases of extinction, and therefore for the retention of extinction (Phelps et al., 2004, Milad et al., 2007).

There are, however, considerable variances and discrepancies between studies. Whereas some studies only report activation of the core network, others do not find these activations or observe activation within additional brain regions, such as the hippocampus, striatum, sensory cortices or thalamus. The choice of conditioning protocol, CS-US contingency, and modality of the US seem to be very important factors modifying brain-activation patterns in fear conditioning studies.

Our review indicates that of these factors, the conditioning protocol has great impact on brain activation. Delay conditioning leads to more rapid learning of the CS-US association than trace conditioning (Prokasy and Whaley, 1963, Gibbon and Balsam, 1981, Jenkins et al., 1981). Thus, from the experimental point of view, delay conditioning has the advantage of a shorter acquisition time, fewer trials, and a more rapid conditioning process than trace conditioning. Additionally, delay conditioning designs are known to extinguish associations faster than those established during trace conditioning (Shors, 2004). Therefore, all studies that investigated extinction employed delay conditioning in advance. By contrast, in trace conditioning, CS is separated from

the US by a temporal gap, resulting in prolonged acquisition times and a larger number of trials being required to form an association. The length of the temporal gap and its distance to the subsequent stimulus also exerts a strong influence. When the US is followed immediately by the next CS, *backward conditioning* (US-CS associations) or *contextual conditioning* can occur. In backward conditioning, the US is associated with the next CS, so that no conditioned response is established (Hall, 1984). Contextual conditioning describes the association of the CS with contextual cues (Marchand et al., 2004, Marschner et al., 2008). Hence, there is no contiguity in trace conditioning. While in general, delay and trace conditioning involve comparable fear-related networks, activation of the hippocampus is typical of trace conditioning. In trace conditioning, hippocampal activation is required to bridge the gap between CS and US, retaining a memory trace which is needed to form an association between CS and US (Bangasser et al., 2006). The hippocampus is involved in trace conditioning irrespective of the length of trace interval. However, animal data show that some neurons in the hippocampus encode the duration of trace interval (McEchron et al., 2003). Thus we assume that the level of hippocampal activation may be enhanced by increasing the length of trace interval.

Another important variable contributing to heterogeneity of neuroimaging results is the CS-US pairing or contingency rate. Effects of CS-US-contingency on conditioning have been repeatedly described in the psychological and behavioural literature (Schurr and Runquist, 1973, Leonard, 1975, Svartdal, 2003, Dunsmoor et al., 2007, Dunsmoor et al., 2008). Contingency rates determine how fast conditioned responses are acquired, and regulate extinction processes. Our review reveals that the activation of the core fear network consisting of amygdala, insula and ACC is independent of pairing rate, but the time courses of neural responses and the degree of activation may be influenced by contingency. In general, a predictable US is less aversive than an unpredictable US. Therefore, the continuous (100%) pairing of CS+ and US reduces fear responses and activity in fear-related brain areas (Dunsmoor et al., 2007, Dunsmoor et al., 2008), and promotes the habituation of the amygdala (Buchel et al., 1998, LaBar et al., 1998, Tabbert et al., 2005, Straube et al., 2007), relative to intermittent pairing. Nevertheless, the majority of the studies cited in this review employed a continuous pairing paradigm. In intermittent procedures, US expectancy and response frequency is decreased, which slows conditioning and prolongs the extinction phase (Phelps et al., 2004, Dunsmoor et

al., 2007, Dunsmoor et al., 2008). The choice of these pairing parameters has important implications for analysis of imaging data. First, in the light of habituation processes, analysis of time by condition interactions may well improve the detection of amygdala activation. Second, the choice of the contingency rate influences the definition of contrasts of interest between test and control conditions. The cited studies differ in their contrasts of interest which may also influence resulting activation and complicate comparing studies even further. For example, in a 100% pairing design resulting differences in neural responses may be confounded by US-induced BOLD changes. In contrast, in a partial reinforcement design, differences in neural responses are only due to the anticipation of the US.

Our review also illustrates that there is an ongoing controversy on the role of contingency awareness. It seems clear that awareness of the CS-US contingency bridges the CS-US gap in trace conditioning (Knight et al., 2006, Weike et al., 2007). Therefore, it may be very important for trace conditioning, but less so for delay conditioning. Still, this topic requires further investigation. While some researchers found autonomic fear reactions only in contingency-aware subjects, others reported activation of the fear-network independently of contingency awareness (Hamm and Weike, 2005, Tabbert et al., 2006, Klucken et al., 2008). For example, Phelps et al. (2001) showed that instructions alone can induce fear and that activation of the amygdala can occur without direct experience of the aversive event (Phelps et al., 2001). Tabbert et al. (2006) explicitly investigated the effect of contingency awareness. They either informed their subjects about the relationship of CS and US or prevented contingency detection by employing a distracter figure or a working-memory task. Amygdala and the OFC were only activated in the unaware group (Tabbert et al., 2006), but Klucken et al. (2008) found activation of fear-related areas independent of awareness (Klucken et al., 2008). However, robust conditioned skin-conductance responses have been observed only in aware participants who acquired a cognitive representation of CS-US-contingencies, and who were able to recall the correct contingency (Hamm and Weike, 2005). At this moment, concrete advice as to whether participants should be informed about contingency to obtain faster conditioning responses, is premature.

Concerning the modality of the US and CS, 33 of the 46 studies employed a tactile US, making it the most frequently applied US. Only nine studies used auditory aversive stimuli which may be due to the surrounding and interfering scanner noise. To the best

of our knowledge, the problem of scanner noise as being aversive itself has not been discussed so far. The activation of the key fear network including amygdala, ACC and insula seems to be independent of the applied stimuli (auditory, olfactory, tactile, and visual). Nevertheless, many studies do not show activation of the key fear network or observe modality-specific activations. In fear conditioning with tactile US, activation of the thalamus, the striatum, somatosensory and of motor cortices is often reported. These areas are also associated with the nociceptive system, pain anticipation and perception (e.g. (Coghill et al., 1994, Rainville et al., 1997, Bornhovd et al., 2002, Porro et al., 2002)). The nociceptive system includes the somatosensory cortices, ACC, insula, prefrontal and parietal cortices (Schnitzler and Ploner, 2000). Koyama et al. (2005) showed that ACC activation increases with the magnitude of expected pain, and pain-intensity (Koyama et al., 2005). The thalamus, a major relay site for nociceptive inputs to cortical and subcortical structures, is thought to be responsible for the onset plasticity in the amygdala during fear conditioning (Quirk et al., 1997). Therefore, we suggest that a "pain-fear network" may be activated during tactile fear conditioning. The one study on olfactory conditioning reported mainly activations of amygdala, ACC and OFC (Gottfried and Dolan, 2004). Odour perception is more often related to disgust than to fear. Disgust and fear are basic emotions with different elicitors and expressions, and appear to be mediated by different neuronal circuits (Schienle et al., 2002, Schafer et al., 2005, Stein et al., 2006, Stark et al., 2007). Therefore, further research is needed to clarify if olfactory conditioning activates a "disgust-fear-network" rather than a mere "fear-network". To conclude, it seems likely that odours, visual or acoustic stimuli may weaken conditioning effects and may cause activations in different brain regions than electrical stimuli. But to the best of our knowledge, this has never been tested directly in neuroimaging studies. Again, research is needed to quantify the effect of common CS-US-modality on neuroimaging results.

Concerning the modality of the CS, the majority of the studies used visual stimuli as CS, especially photographs of human faces. Faces as CS might be more emotionally relevant to human subjects than tones or coloured lights (Vuilleumier and Pourtois, 2007). However, there seems to be a gender-related effect that needs to be considered in neuroimaging studies. For example, in women, the presentation of faces leads to stronger and persisting amygdala activation, while amygdala activation in men decreases rapidly (Williams et al., 2005). Moreover, it is known that the amount of

preexposure influences the outcome of aversive learning. These phenomena, so called "*latent inhibition*" and "*US-preexposure effect*", emphasize that novel and unknown CS and US produce more robust conditioning effects than familiar stimuli (Dunsmoor et al., 2007, Mineka and Oehlberg, 2008). The disadvantage of unfamiliar stimuli is the mixing of novelty effects and conditioning effects.

Finally, it is very important to ensure that conditioning really takes place by sampling a second psycho-physiological or behavioural measure to avoid contamination of successful conditioning with unsuccessful trials. Skin-conductance responses as measures of autonomic responses have been widely investigated and are well validated (Knight et al., 2005). Classifying subjects as "responders" and "non-responders", or classifying single trials as "successful" or "not successful" conditioning based on autonomous measures has proven extremely useful, to exclude erroneous trials or subjects from further analysis (e.g. (Phelps et al., 2004, Cheng et al., 2006)). However, technical issues in the scanner environment have to be solved. Measurement of skin-conductance responses may well prolong the experiment beyond critical time values for such experimental designs. On the other hand, verbal ratings may easily be influenced and consciously manipulated. Alternatives are the assessment of heart rate, or of the startle reflex, which is an elegant measure if an eye-tracker or electromyography is available. In all, the combination of different psycho-physiological and behavioural methods has proven valuable to assure that conditioning has really taken place.

2.5.1 Strengths and Limitations

To the best of our knowledge, this review is the first summarizing current literature on neuroimaging fear conditioning and extinction and providing an overview on similarities and heterogeneities between study results. In this review, we focused on discussing experimental factors that are typical for conditioning paradigms, such as the design (delay, trace), the contingency rate, the contrasts of interests, or the stimuli (CS, US), and that may contribute to the reported heterogeneity in neuroimaging results. Other experimental factors that may influence fear conditioning and fMRI-studies are, for example, the MR-sequence (e.g. (Bellgowan et al., 2006, Stocker et al., 2006)), the sample size, gender of participants (e.g. (Guimaraes et al., 1991, Butler et al., 2005)), genetic variables (e.g. (Garpenstrand et al., 2001, Kamprath et al., 2006, Stoppel et al.,

2006, Finger et al., 2007)), or personality factors (e.g. (Sugiura et al., 2000, Keightley et al., 2003, Rauch et al., 2005, Most et al., 2006, O'Gorman et al., 2006, Gallinat et al., 2007, Otto et al., 2007, Rauch et al., 2007, Hooker et al., 2008)). These variables may also contribute to the diversity of neuroimaging results. Another limitation is that our search did not include conditioning studies that were conducted on context conditioning, on patients, on pharmacological interventions, or that included another experimental task. However, we excluded these studies to limit the number of potential influencing variables.

2.5.2 Conclusion

This review provides an overview of 46 current neuroimaging studies on fear conditioning and extinction. Neuroimaging yields new in-vivo evidence with respect to humans revealing and corroborating a consistent pattern of key areas in aversive conditioning and extinction. These structures encompass the amygdala, ACC, and insular cortex for both associative conditioning and extinction. This confirms previous electrophysiological or lesion studies on animals. The key fear-related brain areas, such as amygdala, ACC and insula, are activated independently of specific design parameters. However, some studies still do not report these findings or observe additional modality-specific activations. We pinpointed a number of methodological differences between the functional imaging studies and conclude that these may contribute to the observed variance between results. Prime candidate factors for modifying brain activation patterns are the choice of conditioning protocol, CS-US contingency, and modality of the US. Thus, the contingency and timing parameters, the modality of the CS and US, as well as the assessment of conditioned responses are important for conducting and interpreting neuroimaging studies on fear conditioning and extinction.

Table 1 Forty-six studies on aversive conditioning and /or extinction, with forty studies on delay conditioning (including seven studies on extinction), two studies on trace, and four studies on delay and trace conditioning, with focus on main results of acquisition and/ or extinction of conditioned responses (in alphabetic order).

No.	Study name	Subjects			Design	Technique	CS-US-contingency	CS	US	Independent assessment of the conditioning process	Neuroanatomical correlates of acquisition and extinction of conditioned responses
		N	M/F	Mean Age in years							
1	Anders et al., 2005	10	6/4	40	Delay	fMRI	50 %	Neutral faces	Verbal	Online: SCR, startle eye blink amplitude, verbal reports of arousal and emotional valence	**Delay conditioning (assessed as (Acquisition > Habituation)):** MPFC (R), FOP (R)
2	Blaxton et al., 1996	7	1/6	27	Delay	PET	100 %	Tones	Air blast	Online: eye blink	**Delay conditioning (assessed as (conditioning > pseudoconditioning)):** ACC, cerebellum (L, R), frontal L (L, R), hippocampal formation (R), lingual G (L), pons, thalamus (L)
3	Buchel et al., 1998	9	7/2	-	Delay	fMRI	50 %	Neutral faces	Sound	Online: SCR	**Delay conditioning (assessed as (CS+unpaired>CS-)):** ACC (L, R), amygdala (L, R), ant insula (L, R), med parietal C (R), PMA (L, R), red N (L, R), SMA (R)
4	Buchel et al., 1999	11	6/5	-	Trace	fMRI	50 %	Tones	Sound	Online: SCR	**Trace conditioning (assessed as (CS+unpaired>CS-)):** ACC (L, R), amygdala (L, R), post secondary auditory C (L, R), DLPFC (L, R), hippocampus (L, R), ant insula (L, R), vent putamen (L, R), med thalamus (L, R)
5	Carlsson et al., 2006	9	4/5	25	Delay	fMRI	100%	Visual Cue	Shock	Post: valence, pain-intensity, anxiety ratings	**Delay Conditioning (assessed as (correlated > uncorrelated trials):** med frontal L (R), post insula (L, R), SII (L, R), SI (L), hippocampus (L, R), amygdala (L), visual C (L, R), cerebellum, OFC (L), premotor area (L)
6	Carter et al., 2006	14	9/5	24.7	Delay Trace	fMRI	Delay: 50 % Trace: 100%	Abstract coloured images	Shock	Online: SCR, US-expectancy rating Post: CS-US-contingency rating	**Delay and Trace conditioning (assessed as correlation between BOLD and SCR):** amygdala (L), hippocampus (L, R), occipital C (Post pole) **Delay and Trace conditioning (assessed as correlation between BOLD and US-expectancy**): mid frontal G (L , R), parahippocampal G (L)
7	Cheng et al., 2003	20	8/12	24.85	Delay	fMRI	100 %	Visual cue	Shock	Online: SCR	**Delay conditioning (assessed as (paired>unpaired subjects); ROI analysis):** amygdala (R), mid occipital G (R)
8	Cheng et al., 2006	17 13	8/9 4/9	23.35 22.38	Delay Trace	fMRI	100 %	Coloured lights	Shock	Online: SCR, US-expectancy rating	**Delay and Trace conditioning (assessed as (CS+response trials > CS+ nonresponse trials); ROI analysis):** amygdala (R)

9	Cheng et al., 2007	12	6/6	20.4	Delay	fMRI	100%	Visual cue	Shock	Online: SCR, US-expectancy rating	**Delay Conditioning (assessed as (CS trials with early period CR > CS trials with late period CR); ROI analysis):** amygdala (R)
10	Cheng et al., 2008	11	6/5	23.6	Delay Trace	fMRI	100 %	Tones	Air blast	Online: eye blink Post: CS-US-contingency questionnaire	**Delay and Trace conditioning (assessed as (late acquisition>early acquisition); ROI analysis):** MTL (L, R) **Delay and Trace conditioning (assessed as (delay and trace)>baseline; ROI analysis):** cerebellum (L) **Trace conditioning (assessed as (trace>delay); ROI analysis):** MTL (R)
11	Dimitrova et al., 2004	20	11/9	26.2	Delay	fMRI	100%	Tone	Shock	Online: heart rate, EMG (leg withdrawal reflex)	**Delay Conditioning (assessed as (Extinction – unpaired phase)):** inf temporal G (L), Hippocampus (R), med temporal G (R, L), fusiform G (R) **Delay conditioning (assessed as linear regression in the acquisition phase):** fusiform G (R), Hippocampus (R), inf temporal G (R), med temporal G (R), lingual G (R), sup temporal G (R)
12	Doronbekov et al., 2005	10	10/0	23.4	Delay	PET	?	Photos	Aversive videotape	Online: CS-fear rating	**Delay conditioning (assessed as (second photo phase > first photo phase)):** amygdala (R), PCC (L), sup frontal G (R), sup temporal G (L) **Delay conditioning (assessed as (conditioning >control condition)):** amygdala (R), PCC (L), parieto-occipital S (R)
13	Dunsmoor et al., 2007	18	7/11	30.17	Delay	fMRI	100 % 50 %	Tones	Noise	Online: SCR, US-expectancy rating	**Delay conditioning (with increasing CS-US-pairing-rate relative to baseline):** ACC (L, R), amygdala (L, R), fusiform G (L, R), inf occipital G (L), precentral G (L), precuneus (L) **Delay conditioning (with 50 % CS-US-pairing relative to 100 % and CS-):** DPFC (L), insula (L, R)
14	Dunsmoor et al., 2008	18	7/11	30.17	Delay	fMRI	100 % 50 %	Tones	Noise	Online: SCR, US-expectancy rating	**Delay conditioning (assessed (as CS50+ > CS100); Regions demonstrating UR diminution):** amygdala (R), ACC (L, R), auditory C (R), cerebellum (L, R), DLPFC (L), inf parietal Lo (L, R), thalamus (L, R)
15	Fischer et al., 2000	8	0/8	25.6	Delay	PET	25 %	Neutral or aversive videotapes	Shock	Online: non-specific electrodermal fluctuations (NSF), SCL, state anxiety (STAI-S), subjective units of distress (SUD), US-expectancy rating	**Delay conditioning (assessed as (rCBF before > rCBF after paired shocks); Regions with increased rCBF):** ACC (L, R), cerebellum, PFC (R), hypothalamus (L, R), midbrain central gray, globus pallidus (L), thalamus (L, R) **Delay conditioning (assessed as (rCBF before > rCBF after paired shocks); Regions with decreased rCBF):** ACC (L), amygdala (L, R), OFC (L), PFC (L, R), occipital C (L, R), parietal C (L, R), temporal C (L, R) **Delay conditioning (assessed as (rCBF before > rCBF after**

											unpaired shocks); Regions with increased rCBF): ACC (R), PFC (R), hypothalamus (L, R), insula (L), midbrain central gray, putamen (L), thalamus (R) **Delay conditioning (assessed as (rCBF before > rCBF after unpaired shocks); Regions with decreased rCBF):** ACC (L), amygdala (R), cingulate C (L) (BA 26, 29, 30), OFC (L), hippocampus (R), occipital C (L, R), temporal C (L, R) **Delay conditioning (assessed as (paired x unpaired shocks)):** cerebellum (L), temporal C (R)
16	Fischer et al., 2002	6	0/6	27.8	Delay	PET	33 %	Visual white noise; snake videotapes	Shock	Online: SCR	**Delay conditioning (biologically relevant CS; Regions with increased rCBF):** frontal C (R) **Delay conditioning (biologically relevant CS; Regions with decreased rCBF):** hippocampus (L), temporal C (L, R)
17	Fredrikson et al., 1995	16	0/16	31.4	Delay	PET	100 %	snake and spider videotape	Shock	Online: heart rate, SCR, state anxiety (STAI-S), subjective units of distress (SUD)	**Delay conditioning (assessed as (scans before>after shock delivery); Regions with increased rCBF):** ACC (L), PCC (L), hypothalamus (L, R), parietal C (L), premotor area (L), SI (L), thalamus (L, R) **Delay conditioning (assessed as (scans before>after shock delivery); Regions with decreased rCBF):** secondary visual C (L)
18	Furmark et al., 1997	8	0/8	30.4	Delay	PET	100 %	Snake video	Shock	Online: SCR	**Delay conditioning (assessed as (scans before>after shock delivery)):** amygdala (L)
19	Gottfried and Dolan, 2004	16	7/9	24	Delay Extinction	fMRI	50 %	Neutral faces	Odours	Online: RT (indication task) Post: CS-US-contingency interview, CS-valence ratings	**Delay conditioning (assessed as (CS+unpaired>CS-)):** dorsomedial amygdala (R), insula (L, R), rostromedial OFC (L), vent midbrain (L) **Delay conditioning + Extinction:** amygdala (L, R), rostromedial OFC (L), VMPFC (L), insula (R), vent striatum (L, R) **Extinction (assessed as (CS+unpaired>CS-)):** amygdala (L, R), caudomedial OFC (R), VMPFC (L), insula (L, R) **Extinction – Conditioning:** amygdala (L, R), cau OFC (R), med OFC (R)
20	Hugdahl et al., 1995	5	5/0	22	Delay	PET	100 %	Tones	Shock	Pre: SCR Post: SCR	**Delay conditioning (assessed as (Extinction – Habituation)):** DLPFC (R), inf frontal C (R), mid frontal C (L), OFC (R), sup frontal C (R), inf temporal C (R), mid temporal C (R), temporo-occipital junction (L),
21	Jensen et al., 2003	11	6/5	28	Delay	fMRI	33 %	Geo. visual figures	Shock	-	**Delay conditioning (assessed as (CS+unpaired>CS-)):** ACC (R), ant insula (L, R), vent striatum (L, R)
22	Klucken et al., 2008	32	14/18	23.26	Delay	fMRI	100 %	Geo. visual figures	Aversive pictures (IAPS)	Online: SCR Post: CS-valence, -arousal, -fear, -disgust ratings, CS-	**Delay conditioning (assessed as (CS+>CS-)):** ACC (L, R), amygdala (R), insula (L), lat OFC (L), N accumbens (L, R), occipital C (L), thalamus (L)

										US-contingency rating	
23	Knight et al., 1999	10	4/6	27.4	Delay	fMRI	100 %	Light	Shock	-	**Delay conditioning (assessed as (paired>control group); ROI analysis):** ACC, retrosplenial C, visual C
24	Knight et al., 2004	30	13/17	24.5	Delay Extinction	fMRI	100 %	Light	Shock	Online: SCR	**Delay conditioning (assessed as (paired>control group); ROI analysis):** amygdala (L, R), hippocampus (L) **Extinction (assessed as (paired>control group) ; ROI analysis)** amygdala (L, R), hippocampus (L)
25	Knight et al., 2004a	17	8/9	23	Delay Trace	fMRI	100 %	Geometric visual figure	Shock	Online: SCR, US-expectancy rating	**Delay and Trace conditioning (assessed as (CS+ delay and trace)>CS-; ROI analysis):** ACC, mid occipital G (L, R), supramarginal G (L), med thalamus (L, R) **Delay and Trace conditioning (Regions with decreased activation):** ACC, PCC, sup frontal G (L), hippocampus, inf temporal G (L), mid temporal G , sup temporal G (L), postcentral G (R) **Trace conditioning (assessed as trace interval > (CS+ and CS-)):** mid frontal G (L, R), hippocampus, frontal operculum (L, R), inf parietal L (R), SMA
26	Knight et al., 2005	9	4/5	28.33	Delay	fMRI	80 %	Tones	Noise	Online: SCR	**Delay conditioning (assessed as association with conditioned SCR):** amygdala (R), cerebellum (R), insula (R), med PFC (L), mid frontal G (L), precentral G (L), sup temporal G (L)
27	LaBar et al., 1998	10	5/5	22.5	Delay Extinction	fMRI	100 %	Geometric visual figure	Shock	Post: CS-US-contingency rating Follow-up study (same sample): SCR	**Delay conditioning (assessed as (CS+>CS-)):** ros ACC, cau ACC, mid frontal G (L), sup frontal G (L), periamygdaloid C (L), precentral G (R), striatum (L, R), sup temporal G (L) **Extinction (assessed as (CS+>CS-)):** amygdala (L), caudate N (L), mid frontal G (L), sup frontal G (L, R), precentral G (R), sup temporal G (R)
28	Li et al., 2008	12	4/8	-	Delay	fMRI	100 %	Odour	Shock	Pre: discrimination test, US-intensity, -valence, -familiarity ratings Online: SCR Post: discrimination test, US-intensity, -valence, -familiarity ratings	**Delay conditioning (assessed as discrimination of perceptual cues; CS+>CS-; postconditioning > preconditioning):** amygdala, OFC (L, R), ant piriform C, post piriform C
29	Logan and Grafton, 1995	12	5/7	23	Delay	PET	90 %	Tone	Air blast	Online: eye blink	**Delay conditioning (assessed as(paired > unpaired scans)):** inf cerebellum (L, R), ant cerebellar vermis, cerebellar C (L), cerebellar deep nuclei or pontine tegmentum (L), hippocampal formation (R), vent striatum (L, R), inf thalamus/ red N (R), mid temporal G (R), occipitotemporal fissure (L)
30	Molchan et al., 1994	8	0/8	22.3	Delay	PET	100 %	Tone	Air blast	Online: eye blink	**Delay conditioning (assessed as (paired > unpaired scans); Regions with increased rCBF:**

					Extinction						PCC (L), transverse temporal C (L, R) **Delay conditioning (assessed as (paired > unpaired scans); Regions with decreased rCBF:** cerebellar C (R), inf frontal C (R), insula (R), neostriatum (R), inf parietal C (R) **Extinction (assessed as (unpaired > paired scans); Regions with increased rCBF:** inf frontal C (L, R) **Extinction (assessed as (unpaired > paired scans); Regions with decreased rCBF:** PCC (L), pons (L), sup temporal C (L, R)
31	Morris et al., 1997	6	6/0	32.7	Delay	PET	100 %	Faces	Noise	Online: SCR Post: CS-US-contingency-awareness assessment	**Delay conditioning (assessed as (CS+>CS-)):** OFC (R), sup frontal G (R), pulvinar N of the thalamus (R), anterolateral thalamus (R)
32	Morris et al., 1998	6	6/0	27.7	Delay	PET	40 %	Tones	Noise	Online: SCR, discrimination task Post: CS-US-contingency - awareness interview	**Delay conditioning (assessed as (CS+ > CS-)):** OFC (R) **Delay conditioning (assessed as auditory cortex regression analysis).** amygdala (L, R), OFC (R), basal forebrain, med geniculate N (L)
33	Morris and Dolan, 2004	12	-	-	Delay	fMRI	33 %	Neutral Faces	Noise	Online: RT (decision task), SCR (unusable)	**Delay conditioning (assessed as (CS+>CS- during acquisition)):** ACC (R), dor amygdala (L, R), insula (R), post thalamus (L, R)
34	Nitschke et al., 2006	21	10/11	19	Trace	fMRI	100%	Geometric visual figure	Aversive pictures (IAPS)	-	**Trace conditioning (assessed as (anticipation of aversive > neutral stimuli); ROI analysis):** dor ACC, ros ACC, amygdala (L, R) DLPFC (R), OFC (L, R), insula (L, R)
35	Petrovic et al., 2008	27	27/0	-	Delay	fMRI	50%	Faces	Shock	Pre: CS-sympathy ratings Online: SCR Post: CS-sympathy ratings, CS-US-contingency-awareness interview	**Delay Conditioning (assessed as (CS+>CS-); ROI analysis):** amygdala (L, R), fusiform G (L, R)
36	Phelps et al., 2001	12	6/6	-	Delay	fMRI	0 %	Blue and yellow squares	Shock	Online: SCR Post: CS-US-contingency-awareness interview	**Delay conditioning (assessed as (threat vs. safe conditions)):** ACC, dor amygdala (L), basal forebrain, PFC, insula (L, R), PMA (R), striatum
37	Phelps et al., 2004	11	5/6	-	Delay Extinction	fMRI	33 %	Geometric visual figure	Shock	Online: SCR	**Delay conditioning (assessed as (CS+>CS-)):** caudate N (L, R), dor ACC, insula (L, R), IPL (L, R) **Extinction (assessed as (CS+>CS-)):** caudate N (R), dor ACC, insula (L, R)
38	Pine et al., 2001	7	4/3	33.6	Delay	fMRI	100 %	Coloured lights	Air blast	-	**Delay conditioning (assessed as (CS+>CS-);ROI analysis):** amygdala (R)
39	Ploghaus et al., 1999	12	7/5	26	Delay	fMRI	100 %	Coloured lights	Thermal stimulus	Post: CS-US-contingency-awareness interview	**Delay conditioning (assessed as (anticipation of aversive > neutral stimuli)):** cerebellum, insula, MFL
40	Schiller et al., 2008	17	9/8	-	Delay	fMRI	33%	Mildly angry faces	Shock	Online: SCR	**Delay Conditioning (assessed as (CS+>CS-)):** dor ACC, amygdala (L), caudate N (L, R), sup frontal G, insula (L, R), midbrain (L), putamen (L), thalamus (R) **Reversal Delay Conditioning (assessed as (new CS->new CS+):** VMPFC

41	Schreurs et al., 1997	10	0/10	24.5	Delay Extinction	PET	100 %	Tone	Air blast	Online: eye blink	**Delay conditioning (assessed as (paired > unpaired scans); Regions with increased rCBF)**: lat temporooccipital G (L), sup temporal G (R), trans temporal G (R) **Delay conditioning (assessed as (paired > unpaired scans); Regions with decreased rCBF)**: cerebellar C (L, R), inf prefrontal L (L), inf temporal pole (L), sup temporal pole (R) **Extinction (assessed as (unpaired > paired scans); Regions with increased rCBF)**: cerebellar C (R) **Extinction (assessed as (unpaired > paired scans); Regions with decreased rCBF)**: lat temporooccipital C (L), sup temporal C (R), trans temporal C (R)
42	Schreurs et al., 2001	10 1	0/10 0/11	22.3 69.2	Delay	PET	100%	Tone	Air blast	Online: eye blink Post: CS-US-contingency-awareness interview	**Delay conditioning (assessed as paired scans; Regions with increased rCBF)**: auditory C (L, R), PCC, MTL (L) **Delay conditioning (assessed as paired scans; Regions with decreased rCBF)**: caudate N (R), cerebellum (L, R), inf PFC (L, R), midbrain
43	Straube et al., 2007	12	2/10	21.1	Delay	fMRI	50 %	Visual stimulus	Shock	Pre: CS-valence, -arousal, -threat ratings Online: RT (discrimination task, distraction task) Post: CS-valence, -arousal, -threat ratings Follow-up study (independent sample): SCR, CS-valence ratings, US-intensity rating, CS-US-contingency rating	**Delay conditioning (assessed as (CS+unpaired>CS-)):** amygdala (L), brainstem (R), cingulate C (L, R), claustrum (R), DLPFC (L, R), DMPFC (L, R), insula (L, R), midbrain (R), PMA (L, R), SII (L, R), SMA (L, R), sup temporal S (L, R), thalamus (R)
44	Tabbert et al., 2005	18	6/12	-	Delay	fMRI	100 %	Geometric visual figure	Shock	Online: SCR	**Delay conditioning (assessed as (CS+>CS-); ROI analysis):** amygdala (L), caudate N (L), OFC (L, R), occipital C (L), SMA (L)
45	Timmann et al., 1996	4	4/0	25.5	Delay	PET	100%	Tones	Shock	Online: eye blink, EMG (flexion response)	**Delay conditioning (assessed as correlation between rCBF and CR):** cerebellum, hippocampus (L, R), frontal C (L, R)
46	Yaguez et al., 2005	8	5/3	22	Delay Extinction	fMRI	Acquisition: 100 % Anticipation: 50 %	Coloured circles	Others, Air blast	-	**Delay conditioning (assessed as (CS->CS+ in the acquisition phase)):** ACC, cerebellum (L, R), mid ACC (R), inf frontal G (L, R), insula (L, R), postcentral G (L, R), SI (R), SII (L, R), SMA (L, R), sup temporal G (L, R) **Delay conditioning (assessed as (CS+>CS- in the anticipation phase)):** angular G (L, R), brainstem (R), mid ACC (R), cerebellum (L), DLPFC (R), inf frontal G (R), insula (L, R), SMA (R),

	supramarginal G (R) **Extinction (assessed as (CS+>CS-)):** ACC (R), mid ACC (R), DLPFC (R), mid frontal G (R), insula (L, R), SII (R), SMA (R)

Abbreviations: ACC: anterior cingulate cortex, ant: anterior; BA: Brodman area, cau: caudal, C: cortex, CR: conditioned response, CS: conditioned stimulus, dor: dorsal, DPFC: dorsal prefrontal cortex, DLPFC: dorsolateral prefrontal cortex, DMPFC: dorsomedial prefrontal cortex, EMG: electromyography, F: female, FOP: frontal operculum, G: gyrus, inf: inferior, IAPS: International Aversive Picture System, IPL: inferior parietal lobe, lat: lateral, L: left, Lo: lobule/ lobe, M: male, med: medial, mid: middle, MFL: medial frontal lobe, MPFC: medial prefrontal cortex, MTL: medial temporal lobe, N: nucleus, No.: number, OFC: orbitofrontal cortex, post: posterior, PCC: posterior cingulate cortex, PFC: prefrontal cortex, PMA: premotor area, R: right, rCBF: regional cerebral blood flow, trans: transverse, RT: reaction time, ros: rostral, SCR: skin-conductance response, SCL: skin-conductance level, SI: primary somatosensory cortex, SII: secondary somatosensory cortex, SMA: supplementary motor area, S: sulcus; sup: superior, vent: ventral, VMPFC: ventromedial prefrontal Cortex, US: unconditioned stimulus

3 Experiment – Fear Conditioning and Extinction[2]

3.1 Introduction

Fear conditioning is vital for the detection of danger, initiation of self-protection mechanisms, and for survival of a species. The term *conditioning* refers to the process of learning the association between two previously unrelated stimuli (Pavlov, 1927). In a typical differential fear conditioning design, a previously neutral stimulus (CS+) is associated with an aversive and fear-inducing US and becomes intrinsically aversive, while another neutral stimulus remains unpaired (CS-) (Maren, 2001). *Extinction* is defined as the repeated exposure of the originally neutral stimulus without presenting the aversive stimulus, which gradually eliminates the learned fear reaction (Myers and Davis, 2002).

Fear conditioning has proven to be an extremely robust and rapid experimental approach for studying the neurobiological substrates of fear and anxiety in animals and humans (Lissek et al., 2005, Anderson and Insel, 2006). Numerous neuroimaging studies revealed a core neural network involved in conditioning and extinction, consisting of amygdala, insula and ACC (see for review (Sehlmeyer et al., 2009)). Thus, amygdala activity is associated with variability in the individual fear-conditioning and -extinction response. In addition, research on humans and animals have highlighted the medial PFC and especially the dorsal ACC as principal structures of the brain's extinction circuitry (Morgan et al., 1993, Quirk et al., 2003, Phelps et al., 2004, Lang et al., 2009). These areas regulate the expression of fear by inhibiting the amygdala, such that the fear-conditioned stimulus is prevented from causing a conditioned fear response (Gottfried and Dolan, 2004, Phelps et al., 2004, Quirk et al., 2006, Sotres-Bayon et al., 2006).

Psychiatric disorders associated with increased anxiety and fear levels, for example posttraumatic stress disorder, phobias, or panic disorder, exemplify how misguided fear conditioning might render originally innocuous stimuli fear-inducing and threatening. In addition, facilitated fear conditioning and impaired extinction of acquired fear are core

[2] Sehlmeyer C, Dannlowski U, Schöning S, Kugel H, Pyka M, Pfleiderer B, Zwitserlood P, Schiffbauer H, Heindel W, Arolt V and Konrad C, "Neural correlates of trait anxiety in fear extinction", Psychological Medicine, 16: 1-10, 2010 © Cambridge University Press, reproduced with permission.

symptoms of anxiety disorders (Blechert et al., 2007, Michael et al., 2007). Accordingly, fear extinction represents the main therapeutic ingredient of exposure-based psychotherapies (Myers and Davis, 2002, Lissek et al., 2005, Anderson and Insel, 2006).

Anxiety-related personality traits, such as trait anxiety, which are regarded as stable and biological predispositions (Pujol et al., 2002, Omura et al., 2005, Rauch et al., 2005, Most et al., 2006), are closely related to pathological anxiety (Schmidt et al., 2008) and may influence the risk of psychiatric disorders (Bienvenu et al., 2001). Trait anxiety reflects an individual's general disposition to experience anxiety-relevant feelings or thoughts or to show anxiety-related behaviours (Spielberger, 1979). It is a stable personality trait describing the tendency to respond fearfully to a wide variety of unspecific stressors (Spielberger, 1972) and is regarded as a risk factor for anxiety disorders (Chambers et al., 2004). Highly trait-anxious subjects tend to perceive more situations as threatening and experience more frequently intense and sustained anxiety states compared to subjects with low trait anxiety (Spielberger, 1972, Spielberger, 1979, Spielberger, 1983, Mathews and MacLeod, 2005). Besides, it is assumed that anxiety-related personality factors are also associated with enhanced conditionability or impaired extinction of learned fear (Hooker et al., 2008, Barrett and Armony, 2009). However, the literature on this topic is still equivocal (Pineles et al., 2009).

An overactive neuronal fear circuitry and reduced recruitment of prefrontal control have been proposed as neural correlates of facilitated fear conditioning and reduced extinction (Bishop et al., 2004, Bishop, 2007, Haas et al., 2007, Hooker et al., 2008, Bishop, 2009). It has been shown, for example, that high trait anxiety is related to amygdala dysregulation during the processing of aversive and neutral stimuli in healthy volunteers (Bishop et al., 2004, Etkin et al., 2004, Dickie and Armony, 2008, Kienast et al., 2008, Mujica-Parodi et al., 2009) or even during the extinction of conditioned fear (Barrett and Armony, 2009). Moreover, anxiety disorders are associated with hypo-activation of the dorsal ACC during the regulation of emotions (Etkin and Wager, 2007). As the relations between anxiety-related personality traits and increased neurobiological vulnerability for fear acquisition and extinction are not fully understood, they are of specific interest in this current study.

We used event-related fMRI to clarify the relationship between amygdala reactivity, the involvement of the medial prefrontal cortex and trait anxiety during the acquisition

and extinction of conditioned fear in healthy subjects. We hypothesize that highly trait-anxious subjects exhibit enhanced fear conditioning and reduced extinction of conditioned responses, reflected by the amounts of amygdala and prefrontal activation.

3.2 Methods

3.2.1 Subjects

Thirty-two healthy volunteers (12 male, 20 female; mean age = 23.6 years, SD = 4.41, range 19 - 39 years) participated in the study. All were right-handed (Edinburgh Handedness Inventory (Oldfield, 1971)), and recruited by notice or advert in the local press. Exclusion criteria were medical, neurological and psychiatric diseases or MRI-contraindications. No family history of mental illness or hereditary neurological disorders in first-degree relatives was reported. All participants gave written informed consent in accordance with the guidelines of the ethical standards of the Declaration of Helsinki. All procedures were approved by the local Ethical Review Board.

On the day of scanning, participants completed the trait version of the German *State-Trait Anxiety Inventory (STAI-T)* (Laux, 1981), a self-report scale to determine the level of trait anxiety. To ensure that the top of the range of trait anxiety scores did not represent individuals with undiagnosed anxiety disorders, standardized clinical assessment with the German version of the *Structured Clinical Interview* (*SCID-I*) was performed according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (Wittchen et al., 1997). No evidence of anxiety disorders or any other current or previous axis I psychiatric disorder was found.

3.2.2 Materials and procedures

In a differential conditioning paradigm, pictures of two different neutral male faces selected from the MacArthur-McDonnell face library (NimStim; (Tottenham et al., 2002)) served as conditioned stimuli (CS-, CS+). Stimuli were grey in color, presented for 2 seconds in the centre of a black screen. A pseudorandomized order was used with the restrictions that (a) no more than two successive presentations of the same CS would occur and (b) that the CSs were equally distributed within each half of the acquisition

period. The two faces were counterbalanced as CS+ between participants. The unconditioned stimulus (US) consisted of an acoustic white noise burst (duration 100ms, 95dB). The experiment was divided into 4 phases. During habituation, each CS was shown five times without US. Each of the two acquisition phases consisted of 15 CS-, 15 CS+ without US ($CS+_{unpaired}$) and 5 CS+ with US ($CS+_{paired}$) trails. In this 25% partial reinforcement schedule, the US co-terminated with the presentation of the $CS+_{paired}$ (delay conditioning). Subjects were not informed about this CS-US-contingency. In the following extinction phase, 25 $CS+_{unpaired}$ and 25 CS- trials were presented. Inter-stimulus intervals ranged from 8.5 to 14.5 seconds, during which subjects had to look at a white fixation cross on a black screen.

After each experimental phase, participants rated the valence and arousal of the CSs by means of a 5-point-Lickert scale, the *Self-Assessment Manikin (SAM)* (Bradley and Lang, 1994), ranging from 0="very unpleasant" to 4="very pleasant" and 0="not arousing" to 4="very arousing". They responded by pressing the response buttons of an MRI-compatible response box with the right index and middle finger. Prior to scanning, detailed task instructions were given and participants were familiarized with the task. Post-experimentally, participants were debriefed.

3.2.3 Image Acquisition

MRI data were acquired in a 3-Tesla whole-body scanner (Gyroscan Intera T 3.0, Philips, Best, NL), equipped with master gradients (nominal gradient strength 30mT/m, maximal slew rate 150mT/m/ms). A circularly polarized transmit/receive birdcage head coil with an HF reflecting screen at the cranial end of the scanner was used for spin excitation and resonance signal acquisition. Functional images were acquired during one fMRI run using a T2*-weighted single shot EPI-sequence (TE 32 ms, TR 2000ms, flip angle 90°, slice thickness 3.6 mm without gap, matrix 64 x 64, FOV 230 mm x 230 mm, in-plane resolution 3.6 mm x 3.6 mm). In total, 825 image volumes of 30 transversal slices orientated parallel to the AC-PC line were acquired, resulting in a total scan time of 27 min.

After the completion of the functional scans, a high-resolution 3D T1-weighted structural scan (TE 3.4 ms, TR 7.4 ms, flip angle 9°, 320 0.5mm sagittal slices, FOV

256 mm × 256 mm, matrix 512 × 512 resulting in isotropic voxels with an edge length of 0.5 mm, scan duration 11:09 min) was acquired for anatomical localization.

3.2.4 Behavioural data analysis

During fMRI-scanning, responses of the CS-arousal and -valence ratings were recorded from all 32 subjects. A repeated-measure analysis of variance (ANOVA) with two within-subject factors *phase* (four levels: habituation, acquisition I, acquisition II, extinction) and *stimulus* (two levels: $CS+_{unpaired}$, CS-) within the general linear model as implemented in SPSS 15 for Windows was performed to validate the conditioning effect.

3.2.5 Functional data analysis

Analysis was performed using the *statistical parametric mapping* version 5 software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm). Images for each subject were realigned, slice time acquisition corrected, normalized to the MNI template (Montreal Neurological Institute), and resliced to a voxel size of 2 mm x 2 mm x 2 mm. Data were smoothed with an 8 mm kernel, and subsequently filtered with a high-pass filter (cut-off period of 128 s). Event-related BOLD responses were analysed in SPM5 using the general linear model with a canonical hemodynamic response function as basic function, and separately one regressor for each condition in each phase: $CS+_{unpaired}$, $CS+_{paired}$, and CS-. Paired CS+ was modelled as one event and included as predictor of no interest in the regression analysis. The six movement parameters of the rigid body transformation determined during realignment were introduced as covariates into the model. In order to investigate differences between the phases of the conditioning and extinction procedure, the time courses of conditioning and extinction were split into two sub-phases. The first and second conditioning phases were separated by the SAM-rating. Each phase consists of 35 trials and has the same length. The extinction section was also divided into two sub-phases of same length each lasting 5 minutes and containing 25 trials, referred to here as early and late extinction phase.

In a first-level fixed-effects analysis, one statistical parametric map, and corresponding contrast images for each subject reflecting the contrasts of interest were derived. The

following contrasts of interest were computed: $CS+_{unpaired}$ >CS-, CS-> $CS+_{unpaired}$ for early and late acquisition and extinction phases. The individual contrast images were entered into a second-level random-effects t-test to obtain activation maps across subjects. Based on our prior knowledge about the core areas involved in fear conditioning and extinction, summarized in our review article (Sehlmeyer et al., 2009), *region of interest* (ROI) analyses focused on the right and left amygdalae and the dorsal ACC. The dorsal ACC was defined as a sphere with a radius of 8 mm placed in the most posterior part of the ACC (center x = 0, y = 2, z = 30) (Dannlowski et al., 2009). The left and right amygdala ROIs were defined according to the AAL-Atlas (Tzourio-Mazoyer et al., 2002). Mean contrast estimates were extracted for left and right amygdala in each experimental phase. Linear regression analyses were calculated to determine the effect of trait anxiety on amygdala and ACC activations, during acquisition and extinction phases. These anxiety scores were entered separately as a parametric variable in the analyses (MacCallum et al., 2002). To control for multiple statistical testing, we maintained a cluster-level false-positive detection rate at $p < 0.05$ using a voxel threshold of $p < 0.05$ with a cluster (k) extent empirically determined by Monte Carlo simulations. These were implemented in AlphaSim which accounted for spatial correlations between BOLD signal changes in neighbouring voxels (Forman et al., 1995) (48 voxels for each amygdala and 53 voxels for the dorsal ACC ROI). For analysis of whole-brain activation during conditioning and extinction, we used a standard whole-brain statistical threshold of $p < 0.001$ and $k > 10$ voxels spatial extent.

3.3 Results

3.3.1 Behavioural Results

The mean trait anxiety score was 35.2 (*S.D.* = 7.5), ranging from 22 to 52. The repeated-measures ANOVA yielded significant main effects for stimulus (F (3, 93) = 6.99; $p < 0.001$; $\eta^2 = 0.18$), phase (F (1, 31) = 22.3; $p < 0.001$; $\eta^2 = 0.42$) and a significant stimulus x phase interaction (F (2.3, 71.6) = 3.61; $p < 0.05$; $\eta^2 = 0.1$) for arousal ratings (for details see Table 2). Post-hoc tests revealed that arousal ratings were significantly higher for the $CS+_{unpaired}$ than CS- after both acquisition phases (early: $t_{31} = 3.30$, $p < 0.005$; late: $t_{31} = 4.77$, $p < 0.001$) and after extinction ($t_{31} = 3.42$, $p < 0.005$).

The repeated measures ANOVA yielded a significant stimulus x phase interaction (F (2.3, 72.3) = 5.7; $p < 0.005$; $\eta^2 = 0.15$) for valence ratings. As expected, valence ratings differed significantly between CS+ $_{unpaired}$ and CS- after the late acquisition phase (t_{31} = -4.0, $p < 0.001$). Correlation analysis revealed no significant interactions between trait anxiety and CS ratings.

Table 2 Mean ratings, *S.D.*s and statistical results for valence and arousal ratings of the CS+ and CS- after the experimental phases.

Phase	Valence			Arousal		
	(*Mean* ± *S.D.*)		Test statistic	(*Mean* ± *S.D.*)		Test statistic
	CS+	CS-	(two-tailed)	CS+	CS-	(two-tailed)
Habituation	1.9±1.0	1.8±0.9	t_{31}=0.27; p=n.s.	1.2±0.9	0.9±0.7	t_{31}=1.7; p=n.s.
Acquisition I	1.5±1.0	1.8±0.8	t_{31}=-1.4; p=n.s.	1.7±1.2	0.9±0.9	t_{31}=3.3; p<0.005*
Acquisition II	1.3±1.0	2.1±0.8	t_{31}=-4.0; p<0.001**	1.8±1.3	0.9±0.9	t_{31}=4.8; p<0.001**
Extinction	1.8±0.9	2.0±0.9	t_{31}=-1.1; p=n.s.	1.2±1.1	0.7±0.9	t_{31}=3.4; p<0.005*

S.D. = standard deviation; CS: conditioned stimulus; * indicating p<0.005, ** indicating p<0.001

3.3.2 fMRI Results

Fear Acquisition

During habituation, the BOLD signal did not differ significantly between CS+$_{unpaired}$ and CS-. During the late acquisition phase, ROI analyses yielded larger activation of the left (x = -30, y = -4, z = -22, t_{31} = 3.27, k = 96 voxels, p = 0.001 uncorrected, p = 0.0057 corrected) and right amygdalae (x = 18, y = 4, z = -18, t_{31} = 2.79, k = 48 voxels, p = 0.004 uncorrected, p = 0.0497 corrected) comparing the presentation of CS+$_{unpaired}$ to CS-. A significant increase in BOLD signal was observed in the dorsal ACC during early (x = 2, y = -2, z = 36, t_{31} = 2.59, k = 97 voxels, p = 0.007 uncorrected, p = 0.0073 corrected) and late conditioning (x = -4, y = -2, z = 28, t_{31} = 3.54, k = 202 voxels, p = 0.001 uncorrected, p < 0.0001 corrected). No significant correlations with trait anxiety were observed within the ROIs corresponding to the ACC or the amygdalae. In addition, whole brain analysis revealed significant conditioning-related (CS+$_{unpaired}$> CS-) neural responses throughout the two acquisition phases in typical fear-related brain

areas, such as the rostral ACC, bilaterally in the insulae, thalamus and striatum ($p < 0.001$ uncorrected, $k > 10$ voxels) (see Table 3, Figure 6).

Table 3 Significant fear-conditioning- and extinction-related brain activations for ($CS+_{unpaired}$>CS-)

Brain region (and hemisphere)	**MNI-coordinates (in mm)**			**Cluster Size (number of voxels)**	**Z-value**
	X	**Y**	**Z**		
Conditioning					
Middle cingulate cortex extending to nucleus caudatus (R/L), precuneus (R/L), thalamus (R/L), pallidum (L), putamen (R/L)	-10	8	-4	2502	5.32
Supplementary motor area extending to middle and superior frontal gyrus (R/L)	16	18	54	573	5.12
Rostral anterior cingulate cortex extending to superior frontal gyrus (R/L)	6	38	20	835	4.61
Superior temporal gyrus extending to inferior parietal gyrus (R)	46	-36	24	1598	4.59
Insula extending to inferior, middle and superior frontal gyrus (R)	28	26	-6	647	4.56
Calacarine gyrus (R/L) extending to lingual gyrus (R/L), middle and superior occipital cortex (R)	0	-84	-6	352	4.50
Middle cingulate cortex (R)	20	12	36	146	4.26
Middle occipital cortex (R)	34	-78	14	53	4.02
Fusiform gyrus (L)	-36	-6	-22	31	3.90
Pallidum, Putamen (R)	18	-2	2	23	3.88
Middle and superior temporal gyrus (L)	-60	-42	10	85	3.87
Superior parietal cortex (R)	20	-46	54	43	3.75
Precentral gyrus extending to middle frontal gyrus (R)	50	10	48	25	3.75
Insula extending to inferior frontal gyrus (L)	-36	22	4	417	3.73
Fusiform gyrus extending to lingual gyrus (R)	28	-68	-10	35	3.56
Middle and superior temporal gyrus (L)	-48	-22	-10	15	3.54
Middle cingulate cortex extending to precuneus (R)	18	-44	40	20	3.48
Middle frontal gyrus (L)	-32	44	28	16	3.35
Supramarginal gyrus (L)	-60	-38	30	15	3.33
Extinction					
Insula extending to inferior frontal gyrus (L)	-40	20	2	378	4.48
Insula extending to inferior frontal gyrus (R)	40	20	-2	396	4.21

Supplementary motor area extending to superior frontal gyrus (R)	10	24	54	112	3.88
Supplementary motor area (L)	-6	12	50	31	3.51

MNI = Montreal Neurological Institute, L = left hemisphere, R = right hemisphere

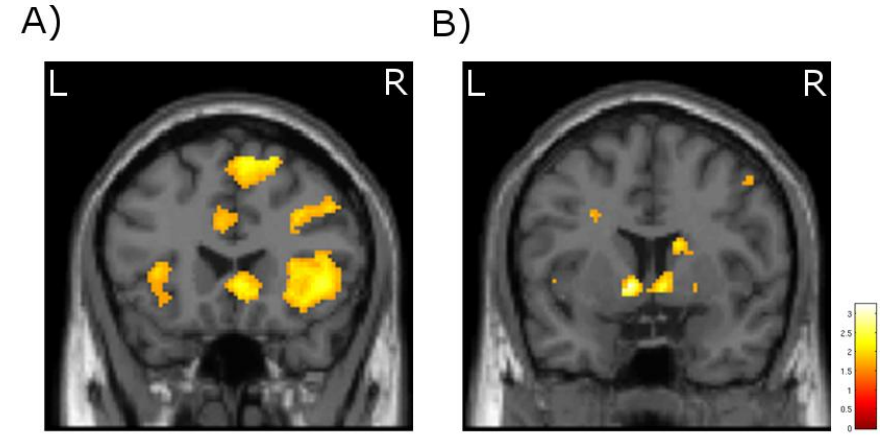


Figure 6 Coronal sections showing statistical parametric maps of significant activation of typical fear-related brain areas (whole brain, $p < 0.001$, $k > 10$ voxels), such as A) bilateral insulae (right insula: x = 28, y = 26, z = -6; left insula: x = -36, y = 22, z = 4), anterior cingulate cortex (x = 6, y = 38, z = 20) and B) striatum (x = 22, y = 6, z = -4) during fear conditioning.

Fear Extinction

No significant activation of the amygdala or the dorsal ACC could be detected comparing the presentation of $CS+_{unpaired}$ to CS- trails in any of the extinction phases. In contrast, the CS- yielded significantly stronger activation of the left amygdala than $CS+_{unpaired}$ during the late extinction phase (x = -26, y = -2, z = -12, t_{31} = 2.47, k = 81 voxels, p = 0.01 uncorrected, p = 0.012 corrected) suggesting a deactivation of the amygdala during extinction. An additional full-factorial ANOVA with *phase* (two levels: acquisition, extinction) and *order* (two levels: first, second) as within-subject factors revealed a significant phase x order interaction (left amygdala: x = -28, y = -4, z = -12, t_{124} = 2.59, k = 85 voxels, p = 0.005 uncorrected, p = 0.0103 corrected; right amygdala: x = 20, y = 6, z = -18, t_{124} = 2.32, k = 63 voxels, p = 0.011 uncorrected, p = 0.0272 corrected). Amygdala activation increased from the first to the second acquisition phase, and decreased during the extinction phases. Contrast estimates of the amygdala activation interaction are shown in Figure 7.

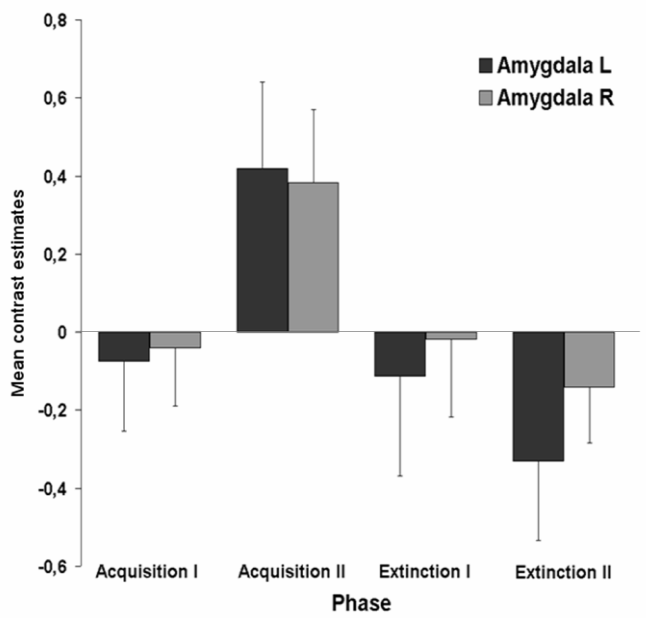
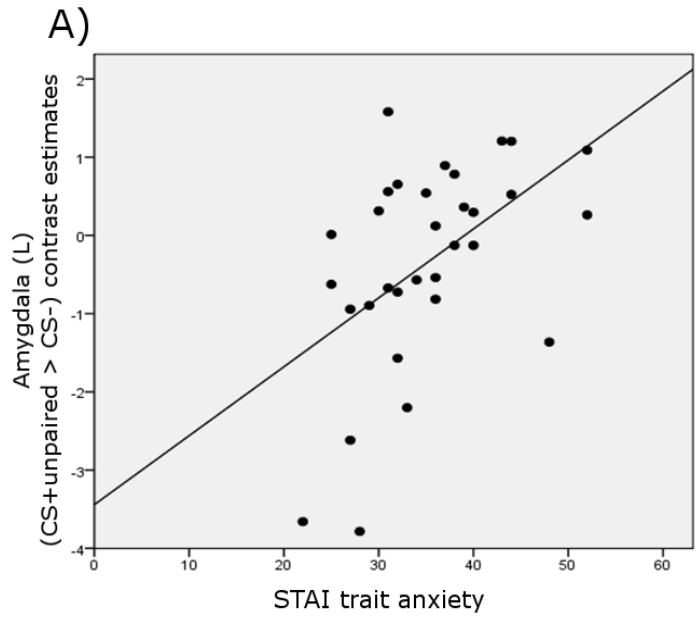
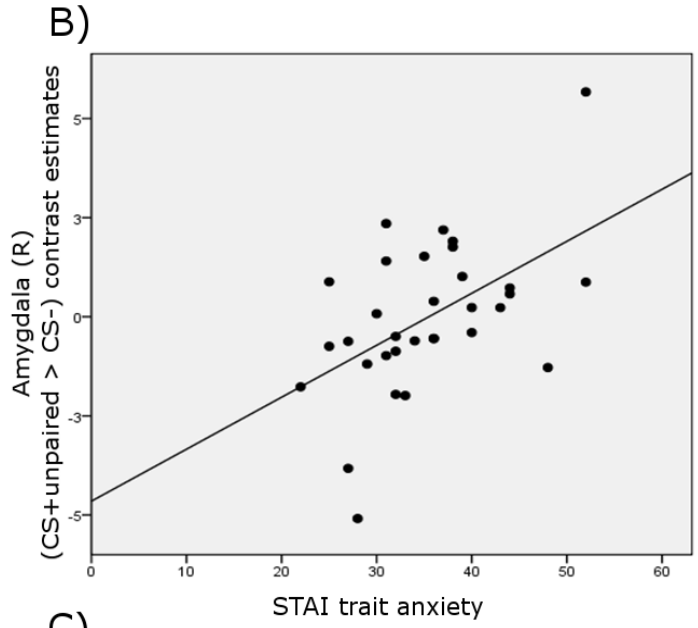


Figure 7 Mean contrast estimates (± SEM) ($CS+_{unpaired}$>CS-) for left and right amygdala ROI for early and late acquisition and extinction phases are presented. The ANOVA revealed a significant phase x order interaction for right and left amygdala (*p*s < 0.05 corrected for multiple comparisons).
Activation increased from the first to the second acquisition phase and decreased during the extinction phases.

Regression analysis revealed significant positive effects of trait anxiety on amygdala reactivity during the early extinction phase (left amygdala: x =-22, y = -8, z = -14, t_{30} = 3.17, r = 0.50, p = 0.002 uncorrected, k = 44 voxels, p = 0.059 corrected; right amygdala: x = 20, y = 0, z = -16, t_{30} = 3.25, r = 0.51, k = 114 voxels, p = 0.001 uncorrected, p = 0.003 corrected) (Figures 8.A, B; 9.A, B). A significant correlation was also found for the late extinction phase (left amygdala: x = -28, y = -4, z = -16, t_{30} = 2.69, r = 0.44, k = 74 voxels, p = 0.006 uncorrected, p = 0.0173 corrected; right amygdala: x = 24, y = -4, z = -18, t_{30} = 2.19, r = 0.37, k = 18 voxels, p = 0.018 uncorrected, p = 0.2 corrected). In addition, significant negative effects of trait anxiety on dorsal ACC activity were observed during late extinction (x = 4, y = -2, z = 28, t_{30} = 3.41, r = -0.53, k = 143 voxels, p = 0.001 uncorrected, p = 0.001 corrected) (Figure 8.C). Trait-anxious subjects showed reduced prefrontal activation during late extinction of conditioned responses. The whole-brain analysis of the extinction phase revealed significant bilateral activation outside the ROIS in the insular cortex and the supplementary motor area for $CS+_{unpaired}$ in contrast to CS- (p < 0.001 uncorrected, k > 10 voxels) (see Table 3, Figure 10).





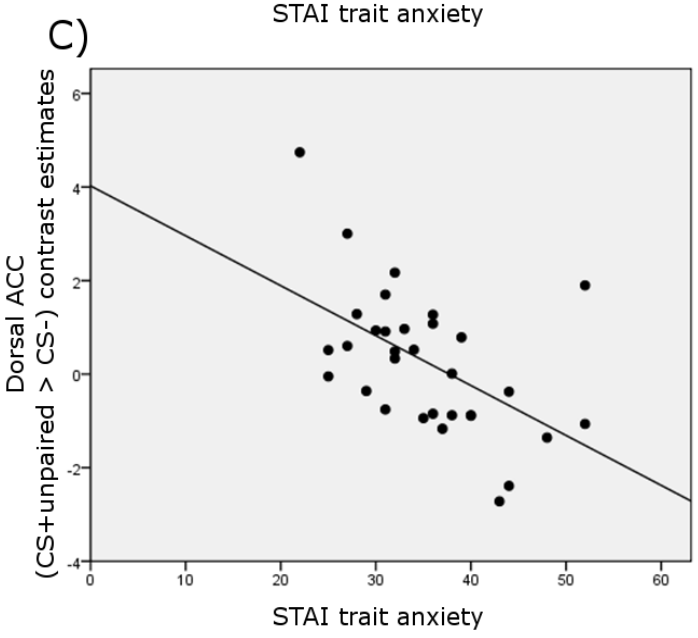


Figure 8 Contrast estimates for the $CS+_{unpaired}$ presentation compared to CS- within the A) left amygdala (r = 0.50) and B) right amygdala (r = 0.51) during early extinction, C) and the dorsal ACC (r = -0.53) during late extinction of conditioned fear.

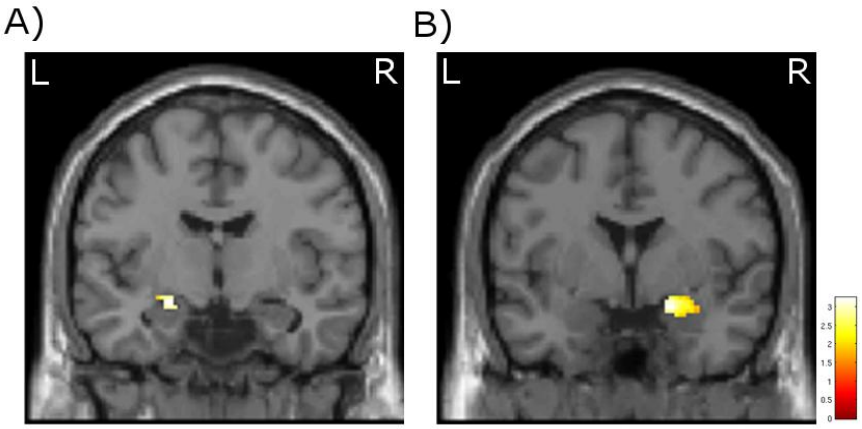


Figure 9 Coronal sections illustrating statistical parametric maps of significant positive relationships between trait anxiety and A) activity within the left amygdala (x = -22, y = -8, z = -14, t_{30} = 3.17, r = 0.50, p = 0.002 uncorrected, k = 44 voxels, p = 0.059 corrected) and B) activation of the right amygdala during the early extinction of conditioned fear (x = 20, y = 0, z = -16, t_{30} = 3.25, r = 0.51, k = 114 voxels, p = 0.001 uncorrected, p = 0.0030 corrected).

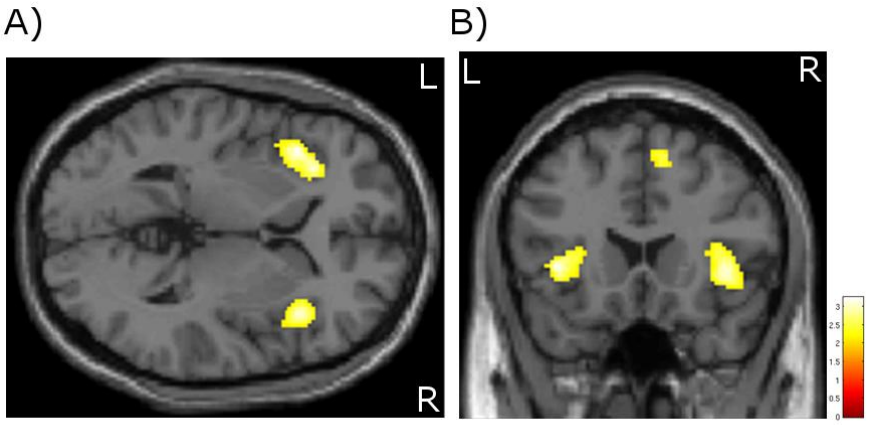


Figure 10 Sections showing statistical parametric maps of significant activations of A)/ B) bilaterally in the insulae (whole brain, p < 0.001, k > 10 voxels; right insula: x = 40, y = 20, z = -2; left insula: x = -40, y = 20, z = 2) and in the right supplementary motor cortex during fear extinction.

3.4 Discussion

In the present study, we used fMRI during a cued fear conditioning design, to identify the neural mechanisms of fear learning, and to investigate whether these neural mechanisms are associated with an important personality trait: trait anxiety (Spielberger, 1972). As expected, analysis of fMRI-data revealed enhanced activation in fear-related brain areas during fear conditioning, such as insula, striatum, rostral and dorsal ACC. Amygdala activation was only significant during the late acquisition phase. During extinction, bilateral activation of the insulae and deactivation of the amygdalae were observed. Interestingly, significant correlations between high trait anxiety, enhanced amygdala reactivity and decreased activation of the dorsal ACC were apparent during the extinction phase, suggesting that subjects with high trait anxiety show delayed and reduced extinction of conditioned responses.

3.4.1 Behavioural Data

Behavioural data indicated successful cued conditioning. During acquisition, ratings of negative valence and arousal were significantly increased for the $CS+_{unpaired}$ as compared to the CS-. Specifically, valence ratings were significantly different during the late acquisition phase, while arousal ratings already differed after the initial acquisition phase. We assume that the evaluation of arousal is more sensitive for conditioning effects than valence rating, which might be confounded by subjects' personal preference, or higher cognitive processes. After extinction, CS- and $CS+_{unpaired}$-ratings became equal.

3.4.2 Neuronal Networks Involved in Fear Conditioning and Extinction

As expected, ROI-analyses revealed larger bilateral activation of the amygdalae during the acquisition phase ($CS+_{unpaired}$>CS-), which is also in accordance with former studies (LaBar et al., 1998, Fischer et al., 2000, Phelps et al., 2001, Morris and Dolan, 2004, Schiller et al., 2008). The only difference to these studies is the occurrence of amygdala activation during the late conditioning phase. The time course of amygdala activation observed here may be due to the small CS-US-contingency rate of 25% used in this study, suggesting that the association between CS and US had only been established

after a certain number of pairings (Phelps et al., 2004, Barrett and Armony, 2009). This pairing rate was employed in our study to deliberately avoid habituation effects occurring before the extinction phase. Furthermore, the lower aversiveness of the tone, compared to the electrical stimulation presented in most studies, may also have contributed to the delayed amygdala response. Consistent with prior studies on human fear conditioning and extinction, the presentation of $CS+_{unpaired}$ compared to the CS- during fear conditioning elicited significant whole-brain activation of fear-related brain areas, such as insula, ACC and striatum. These areas are known to be involved in emotional processing and are regarded as key areas of pain processing and classical fear conditioning (see for review (Sehlmeyer *et al.*, 2009)).

During extinction, the main conditioning effect ($CS+_{unpaired}$ > CS-) was associated with a deactivation of the amygdala. In particular, we found a reversal response in the amygdala, such that the activation was greater for CS- than for $CS+_{unpaired}$ during the late extinction phase. Outside the ROI, significant activations of the bilateral insulae and the supplementary motor cortex were detected. These results are also in line with those of other neuroimaging studies (Buchel and Dolan, 2000, Phelps et al., 2004). The SMA is a key structure for both preparation and execution of movements (Remy et al., 1994, Johnson et al., 2001, Wang et al., 2007). Activation within the extinction phase may reflect a preparatory action in response to the formerly conditioned stimulus, in terms of avoiding or escaping from the threatening stimulation. The insular cortex is assumed to process emotional contents, such as fear (Phelps *et al.*, 2001) or pain (Ploghaus et al., 1999, Ostrowsky et al., 2002, Lopez-Sola et al., 2010). Moreover, the insula is recruited in the context of uncertainty and in anticipation of aversive events (Carlson et al., 2010, Sarinopoulos et al., 2010), which is particularly the case during the extinction phase. To conclude, our data support the development of activity within the amygdala over the course of conditioning and the decline of amygdala activation during extinction. Surprisingly, we did not observe significant activation within the ROI of the dorsal ACC for the main conditioning effect ($CS+_{unpaired}$ > CS-) in any of the extinction phases, although it is preferentially engaged during the inhibition of conditioned responses (Phelps et al., 2004, Lang et al., 2009).

3.4.3 Influence of Trait Anxiety

Significant correlations of trait-anxiety scores with amygdala and dorsal ACC activation were revealed. While the acquisition phases were unaffected by this personality trait, higher levels of trait anxiety were associated with greater sustained conditioned amygdala activation, or rather with less amygdala deactivation ($r = 0.50$), mainly during early extinction. These results are remarkably consistent with earlier studies on healthy subjects and anxiety patients that reported a positive interaction of amygdala responses with anxiety during the processing of fearful stimuli (Bishop et al., 2004, Etkin et al., 2004, Dickie and Armony, 2008), during fear learning (Bremner et al., 2005, Hooker et al., 2008) and fear extinction (Barrett and Armony, 2009).

Moreover, we were able to show that high levels of trait anxiety are also strongly associated with decreased activation of the dorsal ACC – the cognitive part of the ACC (Bush et al., 2000) – during late extinction ($r = -0.53$). At first glance, this finding seems counter-intuitive as we did not observe activation of the ACC in any of the extinction phases. However, regression analysis yielded a significant correlation between ACC activation and trait anxiety. This finding implies that, without controlling for personality, the ACC is not engaged across all subjects to extinguish fear responses. The ACC is rather engaged as a function of trait anxiety. Hence, we conclude that involvement of the ACC during the extinction of fear is modulated by differences in trait anxiety. We assume that the hypo-activation of the ACC reported for anxious subjects, results in a deficient inhibition of conditioned amygdala responses, additionally prolonging extinction and exaggerating fear responses. These findings are consistent with previous neuroimaging studies that reported an association of anxiety traits, pathological anxiety and activation of the PFC/ ACC during fear extinction (Bremner et al., 2005, Rauch et al., 2005, Rauch et al., 2006). Nevertheless, our study extends the current literature showing that high levels of trait-anxiety are associated with both increased amygdala activity and reduced activation of the ACC during the process of extinction. In particular, our results partly confirm and expand recent findings of Barret and Armony (2009). Even though using different conditioning designs, findings seem to converge on trait anxiety correlating with the amygdala and modulating fear extinction rather than fear conditioning. However, results vary in the areas of the ACC examined. While Barret and Armony observed contrary to the

expectations a relation between trait anxiety and enhanced subgenual ACC activation, we were able to show an association of trait anxiety and reduced dorsal ACC activation as expected. Our data show, that this strong and significant relationship was exclusively found during the late extinction phase. The correlation observed during early extinction failed significance. Beside this problem with statistical significance, we assume that activation of the ACC is decreased during the extinction process in anxious subjects leading to the strong negative correlation during late extinction. This suggests that high- and low anxious persons do not differ with respect to the ACC-activation at early stages of extinction, but at a later point of time. We suppose that trait anxious subjects are not able to maintain activation of the inhibitory ACC during the extinction process, which may lead to enhanced vulnerability and risk for relapse.

Taken together, subjects characterized by enhanced trait anxiety show deficits in the extinction of acquired fear. This is not only reflected by sustained amygdala activation during early, but also by additional decreased dorsal ACC activation during late extinction. Highly trait-anxious subjects fail to adapt to altering circumstances and maintain their anticipatory anxiety even when threat-related stimuli (US) are absent (Chan and Lovibond, 1996), as is the case during extinction. Therefore, we assume that the most prominent feature separating high and low anxious subjects may not be conditionability, but the ability to extinguish conditioned responses.

Our simple and robust paradigm has revealed important findings for the understanding of the relation between personality and neurobiological vulnerability in the development of anxiety disorders. We have shown that anxious subjects are characterized by both amygdala hyper-activation and dorsal ACC hypo-activation. This double impact of increased amygdala reactivity and deficient cognitive control may represent enhanced risk for spontaneous recovery of the extinguished response and pathophysiologically for relapse in anxiety disorders.

3.4.4 Limitations

A few limitations should be pointed out in the current study. Our investigation, like others, was limited by the inability to hold for multiple comparisons in the whole brain analysis. For this reason, we chose a frequently used probability-value of $p < 0.001$ with

a spatial voxel extent of 10. Moreover, certain improvements of the experimental paradigm should be mentioned. First, in accordance with previous fear-conditioning studies we employed an acoustic, brief and loud noise as unconditioned stimulus. As we did not conduct a-priori-aversiveness-rating of the US, we cannot rule out that the tone was low aversive and hence caused the observed delayed amygdala response during the acquisition phase. In addition, consistent with most studies we used the subjective measure of valence and arousal only at the end of the experimental blocks. The application of a continuous measure would have improved the investigation of conditioning-related changes in CS-ratings. At least, we used only neutral male faces as conditioned stimuli instead of both female and male.

3.4.5 Conclusion

Our study for the first time reveals that deficits in the extinction of acquired fear in highly trait-anxious subjects are not only due to enhanced amygdala reactivity, but also due to reduced prefrontal inhibition. Therefore, our findings help to elucidate the enhanced neurobiological vulnerability of anxious subjects to develop and maintain an anxiety disorder.

4 Experiment – Response Inhibition[3]

4.1 Introduction

Executive functions control cognitive processes. According to the theoretical model of Norman and Shallice (1986), the executive system is especially involved in planning, error correction, and the adaptation to novel situations (Norman and Shallice, 1986, Posner and Dehaene, 1994). *Response inhibition*, another component of this control system (Mostofsky and Simmonds, 2008), is described as the suppression of actions that are inappropriate in a given context. It can be examined experimentally in a *Go/ Nogo*-task using event-related potentials (ERPs). In such a paradigm, subjects should respond to one target stimulus in the *Go-condition* and withhold responses to the target stimulus in the *Nogo-condition*.

Two fronto-central ERPs have been associated with larger amplitudes in Nogo- than in Go-trials (Eimer, 1993, Falkenstein et al., 1999). These components have been labelled as *Nogo-N2* and *Nogo-P3,* and are considered to represent different sub-processes of response inhibition. The Nogo-N2 is assumed to reflect inhibition or revision of a motor plan prior to motor execution. In contrast, the Nogo-P3 has been associated with motor inhibition (Falkenstein et al., 1999, Smith et al., 2008, Zordan et al., 2008), but due to its long latency it has also been suggested that it reflects the monitoring of the outcome of inhibition (Schmajuk et al., 2006, Righi et al., 2009). Furthermore, both components seem to be differentially modulated by distinct neurobiological systems (Beste et al., 2010a, Beste et al., 2010b, Huster et al., 2010) supporting the assumption of different sub-processes of response inhibition.

Response inhibition and cognitive control have been associated with activity within the ACC and other frontal brain areas (Bokura et al., 2001, Falkenstein, 2006, Beste et al., 2008). Furthermore, the ACC is important for the integration of cognitive and emotional processes (Bush et al., 2000), for the pathophysiology of psychiatric disorders (Damsa et al., 2009), and is a crucial part of the human anxiety circuitry (Sehlmeyer et al., 2009). Patients with anxiety disorders may be characterized by

[3] Sehlmeyer C, Konrad C, Zwitserlood P, Arolt V, Falkenstein M and Beste C, "ERP indices for response inhibition are related to anxiety-related personality traits", Neuropsychologia, 48 (9), 2488-95, 2010

neurocognitive deficits in inhibitory processing and response monitoring. While some studies observed smaller Nogo-N2 amplitudes (Herrmann et al., 2003, Kim et al., 2007), others found hyperactivation of the ACC (Ursu et al., 2003), enhanced Nogo-N2 and consequently increased response inhibition (Ruchsow et al., 2007).

While patients with anxiety disorders may show some degree of response over-inhibition, the question remains whether personality traits, which are closely related to pathological anxiety (Chambers et al., 2004, Schmidt et al., 2008, Naragon-Gainey, 2010), can also modulate cognitive functions, such as response inhibition, and electrophysiology, such as Nogo-components. There are only few studies emphasized the importance of monitoring anxiety traits with regard to cognitive functions (Karch et al., 2008). Two major psychological concepts concerning anxiety-related personality traits may be linked to response inhibition: trait anxiety (TA) and anxiety sensitivity (AS). TA describes the tendency to respond fearfully to a wide variety of unspecific stressors, and the need for both security and cognitive control (Fales et al., 2008). In contrast, AS represents the specific tendency to respond fearfully to one's own bodily sensations and anxiety-related symptoms, which is based on the belief that these symptoms are harmful (McNally, 2002). It has been a matter of controversial debates whether AS and TA represent common or different concepts of anxiety (Lilienfeld, 1996, McNally, 1996, McWilliams and Cox, 2001, Muris et al., 2001). Actually, it is assumed that they both are related to each other and focus each on different facets of anxiety. While TA concentrates on cognitive anxiety symptoms, AS refers to physical and psychological anxiety symptoms.

In general, the interplay of anxiety traits, cognitive individual differences and electrophysiology has been investigated by recent research (Manly et al., 1999, Roche et al., 2005, Karch et al., 2008). For example, it has been shown that subjects with high trait anxiety or anxiety sensitivity display anxiety-related attentional biases (Bar-Haim et al., 2007) and may thus show modified ERP components, cognitive performances (flanker task: (Moser et al., 2005, Dennis and Chen, 2009); n-back: (Holmes et al., 2009); stroop: (Taake et al., 2009) or processing of affective information (Carretie et al., 2004, Li et al., 2005, Rossignol et al., 2005, Mercado et al., 2006, Most et al., 2006, Dennis and Chen, 2007, Fox et al., 2008). So far, only few studies emphasized the importance of monitoring anxiety traits with regard to response inhibition and Nogo-components (Karch et al., 2008, Righi et al., 2009). In particular, Righi et al. reported

that, during a Go/ Nogo-task, the N2-component was increased in trait and state anxious, healthy subjects, while the P3 was decreased in subjects who reported a higher frequency of cognitive failures (Righi et al., 2009).

To the best of our knowledge, this is the first study investigating the influence of two different anxiety-related personality constructs on event-related potentials in a Go/ Nogo-paradigm in healthy subjects. We hypothesize that individuals with high levels of TA and AS show a specific enhancement of executive control in this response-inhibition task. We assume that persons with high anxiety are characterized by increased cognitive control and an enhanced evaluation of their behavioural outcomes, which may be reflected by increased Nogo-N2 and Nogo-P3 responses, and fewer false alarm rates. Moreover, with respect to each anxiety construct (AS, TA), we expect differential effects on Nogo-N2 and -P3 components.

4.2 Methods

4.2.1 Subjects

Subjects were 54 right-handed undergraduates at the University of Muenster without any medical, neurological and psychiatric disorders (39 female, 15 male; mean age = 22.58 years, standard deviation (*S.D.*) = 2.03, range 19 - 28 years). They all gave written informed consent in accordance with the guidelines of the ethical standards of the Declaration of Helsinki. All procedures were approved by the local Institutional Ethical Review Board.

4.2.2 Self-reports

Personality traits were determined on the day of EEG-recording. Participants completed the A*nxiety-Sensitivity Index* (ASI-Revised; (Reiss et al., 1986, Peterson and Reiss, 1987)), a 36-item self-report questionnaire measuring the fear of bodily sensations associated with arousal. Trait anxiety was measured by the *State-Trait Anxiety Inventory (STAI)* (Laux, 1981) which consists of 40 statements differentiating between trait anxiety and the temporary condition of state anxiety. As we focus on stable emotional traits, the state-anxiety score was not further considered.

4.2.3 Stimuli and procedure

In a Go/ Nogo-paradigm, two words were presented on a computer screen in randomized order while EEG was recorded. The stimuli were displayed for 300 ms. The whole experiment took 15 minutes and consisted of two blocks of 100 stimuli each. The subjects had to react upon appearance of the *Go-stimulus* ("press") and to refrain from responding upon appearance of the *Nogo-stimulus* ("stop"). Responses were given by pressing a response button either with the right or left hand thumb, counterbalanced across subjects. The intertrial interval was 1600 ms. Subjects were asked to respond within a reaction-time (RT) deadline. When RTs exceeded this deadline, an auditory feedback stimulus (1000 Hz, 60 dB sound pressure level (SPL)) was given. Subject's responses to Go- and Nogo-stimuli, and RTs were recorded. During the task, participants did not receive any feedback on their performance.

4.2.4 Data processing

EEG data were recorded from 24 Ag-AgCl electrodes (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, left mastoid - M1, right mastoid - M2) against a reference electrode located at Cz. Eye movements were monitored and recorded by means of two lateral and four vertical EOG electrodes.

The sampling rate of all recordings was 500 Hz, applying a filter bandwidth 0-80 Hz to the EEG. Electrode impedances were kept below 5 kΩ. EEG was filtered off-line from 0.5 to 16 Hz and re-referenced to linked mastoids. Artefact-rejection procedures were applied twice: automatically, using an amplitude-threshold of ±80 µV, and visually, rejecting all trials contaminated by technical artefacts. Horizontal and vertical eye movements of the accepted trials were corrected by means of a linear regression for EOG correction (Gratton et al., 1983).

4.2.5 Data analysis

The following electrodes were selected for statistical analysis: Fz, FCz and Cz (Falkenstein et al., 1999). Components of interest were the N2 and P3. After averaging, amplitudes in Go- and Nogo-trials were evaluated using correct trials only. After digital low-pass filtering, the amplitudes were assessed relative to a 200 ms pre-stimulus baseline. The N2 was defined as the most negative peak occurring 200-300 ms after stimulus onset and was measured relative to baseline. The P3 was defined as the most positive peak occurring 300-500 ms after stimulus onset and was measured relative to baseline. For linear regression analyses mean amplitudes and latencies were determined averaging across electrode positions. This scoring method is comparable to that of other studies (Beste et al., 2008).

Variability in Go- and Nogo-components attributable to personality traits was assessed by hierarchical linear regression analyses (Tabachnik and Fidell, 2007). The continuous quantitative variables AS and TA which were correlated were introduced as independent variables in the model. To examine whether age and gender accounted for additional variance in the N2 and P3, these variables were included as additional regressors in the analyses. Go- and Nogo-N2 and -P3 components were used as dependent variables in separate analyses. In order to highlight the differences in waveshapes between the ERPs of Go- and Nogo-trials and to further illustrate the anxiety-related effect on Nogo-potentials, we conducted additional *analyses of variances* (ANOVAs). First, we grouped subjects according to the STAI trait median score (Trait median = 32) into either a *low TA-group* or a *high TA-group. Second, we* defined a *low AS-group* and a *high AS-group* according to the ASI median score (ASI median = 14). The factors *AS-group* (low, high) and *TA-group* (low, high) were included as between-subject factors in separate repeated-measures ANOVAs with *electrode* (three levels: Fz, FCz, Cz) and *condition* (two levels: Go/ Nogo) as within-subject factors. According to Mauchly's test, sphericity cannot be assumed and the Greenhouse-Geisser correction was employed to correct for sphericity. Because of the Bonferroni correction for multiple comparisons, we only reported p-values exceeding 0.001.

4.3 Results

4.3.1 Behavioural data

The mean ASI score was 18.63 (*standard deviation S.D.* = 11.42, range = 3 – 57), the mean STAI trait score 33.90 (*S.D.* = 8.36, range = 21 – 64). The ASI and STAI trait scores were significantly correlated (r = 0.38; $p < 0.01$; R^2 = 0.14). Mean reaction times were 287.04 ms (*S.D.* = 21.77) and the mean false alarm rate 7.1 % (*S.D.* = 2.24). To assess the effects of anxiety on the behavioural performance (RTs, false alarm rates), hierarchical regression analyses with AS, TA, age and gender as regressors were performed (see Table 4). None of the independent variables had significant influence on RTs (F (4, 48) = 1.38; p = n.s.; R^2= 0.103). In combination, the four predictors accounted for 26% of the variance in false alarm rates (F (4, 48) = 4.25; p < 0.01). The predictors were then each examined with the variance associated with the other predictors removed. As hypothesized, TA and AS had significant influence on the criterion variable (TA: R^2 = 0.246; AS: R^2 = 0.096). Gender and Age did not account for additional variance. Particularly, a higher level of anxiety indicates a decrease of false alarms.

Table 4 Regression coefficients (R^2, ΔR^2) and statistical results of hierarchical linear regression analyses on reaction times and false alarm rates with respect to the influence of trait anxiety, anxiety sensitivity, age and gender are shown. Trait anxiety and anxiety sensitivity were significantly associated with reduced false alarm rates.

Variables	**RTs**			**False alarm rates**		
	R^2	ΔR^2	$p <$	R^2	ΔR^2	$p <$
TA alone	0.000		0.91	0.246		0.001
TA added second		0.000	0.99		0.163	0.003
AS alone	0.001		0.81	0.096		0.03
AS added second		0.001	0.83		0.013	0.36
Age added third		0.000	0.89		0.002	0.75
Gender added fourth		0.101	0.03		0.001	0.81
Full Model	0.103		0.26	0.261		0.006

AS: anxiety sensitivity; TA: trait anxiety; RTs: reaction times. *R2* illustrates the regression model, whereas ΔR^2 illustrates the improvement of the regression model when additional independent variables are considered.

4.3.2 Neurophysiological data - Multiple Regression Analyses

N2

The grand means of the ERP waveforms are shown in Figure 11. A hierarchical regression analysis was employed for Nogo-N2 amplitudes. The inclusion of all predictor variables accounted for 58.5 % of the variance in the criterion variable (F (4, 48) = 34.39; $p < 0.001$) (see Table 5). Then, each predictor was examined with the variance associated with the other predictors removed. Whereas TA accounted for 57.8 % of the variance in the Nogo-N2 (see Figure 12.A for scatter plot), AS predicts 14.5 %. No significant correlations were obtained for age and gender.

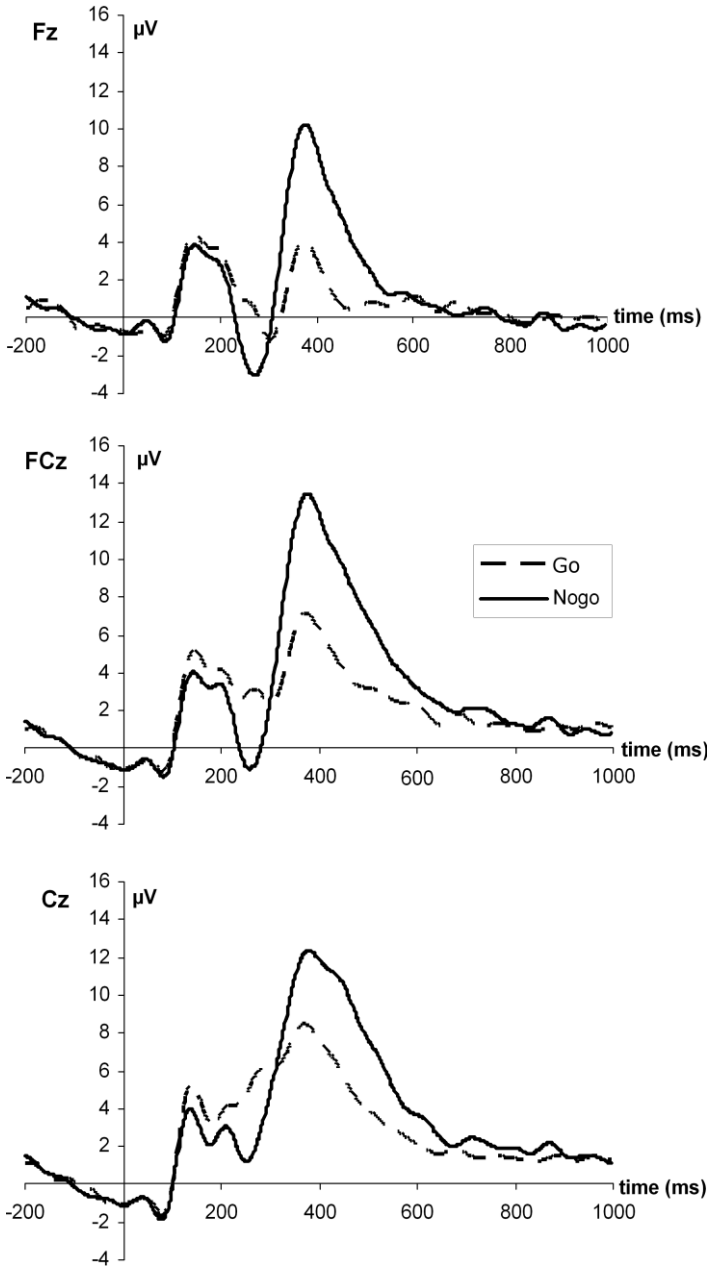


Figure 11
Grandaverage waveforms of the ERPs across all subjects at electrodes Fz, FCz and Cz. Dashed lines denote the ERP on Go-trials, solid lines denote the ERP on Nogo-Trials.

Hierarchical regression analysis on Go-N2 amplitudes revealed that none of the regressors had significant influence (F (4, 48) = 0.98; p = n.s.; R^2 = 0.075). Regression analyses on Go- and Nogo-N2 latencies showed that TA, AS, gender and age had no significant impact on the criterion variables (Nogo-N2 latencies: F (4, 48) = 0.59; p = n.s.; R^2 = 0.047; Go-N2-latencies: F (4, 48) = 0.58; p = n.s.; R^2 = 0.046). To sum up, trait anxiety was principally associated with Nogo-N2 amplitudes.

Table 5 Regression coefficients (R^2, ΔR^2) and statistical results of hierarchical linear regression analyses on Nogo-N2 and -P3 amplitudes with respect to the effects of trait anxiety, anxiety sensitivity, gender and age are given. AS specifically affects the Nogo-P3, whereas TA mainly influences the Nogo-N2.

Variables	**Nogo-N2 amplitude**			**Nogo-P3 amplitude**		
	R^2	ΔR^2	$p <$	R^2	ΔR^2	$p <$
TA alone	0.577		0.001	0.000		0.95
TA added second		0.437	0.001		0.055	0.05
AS alone	0.144		0.006	0.284		0.001
AS added second		0.005	0.47		0.338	0.001
Age added third		0.003	0.58		0.001	0.81
Gender added fourth		0.000	0.97		0.011	0.37
Full Model	0.584		0.001	0.351		0.001

AS: anxiety sensitivity; TA: trait anxiety. Probability values are two-tailed. *R2* illustrates the regression model, whereas ΔR^2 illustrates the improvement of the regression model when additional independent variables are considered.

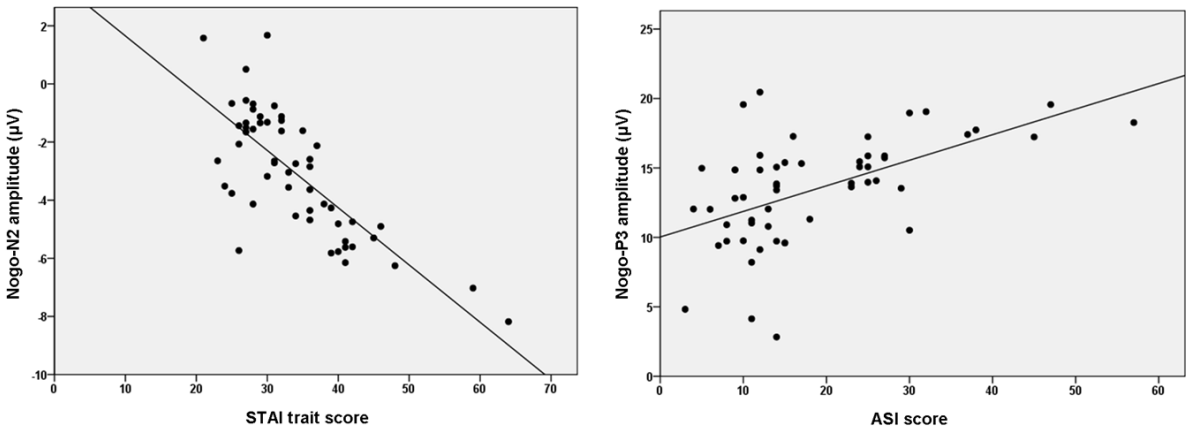


Figure 12 A) Scatter plot of the relation between Nogo-N2 amplitudes and trait anxiety (TA) scores. B) Scatter plot of the relation between Nogo-P3 amplitudes and anxiety sensitivity (AS) scores.

P3

Moreover, the hierarchical regression analysis on Nogo-P3 amplitudes showed that 35 % of the variability in the criterion variable can be explained by the statistical model (F (4, 48) = 6.478; $p < 0.001$) (see Table 5). More than two thirds of the variability in Nogo-P3 amplitudes is predicted by AS (see Figure 12.B for scatter plot). Adding TA to the prediction, results in a small increment of 6 % in R^2. The inclusion of age and gender had no additional impact on the dependent variable. Another hierarchical regression analysis revealed that the inclusion of all predictors did not account significantly for variance in the Go-P3 amplitudes (F (4, 48) = 0.129; p = n.s.; R^2= 0.011). Regression analyses on Nogo-P3 latencies showed that 19 % of the variance in the criterion variable was accounted for by the statistical model (F (4, 48) = 2.88; $p <$ 0.05). Anxiety sensitivity captured 14 % of the variance while the addition of TA, age and gender to the equation did not result in a significant increment of R^2. In the hierarchical regression analysis of Go-P3 latencies, 16.6 % of the variance were explained by the full model (F (4, 48) = 2.32; $p <$ n.s.). AS predicted 11 % of the variance, while the inclusion of TA, age and gender had no significant impact on Go-P3 latencies. To conclude, anxiety sensitivity mainly affected Nogo-P3 amplitudes.

4.3.3 Neurophysiological data - ANOVA

To further illustrate this differential effect of TA on Nogo-N2 amplitudes and of AS on Nogo-P3 amplitudes we performed repeated measures ANOVAs with electrode (Fz, FCz, Cz) and condition (Go, Nogo) as within-subject factors. TA-group (high, low) and AS-group (high, low) were included as between-subject factors in separate analyses[4]. Statistical results with respect to the effects of electrode and condition are presented in Table 6. Effects of TA-groups and AS-groups on Nogo-N2 and -P3 are presented in Table 7.

[4] In a first analysis, we incorporated the factors row (F-electrodes, FC-electrodes and C-electrodes), laterality (left, central, right) and condition (Go, Nogo) as within-subject factors and group as between subject-factor Beste, C., Saft, C., Andrich, J., Gold, R. and Falkenstein, M., 2008. Response inhibition in Huntington's disease-a study using ERPs and sLORETA. Neuropsychologia. 46, 1290-1297.. We accounted for a significant row x laterality x condition x group interaction (F's > 3.1; p < .01). Subsequent repeated measures ANOVAs for the left, middle and right electrode positions revealed a row x condition x group interaction for the middle electrodes, but not for the left- and right-sided electrodes for the Nogo-N2 and Nogo-P3 (all F's < 1; p > .3), suggesting that the effects obtained were not differentially lateralized in the different groups. Therefore, we restricted all further analyses on Nogo-N2 and Nogo-P3 to the middle line of electrodes (i.e. Fz, FCz and Cz).

Table 6 Statistical results of ANOVAs (Test statistic, two-tailed) with respect to the effects of electrode and condition on Nogo-N2 and -P3 amplitudes

	N2 amplitudes		**P3 amplitudes**	
	AS-groups	*TA-groups*	*AS-groups*	*TA-groups*
Electrode	F (1.6,80.7)=4.03 p<0.001 η^2=0.396	F (1.5,77.2)=33.20 p<0.001 η^2=0.39	F (1.7,88.9)=31.86 p<0.001 η^2=0.38	F (1.7,89.2)=32.19 p<0.001 η^2=0.38
Condition	F (1,52)=82.81 p<0.001 η^2=0.614	F (1,52)=116.64 p<0.001 η^2=0.69	F (1,52)=195.04 p<0.001** η^2=0.79	F (1,52)=162.40 p<0.001 η^2=0.76
Electrode x condition	F (1.4,72.9)=34.13 p<0.001 η^2=0.396	F (1.3,69.2)=34.33 p<0.001 η^2=0.40	F (1.2,59.6)=22.29 p<0.001 η^2=0.30	F (1.2,59.7)=22.65 p<0.001 η^2=0.30

AS: anxiety sensitivity; TA: trait anxiety

Table 7 Mean amplitudes (in μV) with standard errors of the means and statistical results for Nogo components with respect to the effects of groups of high and low anxiety sensitivity and trait anxiety are given. AS specifically affects Nogo-P3, whereas TA significantly influences the Nogo-N2.

	Anxiety Sensitivity		**Test statistic (two-tailed)**	**Trait anxiety**		**Test statistic (two-tailed)**
	low	*high*		*low*	*high*	
Nogo-N2 amplitude	-2.26 ± 0.39	-3.86 ± 0.39	F (1,52)=4.03 p=0.05 η^2=0.07	-1.63 ± 0.31	-4.50 ± 0.31	F (1,52)=26.92 p=0.001 η^2=0.34
Nogo-P3 amplitude	11.83 ± 0.68	15.09 ± 0.68	F (1,52)=11.96 p=0.001 η^2=0.19	13.20 ± 0.75	13.72 ± 0.75	F (1,52)=1.25 p=n.s η^2=0.02

Nogo-N2

The ANOVAs on Nogo-N2 amplitudes revealed main effects of electrode, condition and electrode x condition interactions. As shown in Figure 13, the high TA-group revealed larger N2 amplitudes than the low TA-group in the Nogo-condition: condition x TA-group interaction (F (1, 52) = 26.92; p = 0.001; η^2 = 0.34). With respect to AS,

Nogo-N2 amplitudes were slightly enhanced in the high AS-group (-1.20 ± 0.21) compared to the low AS-group (-0.20 ± 0.21) (F (1, 52) = 12.078; p< 0.001; η^2 = 0.188).

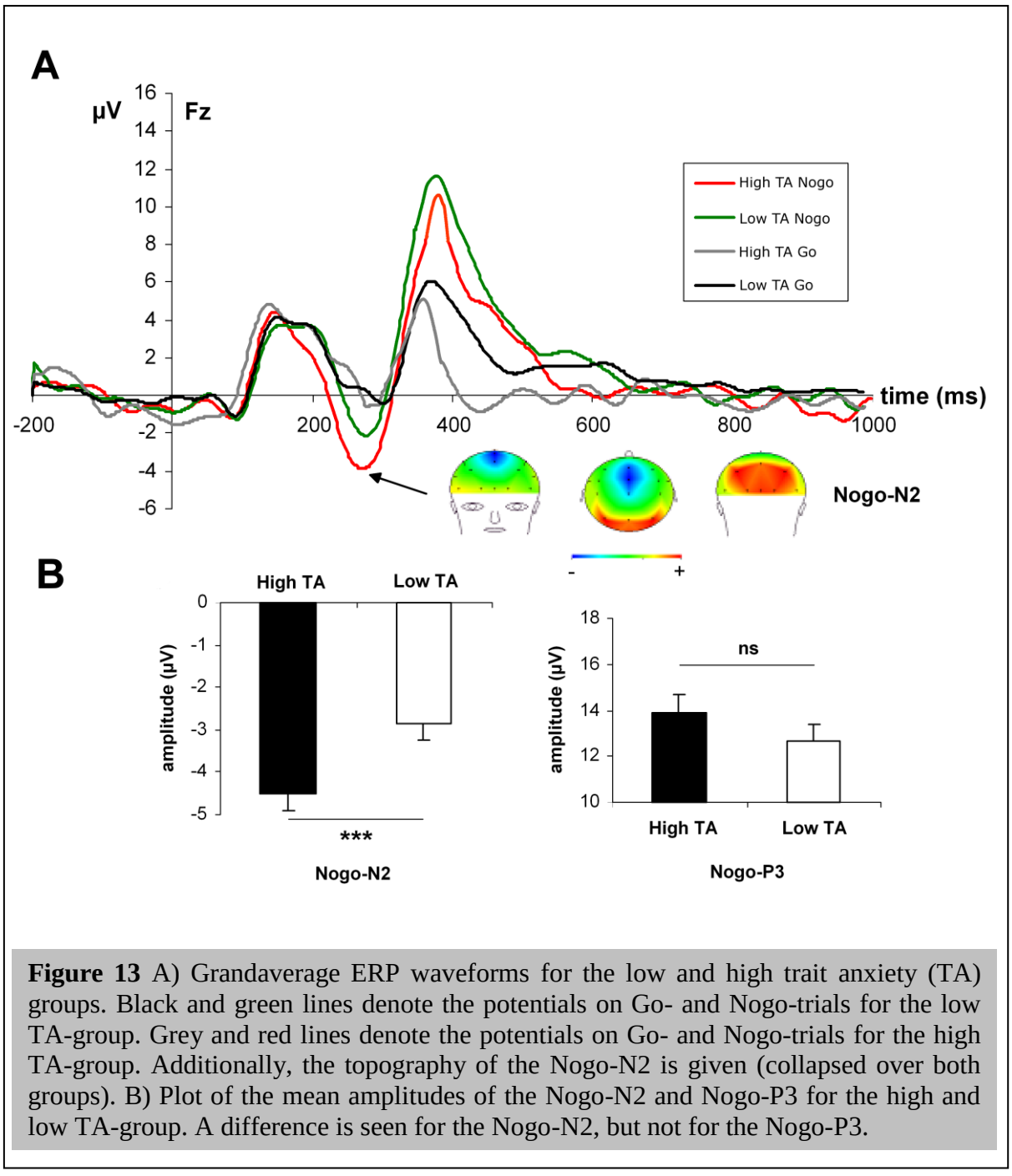


Figure 13 A) Grandaverage ERP waveforms for the low and high trait anxiety (TA) groups. Black and green lines denote the potentials on Go- and Nogo-trials for the low TA-group. Grey and red lines denote the potentials on Go- and Nogo-trials for the high TA-group. Additionally, the topography of the Nogo-N2 is given (collapsed over both groups). B) Plot of the mean amplitudes of the Nogo-N2 and Nogo-P3 for the high and low TA-group. A difference is seen for the Nogo-N2, but not for the Nogo-P3.

Nogo-P3

The ANOVAs on Nogo-P3 amplitudes all revealed main effects of electrode, condition and electrode x condition interactions. As can be seen in Figure 14, the high AS-group showed larger P3 amplitudes (11.27 ± 0.53) than the low AS-group in Nogo-trials: condition x AS-group interaction (F (1, 52) = 11.96; p = 0.001; η^2 = 0.19). P3 amplitudes were not different for the two TA-groups.

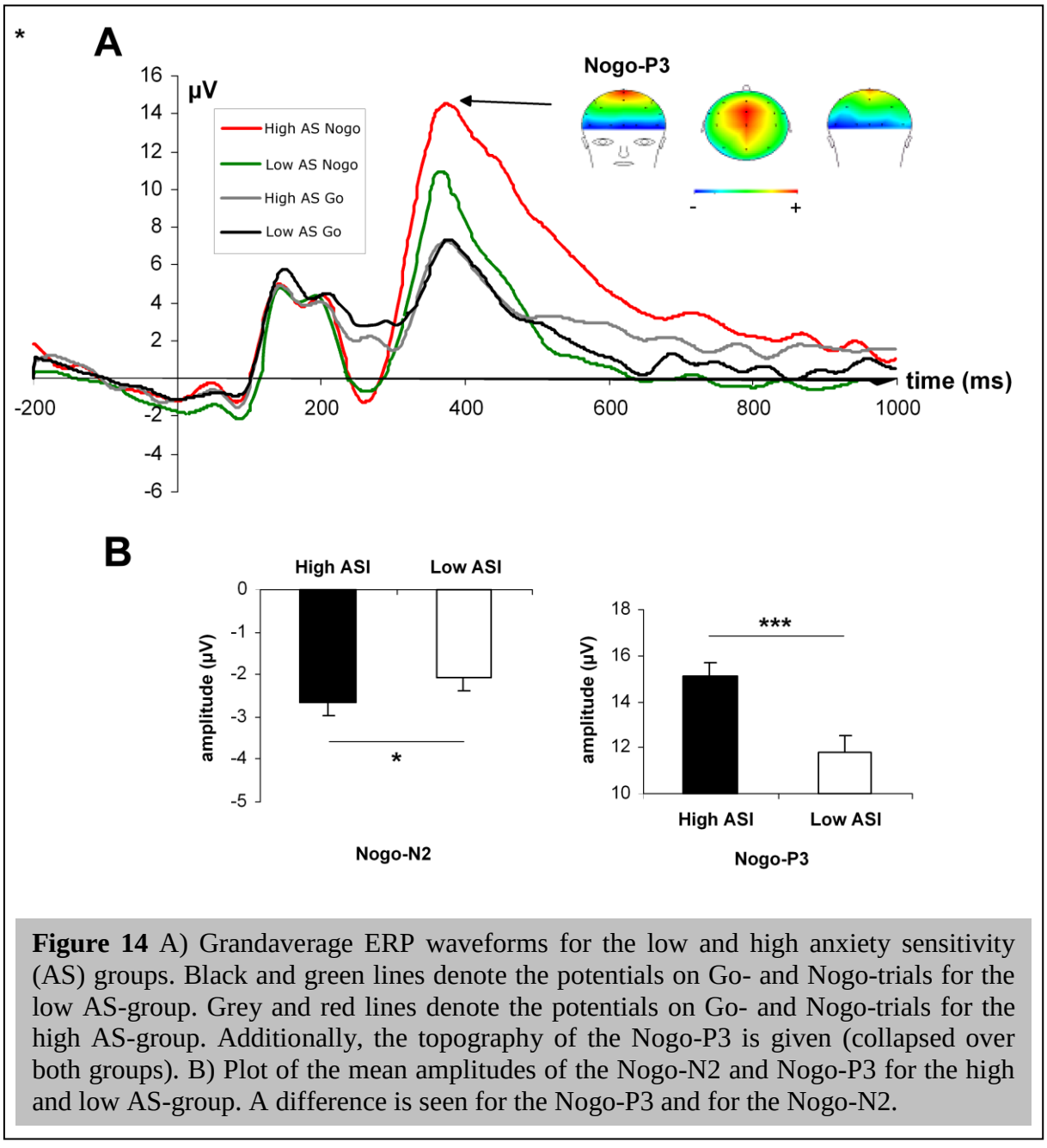


Figure 14 A) Grandaverage ERP waveforms for the low and high anxiety sensitivity (AS) groups. Black and green lines denote the potentials on Go- and Nogo-trials for the low AS-group. Grey and red lines denote the potentials on Go- and Nogo-trials for the high AS-group. Additionally, the topography of the Nogo-P3 is given (collapsed over both groups). B) Plot of the mean amplitudes of the Nogo-N2 and Nogo-P3 for the high and low AS-group. A difference is seen for the Nogo-P3 and for the Nogo-N2.

4.4 Discussion

We examined response inhibition in healthy individuals with respect to the influence of different anxiety-related personality traits. To the best of our knowledge, this study is the first showing that the Nogo-N2 and Nogo-P3, which reflect sub-processes of response inhibition (Falkenstein et al., 1999), are differentially modulated by trait anxiety and anxiety sensitivity in healthy subjects. In line with our prediction, the Nogo-N2 and Nogo-P3 were associated with enhanced anxiety. Particularly, the Nogo-N2 was differentially modulated, that is a higher level of trait anxiety was mainly related to larger Nogo-N2, while fewer effects were obtained for anxiety sensitivity. The Nogo-P3 was best predicted by anxiety sensitivity, while it was slightly affected by trait anxiety.

4.4.1 Behavioural Performance

Behavioural data reflect and corroborate ERP findings as TA and AS contributed significantly to the variance in false alarm rates. Higher Levels of trait anxiety and anxiety sensitivity were correlated with fewer false alarms reflecting enhanced response inhibition. As no significant influences on RTs were obtained, the results are highly specific and unlikely to be biased by speed-accuracy-trade-off effects (SAT).

4.4.2 N2-effects

As expected, and in accordance with the behavioural data, Nogo-N2 amplitudes were significantly enhanced in anxious subjects, particularly with respect to trait anxiety. This anxiety-related effect corroborates studies that reported enhanced Nogo-N2 amplitudes in patients with anxiety disorders (e.g. (Ruchsow et al., 2007)) and anxious subjects (Righi et al., 2009). Yet, others found reduced Nogo-N2 amplitudes in patients with anxiety disorders compared to healthy controls (Kim et al., 2007). High trait-anxious people are more cautious, and exert more cognitive control than low anxious people, for example to inhibit inappropriate motor actions (McNally, 2002) which may result in an increased inhibition-related Nogo-N2 response. This finding and the significant negative correlation of TA scores with N2 amplitudes and false alarm rates support the assumption that the Nogo-N2 specifically reflects (pre-) motor

inhibition processes (Falkenstein et al., 1999). Anxiety sensitivity, which is rather related to a monitoring aspect of anxiety, had a smaller effect on the Nogo-N2.

Studies on the behavioural inhibition (BIS) and behavioural activation system (BAS) are in line with our current finding that anxiety traits are related to enhanced response inhibition. It is proposed that anxiety is an over-activation of the BIS that responds to aversive stimuli and produces behavioural inhibition, increased arousal and attention to outputs (Gray, 1982). Furthermore, it is assumed that high BIS levels represent a vulnerability factor for anxiety or depression (Johnson et al., 2003, McDermott et al., 2009). This is relevant, as these psychiatric disorders are frequently accompanied by alterations in response inhibition processes.

Another effective way to measure response inhibition processes and mainly the capacity to maintain attention is the *Sustained Attention to Response Task (*SART) (Manly et al., 1999). The SART is a variant of a Go/ Nogo paradigm, in which the Nogo stimuli were presented more rarely and more unpredictably than in a standard Go/ Nogo design (Dockree et al., 2005). Studies employing SART found that the amplitudes of Nogo components were negatively correlated with the Nogo-stimulus probability (Braver et al., 2001, Bruin and Wijers, 2002) and that the performance to sustain attention was modulated by individual differences in cognitive performance (Manly et al., 1999, Roche et al., 2005, Righi et al., 2009) or anxiety (Righi et al., 2009). However, compared to standard Nogo-paradigms, SART is determined to mainly investigate the capacity to sustain attention (Manly et al., 1999) and is more sensitive to variations in attentional performance, which may be due to the small Nogo-stimulus probability (Robertson et al., 1997, Manly et al., 1999, Dockree et al., 2005, Roche et al., 2005). Because of these attentional bias effects on ERPs, such as on Nogo-P3, we chose the standard Go/ Nogo-paradigm to investigate response inhibition.

4.4.3 P3-effects

Consistent with previous studies, greater P3 amplitudes were observed in Nogo- than in Go-trials (e.g. (Eimer, 1993)). In contrast to the N2 component, trait anxiety had only an additional influence on the P3 amplitude. Instead, anxiety sensitivity contributed significantly to the variance in Nogo-P3 amplitudes. Anxiety sensitivity is specifically associated with the evaluation and fear of one’s own bodily sensations (McNally, 2002).

We suggest that the tendency to monitor behavioural outcomes leads to the enhanced Nogo-P3 response, as reflected in our data. In this way, the finding supports the assumption that the Nogo-P3 reflects the evaluation of response inhibition (Schmajuk et al., 2006, Beste et al., 2008, Beste et al., 2009). Moreover, our results are consistent with other data showing a magnifying effect of anxiety or cognitive control on P3 amplitudes (Ruchsow et al., 2007, Karch et al., 2008).

Hierarchical regression showed that 19 % of the variance in Nogo-P3 latencies could be explained by AS, TA, age and gender. Particularly AS predicted 14 % of the variance in the dependent variable. These findings are in line with the *processing efficiency theory* of Eysenck et al. (1992), which mainly provides an explanation of the effects of anxiety on task performance (Eysenck and Calvo, 1992, Eysenck et al., 2007, Murray and Janelle, 2007). According to this theory, anxious subjects are thought to be cautious, diligent and ruminative. Moreover, high levels of anxiety are assumed to activate a control system that provides extra processing resources to the task to improve performance. This may be reflected by lengthened processing times (Eysenck and Calvo, 1992) and the above reported prolonged latencies in anxiety. Furthermore, behavioural data show that high levels of anxiety are associated with high quality of task performance, as anxious subjects exhibit fewer false alarms than low anxious subjects. Thus, both behavioural performance and enhanced Nogo-amplitudes illustrate that anxiety is related to an over-inhibition of responses. This is also in line with Eysenck and Calvo (1992) who assume that anxious subjects show enhanced cognitive effort to avoid aversive states and to reach a certain level of performance. To conclude, these findings point to a dysfunctional cerebral activation in anxious people when response inhibition is required (Huang et al., 2009).

The relationship between AS and TA has been a matter of controversial debates (McWilliams and Cox, 2001). In our study, TA and AS are moderately intercorrelated (r = 0.38), which provides an argument for the hypothesis that these personality factors represent a common concept (Lilienfeld, 1996). In contrast, we found that AS and TA are related to different neurophysiological processes, namely Nogo-N2 and -P3. TA, which primarily refers to cognitive symptoms of anxiety and a tendency to respond fearfully in general (McWilliams and Cox, 2001), was primarily associated with the Nogo-N2, reflecting pre-motor response inhibition. AS, focusing on self-evaluation of physical and psychological symptoms (McWilliams and Cox, 2001), was mainly

correlated with the Nogo-P3 which represents the evaluation of the preceding response (Roche et al., 2005) and of the successful outcome of the inhibition process (Schmajuk et al., 2006). Thus, both AS and Nogo-P3 comprise an evaluative component, which is reflected by the strong relationship between AS and Nogo-P3 in our data. To conclude, although the concepts of TA and AS overlap phenotypically in our study, we found a neurophysiological dissociation. This finding provides support for the assumption that TA and AS represent "related, but distinct concepts" of anxiety (McNally, 1996, McWilliams and Cox, 2001, Muris et al., 2001) differentially associated with distinguishable neuronal processes.

4.4.4 Common neuronal network underlying anxiety and response inhibition

The reported functional relation between anxiety and ERPs may well be based on a common neuronal network. Emotional traits and cognitive functions, such as response inhibition, are related to the same neuroanatomical region, i.e. the ACC (Bush et al., 2000, Bokura et al., 2001, Sehlmeyer et al., 2009). Moreover, response inhibition and anxiety-related processes share neurochemical substrates, such as the dopaminergic (DA) and serotonergic system (Fallgatter et al., 1999, Segman et al., 2002, Yoon et al., 2008, Beste et al., 2009). For example, the association between enhanced Nogo-N2 and –P3 and anxiety-related personality traits might be interpreted as an expression of increased dopaminergic activity during response inhibition in anxious subjects. Common underlying factors might influence both characteristics observed here, thus personality traits and electrophysiological components might be affected by common biochemical or genetic factors. Identification of these underlying factors requires further examination.

4.4.5 Conclusion

In summary, the results show that anxiety-related personality traits, such as anxiety sensitivity and trait anxiety, differentially modulate dissociable psychophysiological subprocesses of response inhibition. Even non-affective stimulus material may do so, suggesting a strong generalizability of the examined personality traits and its influence on executive functions. ERPs yielded the psychophysiological correlate of an over-

inhibition in anxious people. Finally, our data demonstrate that the assessment of anxiety traits may be important for studies investigating response inhibition functions.

5 Global Discussion

"A man is but the product of his thoughts. What he thinks, he becomes."

(Mahatma Gandhi, Indian Philosopher, 1869 - 1948)

Investigating the origins of personality still fascinates scientists and provides a wide field of research. Gandhi's citation reflects a certain concept of the origins of human personality. According to the quotation, an individual's personality seems to evolve solely from its own thoughts. On the one hand, this dissertation provides support for the assumption revealing an interaction between personality and cognition. On the other hand, this thesis additionally shows that personality may influence a person's behaviour, emotions and cognition, and is linked to specific brain functions. Specifically, it aims to clarify the relationship between anxiety-traits, behavioural and emotional inhibition, and corresponding brain activations.

Anxiety-related personality traits, such as trait anxiety and anxiety sensitivity, are regarded as stable, basically biological, and as a risk factor for anxiety disorders (Chambers et al., 2004, Schmidt et al., 2008). As anxiety patients, anxious persons show avoidance behaviour and deficits in emotional control. Furthermore, neuroimaging studies suggest an influence of anxiety on inhibitory brain functions (Michael et al., 2007, Barrett and Armony, 2009, Righi et al., 2009). However, findings in both healthy subjects and patients are still ambiguous and therefore considered insufficient (Pineles et al., 2009). Thus, this dissertation investigates the impact of trait anxiety and anxiety sensitivity on emotional and behavioural inhibition in healthy subjects. Two different experimental designs were chosen to analyse the neural processes. First, an aversive fear-conditioning and extinction design was employed to study the influence of trait anxiety on the neurobiology of emotional inhibition using fMRI (chapters 2 and 3). Second, a Go/ Nogo-task was selected to examine the impact of trait anxiety and anxiety sensitivity on the electrophysiology of response inhibition using EEG (chapter 4). The following paragraphs will briefly summarize each chapter.

The literature review in chapter 2 illustrates that neuroimaging studies on fear conditioning and extinction vary in regards to experimental design parameters. They differ for example with respect to the modality of stimuli, timing or neuroimaging technique. Yet, studies with different parameters have reported similar neuroimaging results in healthy subjects. They have described a core neural network of fear conditioning and extinction, including the amygdala, ACC, insula and PFC. Besides, recent investigations indicate that personality and psychopathology may influence fear learning and fear extinction. For example, anxiety patients and anxious subjects are characterized by either facilitated fear learning or impaired fear extinction (Blechert et al., 2007, Michael et al., 2007, Hooker et al., 2008). Neurobiologically, an overactive neuronal fear circuit or reduced prefrontal control was described (Etkin and Wager, 2007). However, the literature on this topic is still equivocal, and even the basic neuronal principles in the context of anxiety are not fully understood. Therefore, the first experiment of this dissertation aimed to clarify the relationship between trait anxiety and the neurobiological processes of fear conditioning and extinction (chapter 3). Twenty healthy women and twelve men were investigated during fMRI-scanning. In agreement with the findings from the literature (chapter 2), the analysis of fMRI-data revealed enhanced activation of the insula, striatum, ACC and amygdala during fear conditioning. During extinction, bilateral activation of the insula and deactivation of the amygdala were observed. Significant correlations between trait anxiety and fMRI-related activity in fear areas were only apparent during extinction. Trait anxiety was associated with both hyper-activation of the amygdala and hypo-activation of the dorsal ACC. These dysregulations implicate impaired inhibition and control of emotional fear responses in healthy anxious subjects. In summary, the first study provided evidence that anxiety comes along with dysregulations of limbic and prefrontal brain activities, and consequently with deficits in emotional inhibition.

It has been demonstrated that patients with anxiety disorders show some degree of behavioural over-inihibition (Herrmann et al., 2003, Kim et al., 2007, Huang et al., 2009). However, experimental and neuroimaging findings on trait-anxious healthy subjects are rare (Righi et al., 2009). Thus, the purpose of the second experiment was to investigate the influence of trait anxiety and anxiety sensitivity on the neurophysiology

of response inhibition in healthy subjects (chapter 3). Thirty-nine women and fifteen men performed a Go/ Nogo-paradigm during EEG-recordings. A cumulative, but differential influence of anxiety traits on response inhibition was observed. Highly trait anxious subjects were characterized by enhanced Nogo-N2, mainly reflecting pre-motor inhibition (Beste et al., 2010b). Anxiety sensitivity was positively correlated with the Nogo-P3 amplitude, primarily representing the evaluation of the outcome of inhibition (Beste et al., 2010b). The PFC and the ACC are major neural generators of the Nogo-N2 and Nogo-P3 (Huster et al., 2010). Our data suggest that these brain areas are hyper-activated during response inhibition in healthy anxious subjects. To conclude, the second investigation confirms the dysregulation of prefrontal brain activation in the context of anxiety, resulting in enhanced behavioural inhibition.

In summary, our findings emphasize the role of the prefrontal cortex and the ACC in inhibition and anxiety. Both experiments found an influence of anxiety traits on the neurobiology of inhibition, in terms of reduced emotional and increased behavioural inhibition. In the first experiment, trait anxiety was related to impaired fear extinction. Neurobiologically, hypo-activation of the PFC and hyper-activation of the amygdala have been observed. The second experiment yielded enhanced response inhibition and anxiety-related hyper-activation of the PFC. Thus, anxiety is related to deficits in behavioural and emotional inhibition. Those results correlate well with observations from daily life. For example, high-anxious subjects show enhanced avoidance behaviour and experience more intense feelings of fright and distress compared to low anxious subjects. Moreover, our findings in healthy subjects are consistent with those reported for anxiety patients. Anxiety disorders have been associated with deficits in response inhibition (e.g. (Ruchsow et al., 2007)), fear conditioning and extinction (e.g. (Lissek et al., 2005)), as well as with dysregulations of the PFC and the limbic system (e.g. (Etkin and Wager, 2007)). For this reason, exposure to threatening stimuli has been successfully used as treatment for anxiety disorders in cognitive behavioural psychotherapies (Anderson and Insel, 2006). In conclusion, prefrontal brain mechanisms and inhibitory functions are disturbed in the context of pathological and "normal" anxiety. These neurobiological dysregulations in healthy anxious subjects may increase the risk of anxiety disorders. Therefore, further research may concentrate

on identifying risky personality profiles to early prevent from developing pathological states.

Yet, this dissertation has made important contributions to the understanding of the pathomechanisms of anxiety. To provide further insight into the basis of anxiety traits and anxiety disorders, research should be extended to genetic investigations and additional methods of analyses. In the following, promising approaches will be presented briefly. First, the integration of molecular and genetic aspects is discussed. So far, genetic and pharmacological studies have reported a number of associations between anxiety disorders, anxiety traits and, for example, dopaminergic, serotonergic and GABAergic mechanisms (Munafo et al., 2003, Furmark et al., 2004, Stoppel et al., 2006, Domschke and Dannlowski, 2009, Gonda et al., 2009, Krystal and Neumeister, 2009, Lonsdorf et al., 2009a, Kuzelova et al., 2010). A few investigations found significant effects of serotonin on fear conditioning and extinction (Garpenstrand et al., 2001, Lonsdorf et al., 2009b). Even individual differences in response-inhibition capacity may be explained by DNA variation in catecholamine genes (Chamberlain et al., 2006, Eagle et al., 2008, Chambers et al., 2009). Moreover, variations in amygdala and prefrontal brain activation can be attributed to genetic factors, such as to the 5-HTTLPR functional polymorphism (Hariri et al., 2002, Canli and Lesch, 2007, Dannlowski et al., 2008, Fakra et al., 2009). In sum, identifying genetic risk factors would help to better understand the relationship between anxiety, inhibition and brain activation.

Second, various methods of analysis such as the exploration of resting state brain activity or connectivity analysis may improve investigating the nature of anxiety. The resting state is defined as a status in which an individual is awake and alert, but not actively involved in a task (Raichle et al., 2001). So far, few studies have revealed resting-state abnormalities in patients with major depression (e.g. (Greicius et al., 2007)). It would be interesting to examine whether anxious subjects show sustained dysregulations of amygdala and PFC also in resting states. Besides, analyses of functional connectivity between prefrontal, limbic and motor areas may be useful to further investigate the process of behavioural and emotional inhibition. For example, recent studies have yielded functional and anatomical connectivity abnormalities in

anxiety patients (Etkin et al., 2010), anxious subjects (Cohen et al., 2009, Cremers et al., 2010) and patients with attention-deficit hyperactivity disorder (ADHD) (Cubillo et al., 2010). Moreover, morphometric methods may identify structural brain differences among high and low anxious subjects (Ashburner and Friston, 2000). In this way, research may determine correlations between brain shape of, for example, the PFC or the amygdala, the degree of emotional and behavioural inhibition and personality traits. At least, multimodal imaging techniques will complement the spatial precision of fMRI with the temporal precision of the EEG (Laufs et al., 2008, Friston, 2009). In future, these above-mentioned techniques will be implemented to improve investigation and clarification of the aetiology of anxiety and it's relation to cognition, emotion and behaviour.

6 Deutsche Zusammenfassung

Die vorliegende Dissertation untersucht in zwei Studien den Einfluss angstbezogener Persönlichkeitsmerkmale a) auf die Neurobiologie der emotionalen Furchtkonditionierung und -extinktion mittels funktioneller Magnetresonanztomographie (fMRT) und b) auf die Elektrophysiologie der kognitiven Verhaltenshemmung mittels Elektroenzephalographie (EEG).

Angstbezogene Persönlichkeitsfaktoren, wie Trait-Angst und Angstsensitivität, werden als stabile und biologische Prädispositionen angesehen (Eysenck, 1963). Während Trait-Angst durch ein hohes Bedürfnis nach Sicherheit und (kognitiver) Kontrolle gekennzeichnet ist (Fales et al., 2008), erfasst Angstsensitivität die verstärkte Beobachtung und Bewertung eigener Körperreaktionen (McNally, 2002). Diese Merkmale stehen in einem engen Zusammenhang zu pathologischer Angst (Chambers et al., 2004, Zvolensky and Schmidt, 2007, Schmidt et al., 2008) und können einen Risikofaktor für die Entwicklung von Angsterkrankungen darstellen (Bienvenu et al., 2001, Simon et al., 2003). Symptomatisch können ängstliche Personen und Angstpatienten durch eine gestörte Kontrolle bzw. Hemmung von Emotionen und Verhalten charakterisiert werden (Melcher et al., 2008).

Experimentell stellt die Furchtkonditionierung und -extintion einen wichtigen Ansatz zur Untersuchung der emotionalen Hemmung dar (Kapitel 2 und 3), während die Verhaltenshemmung anhand der Go/ Nogo-Aufgabe überprüft werden kann (Kapitel 4). Mittels moderner bildgebender Verfahren wie z.B. fMRT oder EEG können die zugrunde liegenden neurobiologischen Korrelate nicht-invasiv untersucht werden.

Wie der Literaturüberblick in Kapitel 2 dieser Dissertation zeigt, lassen sich neuroanatomisch Netzwerke beschreiben, die für das Erlernen und Löschen von Angst zuständig sind. Die Übersicht über die zahlreichen bildgebenden Studien konnte bestätigen, dass unabhängig vom Design der Studie vor allem die Amygdala, die Insula, der Anteriore Cinguläre Cortex (ACC) und das Striatum in die Furchtkonditionierung involviert sind (Sehlmeyer et al., 2009). Die Furchtextinktion aktiviert vor allem Interaktionen zwischen kortikalen und subkortikalen Gehirnregionen wie dem Präfrontalen Kortex (PFK) und der Amygdala. Es wird angenommen, dass der mediale PFK und vor allem der dorsale ACC die konditionierten Furchtreaktionen durch

Hemmung der Neurone der lateralen Amygdala unterdrücken (Phelps et al., 2004, Lang et al., 2009). Diese Kreisläufe können im krankhaften Zustand, wie z.B. bei einer Angsterkrankung, aber auch bei erhöhter Ängstlichkeit im gesunden Zustand in Form einer verstärkten Aktivierung der Amygdala und einer verminderten präfrontalen Hemmung dysreguliert sein (Bremner et al., 2005, Lissek et al., 2008). Das Furchtlernen kann dadurch bei ängstlichen Personen und Angstpatienten erleichtert sein, die Löschung von Furchtreaktionen erschwert oder gar verhindert werden (Michael et al., 2007, Barrett and Armony, 2009). Die Befunde dazu sind jedoch nicht eindeutig (Pineles et al., 2009). Daher wurde in der ersten Studie dieser Dissertation (Kapitel 3) der Einfluss des Persönlichkeitsmerkmals Trait-Angst auf die Neurobiologie der Furchtkonditionierung und -extinktion mittels fMRT untersucht. In diese Untersuchung wurden 32 gesunde, rechtshändige Probanden (12 Männer, 20 Frauen; 23,6 ± 4,1 Jahre) einbezogen. Während der fMRT-Messung (Philips Gyroscan Intera T3.0) wurde den Probanden ein aversives Konditionierungsparadigma präsentiert, bei dem neutrale Gesichter (Tottenham et al., 2002) zu 25 % mit einem aversiven Schreckton gepaart wurden. Nach jeder experimentellen Phase (Familiarisierung, Akquisition, Extinktion) beurteilten die Probanden Valenz und Erregung der Gesichter über die Self-Assessment Manikin Skala (SAM) (Bradley and Lang, 1994). Trait-Angst wurde mit Hilfe des State-Trait-Angst-Inventars (STAI) (Laux, 1981) erfasst. Während der fMRT-Untersuchung (multislice single shot EPI, 30 Schichten, TR 2 s, TE 32 ms, Voxel von 3,6 mm Kantenlänge) wurden die Stimuli mittels Presentation Software® (Version 12.2, 2004, Neurobehavioral Systems Inc., Albany, CA, USA) und einer MRT-kompatiblen Projektionseinrichtung präsentiert. Die Datenanalyse der fMRT-Daten erfolgte mit SPM5 (Wellcome Department of Cognitive Neurology, London).

In Übereinstimmung mit bisherigen bildgebenden Studien zur Furchtkonditionierung und -extinktion zeigten sich in der vorliegenden Arbeit Aktivierungen typischer furchtrelevanter Areale wie der Insula, dem ACC und dem Striatum während der Furchtkonditionierung (Sehlmeyer et al., 2009). Für die Amygdala konnte eine Aktivierung vor allem während der späten Konditionierungsphase gefunden werden. Die Aktivierungen der Insula, des ACC und des motorischen Kortex während der Extinktion entsprechen ebenfalls denen der einschlägigen Literatur (Phelps et al., 2004). In der späten Extintionsphase konnte eine

starke Deaktivierung der Amygdala beobachtet werden. Auch die Verhaltensdaten zeigten, dass eine erfolgreiche Konditionierung stattgefunden hat. Der konditionierte Stimulus wurde im Verlauf des Experiments signifikant negativer und erregender bewertet als der nicht konditionierte.

Einflüsse des Persönlichkeitsmerkmals Trait-Angst auf die Neurobiologie der Amygdala und des dorsalen ACC konnten ausschließlich während der Extinktion gefunden werden. Trait-ängstliche Probanden zeigten neben einer Hyperaktivierung der Amygdala, auch eine Hypoaktivierung des dorsalen ACC während der Extinktion. Diese neurobiologischen Dysregulationen könnten zu einer schlechteren Hemmung bzw. Löschung der konditionierten Angstreaktionen und somit zu einem erhöhten Risiko für die Entwicklung einer Angsterkrankung beitragen. Die Ergebnisse der ersten Studie unterstreichen die Bedeutung von angstbezogenen Persönlichkeitsmerkmalen für die Hemmung und Löschung von Furchtreaktionen.

In der zweiten Studie der Dissertation (Kapitel 4) wurde der Einfluss der Persönlichkeitsmerkmale Trait-Angst und Angstsensitivität auf die Elektrophysiologie der Verhaltenshemmung mittels EEG untersucht. Während bei Patienten mit einer Angsterkrankung eine stärkere Verhaltenshemmung als bei gesunde Kontrollen nachgewiesen worden ist (Ruchsow et al., 2007), haben nur wenige Studien den Einfluss von Angst als Persönlichkeitsmerkmal auf die Verhaltenshemmung beschrieben (Righi et al., 2009). Aus diesem Grund untersuchte das zweite Experiment der Dissertation, ob die ereigniskorrelierten Potentiale (EKPs) der Verhaltenshemmung (Nogo-N2 und Nogo-P3) durch Trait-Angst und Angstsensitivität moduliert werden können.

Mittels EEG wurden 54 gesunde Probanden (15 Männer, 39 Frauen; 22,6 ± 2,0 Jahre) während einer Go/Nogo-Aufgabe untersucht. Auf den „Go“-Reiz sollte mit einem möglichst schnellen Tastendruck reagiert, bei dem „Nogo“-Reiz eine motorische Antwort unterdrückt werden. Angstsensitivität wurde anhand des Angstsensitivitäts-Index (ASI-Revised) (Reiss et al., 1986, Peterson and Reiss, 1987), Trait-Angst mit Hilfe des STAI erfasst. Die Ergebnisse verdeutlichen, dass Personen mit hoher Trait-Angst eine stärkere Nogo-N2 sowie weniger falsch-positive Reaktionen bei Präsentation des Nogo-Signals zeigten als wenig trait-ängstliche Probanden. Angstsensitivität wies keinen signifikanten Einfluss auf die Ausprägung dieser Komponente auf. Im Gegensatz

dazu zeigten Personen mit hoher Angstsensitivität eine größere Nogo-P3 als Personen mit geringeren Werten. Diese Modulation stand in einem geringen Zusammenhang mit Trait-Angst.

Die Studie verdeutlicht, dass angstbezogene Persönlichkeitsmerkmale elektrophysiologische Korrelate und kognitive Verhaltenshemmung differentiell modulieren können. Personen mit hoher Trait-Angst und einem hohen Bedürfnis nach kognitiver Kontrolle weisen eine erhöhte Nogo-N2 und somit eine stärkere Verhaltenshemmung auf als wenig trait-ängstliche Probanden. Hohe Angstsensitivität geht mit einer erhöhten Nogo-P3 einher, was auf eine verstärkte Bewertung eigener Handlungen hinweist. Diese Dissoziation unterstützt die Hypothese der funktionellen Unterschiedlichkeit von Nogo-N2 und Nogo-P3 (Falkenstein et al., 1999). In dieser Studie gehen hohe Ausprägungen von Trait-Angst und Angstsensitivität mit einer Hyperativität des PFK und einer erhöhten Verhaltenshemmung einher. Zusammenfassend konnte in dieser Dissertation also gezeigt werden, dass kognitive Prozesse, insbesondere die Verhaltenshemmung und die Löschung von Furchtreaktionen, durch angstbezogene Persönlichkeitsmerkmale moduliert werden können. Angst als Persönlichkeitsmerkmal geht bereits im gesunden Zustand mit einer starken Verhaltenshemmung, einer geringen Hemmung von emotionalen Reaktionen und einer Dysregulation des PFK einher.

7 References

Anders, S., Lotze, M., Wildgruber, D., Erb, M., Grodd, W. and Birbaumer, N., 2005. Processing of a simple aversive conditioned stimulus in a divided visual field paradigm: an fMRI study. Experimental Brain Research. 162, 213-219.

Anderson, K. C. and Insel, T. R., 2006. The promise of extinction research for the prevention and treatment of anxiety disorders. Biological Psychiatry. 60, 319-321.

Aron, A. R., 2007. The neural basis of inhibition in cognitive control. Neuroscientist. 13, 214-228.

Aron, A. R., 2009. Introducing a special issue on stopping action and cognition. Neuroscience and biobehavioral reviews. 33, 611-612.

Ashburner, J. and Friston, K. J., 2000. Voxel-based morphometry--the methods. Neuroimage. 11, 805-821.

Bangasser, D. A., Waxler, D. E., Santollo, J. and Shors, T. J., 2006. Trace conditioning and the hippocampus: the importance of contiguity. The Journal of Neuroscience. 26, 8702-8706.

Banich, M. T., Mackiewicz, K. L., Depue, B. E., Whitmer, A. J., Miller, G. A. and Heller, W., 2009. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. Neuroscience and biobehavioral reviews. 33, 613-630.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J. and van, I. M. H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychological Bulletin. 133, 1-24.

Barad, M., Gean, P. W. and Lutz, B., 2006. The role of the amygdala in the extinction of conditioned fear. Biological Psychiatry. 60, 322-328.

Barrett, J. and Armony, J. L., 2009. Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. Psychological Medicine. 39, 255-265.

Bellgowan, P. S., Bandettini, P. A., van Gelderen, P., Martin, A. and Bodurka, J., 2006. Improved BOLD detection in the medial temporal region using parallel imaging and voxel volume reduction. Neuroimage. 29, 1244-1251.

Beste, C., Saft, C., Andrich, J., Gold, R. and Falkenstein, M., 2008. Response inhibition in Huntington's disease-a study using ERPs and sLORETA. Neuropsychologia. 46, 1290-1297.

Beste, C., Dziobek, I., Hielscher, H., Willemssen, R. and Falkenstein, M., 2009. Effects of stimulus-response compatibility on inhibitory processes in Parkinson's disease. The European Journal of Neuroscience. 29, 855-860.

Beste, C., Baune, B. T., Domschke, K., Falkenstein, M. and Konrad, C., 2010a. Paradoxical association of the brain-derived-neurotrophic-factor val66met genotype with response inhibition. Neuroscience. 166, 178-184.

Beste, C., Willemssen, R., Saft, C. and Falkenstein, M., 2010b. Response inhibition subprocesses and dopaminergic pathways: basal ganglia disease effects. Neuropsychologia. 48, 366-373.

Bienvenu, O. J., Brown, C., Samuels, J. F., Liang, K. Y., Costa, P. T., Eaton, W. W. and Nestadt, G., 2001. Normal personality traits and comorbidity among phobic, panic and major depressive disorders. Psychiatry Research. 102, 73-85.

Bishop, S. J., Duncan, J. and Lawrence, A. D., 2004. State anxiety modulation of the amygdala response to unattended threat-related stimuli. The Journal of Neuroscience. 24, 10364-10368.

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

Bishop, S. J., 2009. Trait anxiety and impoverished prefrontal control of attention. Nature Neuroscience. 12, 92-98.

Blair, H. T., Sotres-Bayon, F., Moita, M. A. and Ledoux, J. E., 2005. The lateral amygdala processes the value of conditioned and unconditioned aversive stimuli. Neuroscience. 133, 561-569.

Blaxton, T. A., Zeffiro, T. A., Gabrieli, J. D., Bookheimer, S. Y., Carrillo, M. C., Theodore, W. H. and Disterhoft, J. F., 1996. Functional mapping of human learning: a positron emission tomography activation study of eyeblink conditioning. The Journal of Neuroscience. 16, 4032-4040.

Blechert, J., Michael, T., Vriends, N., Margraf, J. and Wilhelm, F. H., 2007. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behaviour Research and Therapy. 45, 2019-2033.

Bokura, H., Yamaguchi, S. and Kobayashi, S., 2001. Electrophysiological correlates for response inhibition in a Go/NoGo task. Clinical Neurophysiology. 112, 2224-2232.

Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C. and Buchel, C., 2002. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain. 125, 1326-1336.

Bradley, M. M. and Lang, P. J., 1994. Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. Journal of behavior therapy and experimental psychiatry. 25, 49-59.

Braver, T. S., Barch, D. M., Gray, J. R., Molfese, D. L. and Snyder, A., 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cerebral Cortex. 11, 825-836.

Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., Grillon, C. and Charney, D. S., 2005. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. Psychological Medicine. 35, 791-806.

Bruin, K. J. and Wijers, A. A., 2002. Inhibition, response mode, and stimulus probability: a comparative event-related potential study. Clinical Neurophysiology. 113, 1172-1182.

Buchanan, S. L. and Powell, D. A., 1982. Cingulate cortex: its role in Pavlovian conditioning. Journal of comparative and physiological psychology. 96, 755-774.

Buchel, C., Morris, J., Dolan, R. J. and Friston, K. J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron. 20, 947-957.

Buchel, C., Dolan, R. J., Armony, J. L. and Friston, K. J., 1999. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. The Journal of Neuroscience. 19, 10869-10876.

Buchel, C. and Dolan, R. J., 2000. Classical fear conditioning in functional neuroimaging. Current opinion in neurobiology. 10, 219-223.

Bush, G., Luu, P. and Posner, M. I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Science. 4, 215-222.

Butler, T., Pan, H., Epstein, J., Protopopescu, X., Tuescher, O., Goldstein, M., Cloitre, M., Yang, Y., Phelps, E., Gorman, J., Ledoux, J., Stern, E. and Silbersweig, D., 2005. Fear-related activity in subgenual anterior cingulate differs between men and women. Neuroreport. 16, 1233-1236.

Canli, T. and Lesch, K. P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. Nature Neuroscience. 10, 1103-1109.

Carlson, J. M., Greenberg, T., Rubin, D. and Mujica-Parodi, L. R., 2010. Feeling anxious: anticipatory amygdalo-insular response predicts the feeling of anxious anticipation. Soc Cogn Affect Neurosci.

Carlsson, K., Andersson, J., Petrovic, P., Petersson, K. M., Ohman, A. and Ingvar, M., 2006. Predictability modulates the affective and sensory-discriminative neural processing of pain. Neuroimage. 32, 1804-1814.

Carretie, L., Mercado, F., Hinojosa, J. A., Martin-Loeches, M. and Sotillo, M., 2004. Valence-related vigilance biases in anxiety studied through event-related potentials. Journal of Affective Disorders. 78, 119-130.

Carter, R. M., O'Doherty, J. P., Seymour, B., Koch, C. and Dolan, R. J., 2006. Contingency awareness in human aversive conditioning involves the middle frontal gyrus. Neuroimage. 29, 1007-1012.

Carver, C. S. and Scheier, M. F., 2000. Perspectives on Personality. 4th edition Allyn and Bacon.

Chamberlain, S. R., Muller, U., Blackwell, A. D., Clark, L., Robbins, T. W. and Sahakian, B. J., 2006. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science. 311, 861-863.

Chambers, C. D., Garavan, H. and Bellgrove, M. A., 2009. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neuroscience and biobehavioral reviews. 33, 631-646.

Chambers, J. A., Power, K. G. and Durham, R. C., 2004. The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of Generalized Anxiety Disorder. Journal of Anxiety Disorders. 18, 587-607.

Chan, C. K. and Lovibond, P. F., 1996. Expectancy bias in trait anxiety. Journal of Abnormal Psychology. 105, 637-647.

Cheng, D. T., Knight, D. C., Smith, C. N., Stein, E. A. and Helmstetter, F. J., 2003. Functional MRI of human amygdala activity during Pavlovian fear conditioning: stimulus processing versus response expression. Behavioral neuroscience. 117, 3-10.

Cheng, D. T., Knight, D. C., Smith, C. N. and Helmstetter, F. J., 2006. Human amygdala activity during the expression of fear responses. Behavioral neuroscience. 120, 1187-1195.

Cheng, D. T., Richards, J. and Helmstetter, F. J., 2007. Activity in the human amygdala corresponds to early, rather than late period autonomic responses to a signal for shock. Learning & Memory. 14, 485-490.

Cheng, D. T., Disterhoft, J. F., Power, J. M., Ellis, D. A. and Desmond, J. E., 2008. Neural substrates underlying human delay and trace eyeblink conditioning. Proceedings of the National Academy of Sciences of the United States of America. 105, 8108-8113.

Cloninger, C. R., 1986. A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatric developments. 4, 167-226.

Cloninger, C. R., 1987. A systematic method for clinical description and classification of personality variants. A proposal. Archives of General Psychiatry. 44, 573-588.

Coghill, R. C., Talbot, J. D., Evans, A. C., Meyer, E., Gjedde, A., Bushnell, M. C. and Duncan, G. H., 1994. Distributed processing of pain and vibration by the human brain. The Journal of Neuroscience. 14, 4095-4108.

Cohen, M. X., Schoene-Bake, J. C., Elger, C. E. and Weber, B., 2009. Connectivity-based segregation of the human striatum predicts personality characteristics. Nat Neurosci. 12, 32-34.

Cremers, H. R., Demenescu, L. R., Aleman, A., Renken, R., van Tol, M. J., van der Wee, N. J., Veltman, D. J. and Roelofs, K., 2010. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. Neuroimage. 49, 963-970.

Cubillo, A., Halari, R., Ecker, C., Giampietro, V., Taylor, E. and Rubia, K., 2010. Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. Journal of Psychiatric Research. In press.

Damsa, C., Kosel, M. and Moussally, J., 2009. Current status of brain imaging in anxiety disorders. Curr Opin Psychiatry. 22, 96-110.

Dannlowski, U., Ohrmann, P., Bauer, J., Deckert, J., Hohoff, C., Kugel, H., Arolt, V., Heindel, W., Kersting, A., Baune, B. T. and Suslow, T., 2008. 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. Neuropsychopharmacology. 33, 418-424.

Dannlowski, U., Ohrmann, P., Konrad, C., Domschke, K., Bauer, J., Kugel, H., Hohoff, C., Schoning, S., Kersting, A., Baune, B. T., Mortensen, L. S., Arolt, V., Zwitserlood, P., Deckert, J., Heindel, W. and Suslow, T., 2009. Reduced amygdala-prefrontal coupling in major depression: association with MAOA genotype and illness severity. International Journal of Neuropsychopharmacology. 12, 11-22.

Delgado, M. R., Olsson, A. and Phelps, E. A., 2006. Extending animal models of fear conditioning to humans. Biological Psychology. 73, 39-48.

Dennis, T. A. and Chen, C. C., 2007. Emotional face processing and attention performance in three domains: neurophysiological mechanisms and moderating effects of trait anxiety. International Journal of Psychophysiology. 65, 10-19.

Dennis, T. A. and Chen, C. C., 2009. Trait anxiety and conflict monitoring following threat: an ERP study. Psychophysiology. 46, 122-131.

Dickie, E. W. and Armony, J. L., 2008. Amygdala responses to unattended fearful faces: Interaction between sex and trait anxiety. Psychiatry Research. 162, 51-57.

Digman, J. M., 1990. Personality structure: Emergence of the five-factor model. Annual Review of Psychology. 41.

Dimitrova, A., Kolb, F. P., Elles, H. G., Maschke, M., Gerwig, M., Gizewski, E. and Timmann, D., 2004. Cerebellar activation during leg withdrawal reflex conditioning: an fMRI study. Clinical Neurophysiology. 115, 849-857.

Dockree, P. M., Kelly, S. P., Robertson, I. H., Reilly, R. B. and Foxe, J. J., 2005. Neurophysiological markers of alert responding during goal-directed behavior: a high-density electrical mapping study. Neuroimage. 27, 587-601.

Domschke, K. and Dannlowski, U., 2009. Imaging genetics of anxiety disorders. Neuroimage. In press.

Domschke, K., Stevens, S., Pfleiderer, B. and Gerlach, A. L., 2010. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clinical Psychology Review. 30, 1-11.

Doronbekov, T. K., Tokunaga, H., Ikejiri, Y., Kazui, H., Hatta, N., Masaki, Y., Ogino, A., Miyoshi, N., Oku, N., Nishikawa, T. and Takeda, M., 2005. Neural basis of fear conditioning induced by video clip: positron emission tomography study. Psychiatry and clinical neurosciences. 59, 155-162.

Dunsmoor, J. E., Bandettini, P. A. and Knight, D. C., 2007. Impact of continuous versus intermittent CS-UCS pairing on human brain activation during Pavlovian fear conditioning. Behavioral Neuroscience. 121, 635-642.

Dunsmoor, J. E., Bandettini, P. A. and Knight, D. C., 2008. Neural correlates of unconditioned response diminution during Pavlovian conditioning. Neuroimage. 40, 811-817.

Eagle, D. M., Bari, A. and Robbins, T. W., 2008. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology (Berl). 199, 439-456.

Eimer, M., 1993. Effects of attention and stimulus probability on ERPs in a Go/Nogo task. Biological Psychology. 35, 123-138.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R. and Hirsch, J., 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron. 44, 1043-1055.

Etkin, A. and Wager, T. D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry. 164, 1476-1488.

Etkin, A., Prater, K. E., Hoeft, F., Menon, V. and Schatzberg, A. F., 2010. Failure of Anterior Cingulate Activation and Connectivity With the Amygdala During Implicit Regulation of Emotional Processing in Generalized Anxiety Disorder. American Journal of Psychiatry. In press.

Eysenck, H. J., 1963. Biological Basis of Personality. Nature. 199, 1031-1034.

Eysenck, M. W., 1967. The Biological Basis of Personality. IL: Thomas, Springfield

Eysenck, M. W. and Calvo, M. G., 1992. Anxiety and Performance: The processing efficiency theory. Cognition &Emotion. 6, 409 - 434.

Eysenck, M. W., Derakshan, N., Santos, R. and Calvo, M. G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion. 7, 336-353.

Fakra, E., Hyde, L. W., Gorka, A., Fisher, P. M., Munoz, K. E., Kimak, M., Halder, I., Ferrell, R. E., Manuck, S. B. and Hariri, A. R., 2009. Effects of HTR1A C(-1019)G on amygdala reactivity and trait anxiety. Archives of General Psychiatry. 66, 33-40.

Fales, C. L., Barch, D. M., Burgess, G. C., Schaefer, A., Mennin, D. S., Gray, J. R. and Braver, T. S., 2008. Anxiety and cognitive efficiency: differential modulation of transient and sustained neural activity during a working memory task. Cognitive, affective & behavioral neuroscience. 8, 239-253.

Falkenstein, M., Hoormann, J. and Hohnsbein, J., 1999. ERP components in Go/Nogo tasks and their relation to inhibition. Acta Psychologica (Amst). 101, 267-291.

Falkenstein, M., 2006. Inhibition, conflict and the Nogo-N2. Clinical Neurophysiology. 117, 1638-1640.

Fallgatter, A. J., Jatzke, S., Bartsch, A. J., Hamelbeck, B. and Lesch, K. P., 1999. Serotonin transporter promoter polymorphism influences topography of inhibitory motor control. The International Journal of Neuropsychopharmacology. 2, 115-120.

Fendt, M. and Fanselow, M. S., 1999. The neuroanatomical and neurochemical basis of conditioned fear. Neuroscience and biobehavioral reviews. 23, 743-760.

Ferrari, M. C., Busatto, G. F., McGuire, P. K. and Crippa, J. A., 2008. Structural magnetic resonance imaging in anxiety disorders: an update of research findings. Revista brasileira de psiquiatria. 30, 251-264.

Finger, E. C., Marsh, A. A., Buzas, B., Kamel, N., Rhodes, R., Vythilingham, M., Pine, D. S., Goldman, D. and Blair, J. R., 2007. The impact of tryptophan depletion and 5-HTTLPR genotype on passive avoidance and response reversal instrumental learning tasks. Neuropsychopharmacology. 32, 206-215.

Fischer, H., Andersson, J. L., Furmark, T. and Fredrikson, M., 2000. Fear conditioning and brain activity: a positron emission tomography study in humans. Behavioral Neuroscience. 114, 671-680.

Fischer, H., Andersson, J. L., Furmark, T., Wik, G. and Fredrikson, M., 2002. Right-sided human prefrontal brain activation during acquisition of conditioned fear. Emotion. 2, 233-241.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A. and Noll, D. C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magnetic Resonance in Medicine. 33, 636-647.

Fox, E., Derakshan, N. and Shoker, L., 2008. Trait anxiety modulates the electrophysiological indices of rapid spatial orienting towards angry faces. Neuroreport. 19, 259-263.

Fredrikson, M., Wik, G., Fischer, H. and Andersson, J., 1995. Affective and attentive neural networks in humans: a PET study of Pavlovian conditioning. Neuroreport. 7, 97-101.

Freeman, J. H., Jr., Cuppernell, C., Flannery, K. and Gabriel, M., 1996. Limbic thalamic, cingulate cortical and hippocampal neuronal correlates of discriminative approach learning in rabbits. Behavioural brain research. 80, 123-136.

Friston, K. J., 2009. Modalities, modes, and models in functional neuroimaging. Science. 326, 399-403.

Furmark, T., Fischer, H., Wik, G., Larsson, M. and Fredrikson, M., 1997. The amygdala and individual differences in human fear conditioning. Neuroreport. 8, 3957-3960.

Furmark, T., Tillfors, M., Garpenstrand, H., Marteinsdottir, I., Langstrom, B., Oreland, L. and Fredrikson, M., 2004. Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. Neuroscience Letters. 362, 189-192.

Gallinat, J., Kunz, D., Lang, U. E., Neu, P., Kassim, N., Kienast, T., Seifert, F., Schubert, F. and Bajbouj, M., 2007. Association between cerebral glutamate and human behaviour: the sensation seeking personality trait. Neuroimage. 34, 671-678.

Gardini, S., Cloninger, C. R. and Venneri, A., 2009. Individual differences in personality traits reflect structural variance in specific brain regions. Brain research bulletin. 79, 265-270.

Garpenstrand, H., Annas, P., Ekblom, J., Oreland, L. and Fredrikson, M., 2001. Human fear conditioning is related to dopaminergic and serotonergic biological markers. Behavioral neuroscience. 115, 358-364.

Gibbon, J. and Balsam, P., 1981. Spreading association in time. In C M Locurto, H S Terrace & J Gibbon (Eds), Autoshaping and conditioning theory New York: Academy Press, 219-253.

Gonda, X., Fountoulakis, K. N., Juhasz, G., Rihmer, Z., Lazary, J., Laszik, A., Akiskal, H. S. and Bagdy, G., 2009. Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. European archives of psychiatry and clinical neuroscience. 259, 106-113.

Gottfried, J. A. and Dolan, R. J., 2004. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nature Neuroscience. 7, 1144-1152.

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

Gray, J. A., 1970. The psychophysiological basis of introversion-extraversion. Behaviour research and therapy. 8, 249-266.

Gray, J. A., 1982. The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system Oxford: Oxford University Press.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L. and Schatzberg, A. F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biological Psychiatry. 62, 429-437.

Guimaraes, F. S., Hellewell, J., Hensman, R., Wang, M. and Deakin, J. F., 1991. Characterization of a psychophysiological model of classical fear conditioning in healthy volunteers: influence of gender, instruction, personality and placebo. Psychopharmacology (Berl). 104, 231-236.

Haas, B. W., Omura, K., Constable, R. T. and Canli, T., 2007. Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. Behavioral Neuroscience. 121, 249-256.

Hall, J. F., 1984. Backward conditioning in Pavlovian type studies. Reevaluation and present status. The Pavlovian journal of biological science. 19, 163-168.

Hamm, A. O. and Weike, A. I., 2005. The neuropsychology of fear learning and fear regulation. International Journal of Psychophysiology. 57, 5-14.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M. F. and Weinberger, D. R., 2002. Serotonin transporter genetic variation and the response of the human amygdala. Science. 297, 400-403.

Herrmann, M. J., Jacob, C., Unterecker, S. and Fallgatter, A. J., 2003. Reduced response-inhibition in obsessive-compulsive disorder measured with topographic evoked potential mapping. Psychiatry Research. 120, 265-271.

Herry, C., Ferraguti, F., Singewald, N., Letzkus, J. J., Ehrlich, I. and Lüthi, A., 2010. Neuronal Circuits of Fear Extinction. European Journal of Neuroscience. 31, 599-612.

Hirschfeld, R. M., Klerman, G. L., Andreasen, N. C., Clayton, P. J. and Keller, M. B., 1986. Psycho-social predictors of chronicity in depressed patients. The British journal of psychiatry. 148, 648-654.

Hirschfeld, R. M., Klerman, G. L., Lavori, P., Keller, M. B., Griffith, P. and Coryell, W., 1989. Premorbid personality assessments of first onset of major depression. Archives of General Psychiatry. 46, 345-350.

Holmes, A., Nielsen, M. K., Tipper, S. and Green, S., 2009. An electrophysiological investigation into the automaticity of emotional face processing in high versus low trait anxious individuals. Cognitive, Affective & Behavioral Neuroscience. 9, 323-334.

Hooker, C. I., Verosky, S. C., Miyakawa, A., Knight, R. T. and D'Esposito, M., 2008. The influence of personality on neural mechanisms of observational fear and reward learning. Neuropsychologia. 46, 2709-2724.

Huang, Y. X., Bai, L., Ai, H., Li, W., Yu, C., Liu, J. and Luo, Y. J., 2009. Influence of trait-anxiety on inhibition function: evidence from ERPs study. Neuroscience Letters. 456, 1-5.

Hugdahl, K., Berardi, A., Thompson, W. L., Kosslyn, S. M., Macy, R., Baker, D. P., Alpert, N. M. and LeDoux, J. E., 1995. Brain mechanisms in human classical conditioning: a PET blood flow study. Neuroreport. 6, 1723-1728.

Huster, R. J., Westerhausen, R., Pantev, C. and Konrad, C., 2010. The role of the cingulate cortex as neural generator of the N200 and P300 in a tactile response inhibition task. Human Brain Mapping. In press.

Jenkins, H. M., Barnes, R. and Barrera, F. J., 1981. Why autoshaping depends on trial spacing. In C M Locurto, H S Terrace & J Gibbon (Eds), Autoshaping and conditioning theory New York: Academy Press, 255-284.

Jensen, J., McIntosh, A. R., Crawley, A. P., Mikulis, D. J., Remington, G. and Kapur, S., 2003. Direct activation of the ventral striatum in anticipation of aversive stimuli. Neuron. 40, 1251-1257.

Johnson, K. A., Cunnington, R., Iansek, R., Bradshaw, J. L., Georgiou, N. and Chiu, E., 2001. Movement-related potentials in Huntington's disease: movement preparation and execution. Exp Brain Res. 138, 492-499.

Johnson, S. L., Turner, R. J. and Iwaka, N., 2003. BIS/BAS levels and psychiatric disorder: an epidemiological study Journal of Psychopathology and Assessment. 25, 25-36.

Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C. and Weisbrod, M., 2003. Executive control deficit in depression: event-related potentials in a Go/Nogo task. Psychiatry Research. 122, 169-184.

Kamprath, K., Marsicano, G., Tang, J., Monory, K., Bisogno, T., Di Marzo, V., Lutz, B. and Wotjak, C. T., 2006. Cannabinoid CB1 receptor mediates fear extinction via habituation-like processes. The Journal of Neuroscience. 26, 6677-6686.

Karch, S., Jager, L., Karamatskos, E., Graz, C., Stammel, A., Flatz, W., Lutz, J., Holtschmidt-Taschner, B., Genius, J., Leicht, G., Pogarell, O., Born, C., Moller, H. J., Hegerl, U., Reiser, M., Soyka, M. and Mulert, C., 2008. Influence of trait anxiety on inhibitory control in alcohol-dependent patients: simultaneous acquisition of ERPs and BOLD responses. Journal of Psychiatric Research. 42, 734-745.

Keightley, M. L., Seminowicz, D. A., Bagby, R. M., Costa, P. T., Fossati, P. and Mayberg, H. S., 2003. Personality influences limbic-cortical interactions during sad mood induction. Neuroimage. 20, 2031-2039.

Kienast, T., Hariri, A. R., Schlagenhauf, F., Wrase, J., Sterzer, P., Buchholz, H. G., Smolka, M. N., Grunder, G., Cumming, P., Kumakura, Y., Bartenstein, P., Dolan, R. J. and Heinz, A., 2008. Dopamine in amygdala gates limbic processing of aversive stimuli in humans. Nature Neuroscience. 11, 1381-1382.

Kim, J. J. and Jung, M. W., 2006. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. Neuroscience and biobehavioral reviews. 30, 188-202.

Kim, M. S., Kim, Y. Y., Yoo, S. Y. and Kwon, J. S., 2007. Electrophysiological correlates of behavioral response inhibition in patients with obsessive-compulsive disorder. Depression and Anxiety. 24, 22-31.

Klucken, T., Kagerer, S., Schweckendiek, J., Tabbert, K., Vaitl, D. and Stark, R., 2008. Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture-picture conditioning paradigm. Neuroscience. 158, 721-731.

Knight, D. C., Smith, C. N., Stein, E. A. and Helmstetter, F. J., 1999. Functional MRI of human Pavlovian fear conditioning: patterns of activation as a function of learning. Neuroreport. 10, 3665-3670.

Knight, D. C., Smith, C. N., Cheng, D. T., Stein, E. A. and Helmstetter, F. J., 2004. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. Cognitive, affective & behavioral neuroscience. 4, 317-325.

Knight, D. C., Cheng, D. T., Smith, C. N., Stein, E. A. and Helmstetter, F. J., 2004a. Neural substrates mediating human delay and trace fear conditioning. The Journal of Neuroscience. 24, 218-228.

Knight, D. C., Nguyen, H. T. and Bandettini, P. A., 2005. The role of the human amygdala in the production of conditioned fear responses. Neuroimage. 26, 1193-1200.

Knight, D. C., Nguyen, H. T. and Bandettini, P. A., 2006. The role of awareness in delay and trace fear conditioning in humans. Cognitive, affective & behavioral neuroscience. 6, 157-162.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M. and Miyashita, Y., 1999. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain. 122 (Pt 5), 981-991.

Koyama, T., McHaffie, J. G., Laurienti, P. J. and Coghill, R. C., 2005. The subjective experience of pain: where expectations become reality. Proceedings of the National Academy of Sciences of the United States of America. 102, 12950-12955.

Krystal, J. H. and Neumeister, A., 2009. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. Brain Research. 1293, 13-23.

Kuzelova, H., Ptacek, R. and Milan, M., 2010. The serotonin transporter gene (5-HTT) variant and psychiatric disorders: review of current literature. Neuro endocrinology letters. 31, 5.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E. and Phelps, E. A., 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron. 20, 937-945.

Lang, P. J., Bradley, M. M. and Cuthbert, B. N., 1990. International Affective Picture System (IAPS): instrcuction manual and affective ratings, technical report A4. Gainsville: Center of Research in Psychophysiology, University of Florida.

Lang, S., Kroll, A., Lipinski, S. J., Wessa, M., Ridder, S., Christmann, C., Schad, L. R. and Flor, H., 2009. Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. The European Journal of Neuroscience. 29, 823-832.

Laufs, H., Daunizeau, J., Carmichael, D. W. and Kleinschmidt, A., 2008. Recent advances in recording electrophysiological data simultaneously with magnetic resonance imaging. Neuroimage. 40, 515-528.

Laux, L., Glanzmann, P, Schaffner, P, Spielberger, C D, 1981. Das State-Trait-Angstinventar (Testmappe mit Handanweisung, Fragebogen STAI-G Form X 1 und Fragebogen STAI-G Form X 2). Weinheim: Beltz.

LeDoux, J. E., 2000. Emotion circuits in the brain. Annual review of neuroscience. 23, 155-184.

Leonard, D. W., 1975. Partial reinforcement effects in classical aversive conditioning in rabbits and human beings. Journal of comparative and physiological psychology. 88, 596-608.

Li, W., Howard, J. D., Parrish, T. B. and Gottfried, J. A., 2008. Aversive learning enhances perceptual and cortical discrimination of indiscriminable odor cues. Science. 319, 1842-1845.

Li, X., Li, X. and Luo, Y. J., 2005. Anxiety and attentional bias for threat: an event-related potential study. Neuroreport. 16, 1501-1505.

Lilienfeld, S. O., 1996. Anxiety sensitivity is not distinct from trait anxiety In RM Rapee: Current cotroversies in the anxiety disorders. New York: The Guilford Press, 228-244.

Liotti, M., Mayberg, H. S., Brannan, S. K., McGinnis, S., Jerabek, P. and Fox, P. T., 2000. Differential limbic--cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biological Psychiatry. 48, 30-42.

Lissek, S., Levenson, J., Biggs, A. L., Johnson, L. L., Ameli, R., Pine, D. S. and Grillon, C., 2008. Elevated fear conditioning to socially relevant unconditioned stimuli in social anxiety disorder. American Journal of Psychiatry. 165, 124-132.

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C. and Pine, D. S., 2005. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behaviour Research and Therapy. 43, 1391-1424.

Logan, C. G. and Grafton, S. T., 1995. Functional anatomy of human eyeblink conditioning determined with regional cerebral glucose metabolism and positron-emission tomography. Proceedings of the National Academy of Sciences of the United States of America. 92, 7500-7504.

Lonsdorf, T. B., Ruck, C., Bergstrom, J., Andersson, G., Ohman, A., Schalling, M. and Lindefors, N., 2009a. The symptomatic profile of panic disorder is shaped by the 5-HTTLPR polymorphism. Progress in neuro-psychopharmacology & biological psychiatry. 33, 1479-1483.

Lonsdorf, T. B., Weike, A. I., Nikamo, P., Schalling, M., Hamm, A. O. and Ohman, A., 2009b. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. Psychological Science. 20, 198-206.

Lopez-Sola, M., Pujol, J., Hernandez-Ribas, R., Harrison, B. J., Ortiz, H., Soriano-Mas, C., Deus, J., Menchon, J. M., Vallejo, J. and Cardoner, N., 2010. Dynamic assessment of the right lateral frontal cortex response to painful stimulation. Neuroimage. 50, 1177-1187.

MacCallum, R. C., Zhang, S., Preacher, K. J. and Rucker, D. D., 2002. On the practice of dichotomization of quantitative variables. Psychological Methods. 7, 19-40.

Manly, T., Robertson, I. H., Galloway, M. and Hawkins, K., 1999. The absent mind: further investigations of sustained attention to response. Neuropsychologia. 37, 661-670.

Marchand, A. R., Luck, D. and Di Scala, G., 2004. Trace fear conditioning: a role for context? Archives italiennes de biologie. 142, 251-263.

Maren, S., 2001. Neurobiology of Pavlovian fear conditioning. Annual Review of Neuroscience. 24, 897-931.

Marschner, A., Kalisch, R., Vervliet, B., Vansteenwegen, D. and Buchel, C., 2008. Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning. The Journal of Neuroscience. 28, 9030-9036.

Mathews, A. and MacLeod, C., 2005. Cognitive vulnerability to emotional disorders. Annual Review of Clinical Psychology. 1, 167-195.

McCrae, R. R. and Costa, P. T., Jr., 1987. Validation of the five-factor model of personality across instruments and observers. Journal of personality and social psychology. 52, 81-90.

McDermott, J. M., Perez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S. and Fox, N. A., 2009. A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. Biological Psychiatry. 65, 445-448.

McEchron, M. D., Tseng, W. and Disterhoft, J. F., 2003. Single neurons in CA1 hippocampus encode trace interval duration during trace heart rate (fear) conditioning in rabbit. The Journal of Neuroscience. 23, 1535-1547.

McNally, R. J., 1996. Anxiety sensitivity is distinguishable from trait anxiety In RM Rapee: Current cotroversies in the anxiety disorders. New York: The Guilford Press, 214-227.

McNally, R. J., 2002. Anxiety sensitivity and panic disorder. Biological Psychiatry. 52, 938-946.

McWilliams, L. A. and Cox, B. J., 2001. How distinct is anxiety sensitivity from trait anxiety?A re-examination from a multidimensional perspective Personality and Individual Differences. 31, 813-818.

Melcher, T., Falkai, P. and Gruber, O., 2008. Functional brain abnormalities in psychiatric disorders: neural mechanisms to detect and resolve cognitive conflict and interference. Brain Research Reviews. 59, 96-124.

Mercado, F., Carretie, L., Tapia, M. and Gomez-Jarabo, G., 2006. The influence of emotional context on attention in anxious subjects: neurophysiological correlates. Journal of Anxiety Disorders. 20, 72-84.

Michael, T., Blechert, J., Vriends, N., Margraf, J. and Wilhelm, F. H., 2007. Fear conditioning in panic disorder: Enhanced resistance to extinction. Journal of Abnormal Psychology. 116, 612-617.

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J. and Rauch, S. L., 2007. Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. Biological Psychiatry. 62, 446-454.

Mineka, S. and Oehlberg, K., 2008. The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. Acta psychologica (Amst). 127, 567-580.

Molchan, S. E., Sunderland, T., McIntosh, A. R., Herscovitch, P. and Schreurs, B. G., 1994. A functional anatomical study of associative learning in humans. Proceedings of the National Academy of Sciences of the United States of America. 91, 8122-8126.

Morawetz, C., Holz, P., Lange, C., Baudewig, J., Weniger, G., Irle, E. and Dechent, P., 2008. Improved functional mapping of the human amygdala using a standard functional magnetic resonance imaging sequence with simple modifications. Magnetic resonance imaging. 26, 45-53.

Morgan, M. A., Romanski, L. M. and LeDoux, J. E., 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. Neuroscience Letters. 163, 109-113.

Morris, J. S., Friston, K. J. and Dolan, R. J., 1997. Neural responses to salient visual stimuli. Proceedings Biological sciences. 264, 769-775.

Morris, J. S., Friston, K. J. and Dolan, R. J., 1998. Experience-dependent modulation of tonotopic neural responses in human auditory cortex. Proceedings Biological sciences. 265, 649-657.

Morris, J. S. and Dolan, R. J., 2004. Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. Neuroimage. 22, 372-380.

Moser, J. S., Hajcak, G. and Simons, R. F., 2005. The effects of fear on performance monitoring and attentional allocation. Psychophysiology. 42, 261-268.

Most, S. B., Chun, M. M., Johnson, M. R. and Kiehl, K. A., 2006. Attentional modulation of the amygdala varies with personality. Neuroimage. 31, 934-944.

Mostofsky, S. H. and Simmonds, D. J., 2008. Response inhibition and response selection: two sides of the same coin. Journal of Cognitive Neuroscience. 20, 751-761.

Mujica-Parodi, L. R., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., Ardekani, B., Guilfoyle, D., Khan, S., Zhong, Y., Chon, K. and Malaspina, D., 2009. Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. Human Brain Mapping. 30, 47-58.

Munafo, M. R., Clark, T. G., Moore, L. R., Payne, E., Walton, R. and Flint, J., 2003. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. Molecular Psychiatry. 8, 471-484.

Muris, P., Schmidt, H., Merckelbach, H. and Schouten, E., 2001. Anxiety sensitivity in adolescents: factor structure and relationships to trait anxiety and symptoms of anxiety disorders and depression. Behaviour Research and Therapy. 39, 89-100.

Murray, N. P. and Janelle, C. M., 2007. Event-related potential evidence for the processing efficiency theory. Journal of Sports Sciences. 25, 161-171.

Myers, K. M. and Davis, M., 2002. Behavioral and neural analysis of extinction. Neuron. 36, 567-584.

Nakamura, H., Kitagawa, H., Kawaguchi, Y. and Tsuji, H., 1997. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. The Journal of Physiology. 498 (Pt 3), 817-823.

Naragon-Gainey, K., 2010. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. Psychological Bulletin. 136, 128-150.

Neumann, D. L. and Waters, A. M., 2006. The use of an unpleasant sound as an unconditional stimulus in a human aversive Pavlovian conditioning procedure. Biological Psychology. 73, 175-185.

Nitschke, J. B., Sarinopoulos, I., Mackiewicz, K. L., Schaefer, H. S. and Davidson, R. J., 2006. Functional neuroanatomy of aversion and its anticipation. Neuroimage. 29, 106-116.

Norman, D. A. and Shallice, T., 1986. Attention to Action. In RJ Davidson, GE Schwartz & D Shapiro (Eds) Conciousness and self-regulation New York: Plenum Press. 4, 1-18.

O'Gorman, R. L., Kumari, V., Williams, S. C., Zelaya, F. O., Connor, S. E., Alsop, D. C. and Gray, J. A., 2006. Personality factors correlate with regional cerebral perfusion. Neuroimage. 31, 489-495.

Oldfield, R. C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 9, 97-113.

Omura, K., Todd Constable, R. and Canli, T., 2005. Amygdala gray matter concentration is associated with extraversion and neuroticism. Neuroreport. 16, 1905-1908.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M. and Mauguiere, F., 2002. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex. 12, 376-385.

Otto, M. W., Leyro, T. M., Christian, K., Deveney, C. M., Reese, H., Pollack, M. H. and Orr, S. P., 2007. Prediction of "fear" acquisition in healthy control participants in a de novo fear-conditioning paradigm. Behavior modification. 31, 32-51.

Pape, H. C., Pare, D. and Driesang, R. B., 1998. Two types of intrinsic oscillations in neurons of the lateral and basolateral nuclei of the amygdala. J Neurophysiol. 79, 205-216.

Pape, H. C., Driesang, R. B., Heinbockel, T., Laxmi, T. R., Meis, S., Seidenbecher, T., Szinyei, C., Frey, U. and Stork, O., 2001. Cellular processes in the amygdala: gates to emotional memory? Zoology (Jena). 104, 232-240.

Pape, H. C. and Stork, O., 2003. Genes and mechanisms in the amygdala involved in the formation of fear memory. Ann N Y Acad Sci. 985, 92-105.

Pape, H. C., Munsch, T. and Budde, T., 2004. Novel vistas of calcium-mediated signalling in the thalamus. Pflugers Arch. 448, 131-138.

Pape, H. C., Narayanan, R. T., Smid, J., Stork, O. and Seidenbecher, T., 2005. Theta activity in neurons and networks of the amygdala related to long-term fear memory. Hippocampus. 15, 874-880.

Pape, H. C., 2005. GABAergic neurons: gate masters of the amygdala, mastered by dopamine. Neuron. 48, 877-879.

Pavlov, I. P., 1927. Conditioned reflexes. Oxford, England: Oxford University Press

Peterson, R. A. and Reiss, S., 1987. Test manual for the anxiety sensitivity index (ASI). . Orland Park: International Diagnostic System.

Petrovic, P., Kalisch, R., Pessiglione, M., Singer, T. and Dolan, R. J., 2008. Learning affective values for faces is expressed in amygdala and fusiform gyrus. Social cognitive and affective neuroscience. 3, 109-118.

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Gore, J. C., Grillon, C. and Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nature Neuroscience. 4, 437-441.

Phelps, E. A., Delgado, M. R., Nearing, K. I. and LeDoux, J. E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 43, 897-905.

Pine, D. S., Fyer, A., Grun, J., Phelps, E. A., Szeszko, P. R., Koda, V., Li, W., Ardekani, B., Maguire, E. A., Burgess, N. and Bilder, R. M., 2001. Methods for developmental studies of fear conditioning circuitry. Biological Psychiatry. 50, 225-228.

Pineles, S. L., Vogt, D. S. and Orr, M. R., 2009. Personality and fear responses during conditioning: beyond extraversion. Personality and individual differences. 46, 48-53.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M. and Rawlins, J. N., 1999. Dissociating pain from its anticipation in the human brain. Science. 284, 1979-1981.

Porro, C. A., Baraldi, P., Pagnoni, G., Serafini, M., Facchin, P., Maieron, M. and Nichelli, P., 2002. Does anticipation of pain affect cortical nociceptive systems? The Journal of Neuroscience. 22, 3206-3214.

Posner, M. I. and Dehaene, S., 1994. Attentional networks. Trends in Neurosciences. 17, 75-79.

Prokasy, W. F. and Whaley, F. L., 1963. Intertrial interval range shift in classical eyelid conditioning. Psychological Reports. 12, 55-58.

Pujol, J., Lopez, A., Deus, J., Cardoner, N., Vallejo, J., Capdevila, A. and Paus, T., 2002. Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. Neuroimage. 15, 847-855.

Quirk, G. J., Armony, J. L. and LeDoux, J. E., 1997. Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. Neuron. 19, 613-624.

Quirk, G. J., Likhtik, E., Pelletier, J. G. and Pare, D., 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. The Journal of Neuroscience. 23, 8800-8807.

Quirk, G. J., Garcia, R. and Gonzalez-Lima, F., 2006. Prefrontal mechanisms in extinction of conditioned fear. Biological Psychiatry. 60, 337-343.

Rachman, S., 1977. The conditioning theory of fear-acquisition: a critical examination. Behaviour research and therapy. 15, 375-387.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A. and Shulman, G. L., 2001. A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America. 98, 676-682.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. and Bushnell, M. C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science. 277, 968-971.

Rauch, A. V., Ohrmann, P., Bauer, J., Kugel, H., Engelien, A., Arolt, V., Heindel, W. and Suslow, T., 2007. Cognitive coping style modulates neural responses to emotional faces in healthy humans: a 3-T FMRI study. Cerebral Cortex. 17, 2526-2535.

Rauch, S. L., Milad, M. R., Orr, S. P., Quinn, B. T., Fischl, B. and Pitman, R. K., 2005. Orbitofrontal thickness, retention of fear extinction, and extraversion. Neuroreport. 16, 1909-1912.

Rauch, S. L., Shin, L. M. and Phelps, E. A., 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. Biological Psychiatry. 60, 376-382.

Reiss, S., Peterson, R. A., Gursky, D. M. and McNally, R. J., 1986. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behaviour Research and Therapy. 24, 1-8.

Remy, P., Zilbovicius, M., Leroy-Willig, A., Syrota, A. and Samson, Y., 1994. Movement- and task-related activations of motor cortical areas: a positron emission tomographic study. Ann Neurol. 36, 19-26.

Righi, S., Mecacci, L. and Viggiano, M. P., 2009. Anxiety, cognitive self-evaluation and performance: ERP correlates. Journal of Anxiety Disorders. 23, 1132-1138.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T. and Yiend, J., 1997. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia. 35, 747-758.

Roche, R. A., Garavan, H., Foxe, J. J. and O'Mara, S. M., 2005. Individual differences discriminate event-related potentials but not performance during response inhibition. Experimental Brain Research. 160, 60-70.

Rossignol, M., Philippot, P., Douilliez, C., Crommelinck, M. and Campanella, S., 2005. The perception of fearful and happy facial expression is modulated by anxiety: an event-related potential study. Neuroscience Letters. 377, 115-120.

Ruchsow, M., Reuter, K., Hermle, L., Ebert, D., Kiefer, M. and Falkenstein, M., 2007. Executive control in obsessive-compulsive disorder: event-related potentials in a Go/Nogo task. Journal of Neural Transmission. 114, 1595-1601.

Sarinopoulos, I., Grupe, D. W., Mackiewicz, K. L., Herrington, J. D., Lor, M., Steege, E. E. and Nitschke, J. B., 2010. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb Cortex. 20, 929-940.

Schafer, A., Schienle, A. and Vaitl, D., 2005. Stimulus type and design influence hemodynamic responses towards visual disgust and fear elicitors. International Journal of Psychophysiology. 57, 53-59.

Schienle, A., Stark, R., Walter, B., Blecker, C., Ott, U., Kirsch, P., Sammer, G. and Vaitl, D., 2002. The insula is not specifically involved in disgust processing: an fMRI study. Neuroreport. 13, 2023-2026.

Schiller, D., Levy, I., Niv, Y., LeDoux, J. E. and Phelps, E. A., 2008. From fear to safety and back: reversal of fear in the human brain. The Journal of Neuroscience. 28, 11517-11525.

Schmajuk, M., Liotti, M., Busse, L. and Woldorff, M. G., 2006. Electrophysiological activity underlying inhibitory control processes in normal adults. Neuropsychologia. 44, 384-395.

Schmidt, N. B., Mitchell, M. A. and Richey, J. A., 2008. Anxiety sensitivity as an incremental predictor of later anxiety symptoms and syndromes. Comprehensive Psychiatry. 49, 407-412.

Schnitzler, A. and Ploner, M., 2000. Neurophysiology and functional neuroanatomy of pain perception. Journal of clinical neurophysiology. 17, 592-603.

Schreurs, B. G., Bahro, M., Molchan, S. E., Sunderland, T. and McIntosh, A. R., 2001. Interactions of prefrontal cortex during eyeblink conditioning as a function of age. Neurobiology of Aging. 22, 237-246.

Schreurs, B. G., McIntosh, A. R., Bahro, M., Herscovitch, P., Sunderland, T. and Molchan, S. E., 1997. Lateralization and behavioral correlation of changes in regional cerebral blood flow with classical conditioning of the human eyeblink response. Journal of neurophysiology. 77, 2153-2163.

Schurr, B. C. and Runquist, W. N., 1973. Acquisition and extinction of human eyelid conditioned response as a function of schedule of reinforcement and unconditioned stimulus intensity under two masked conditioning procedures. Journal of experimental psychology. 101, 398-401.

Segman, R. H., Cooper-Kazaz, R., Macciardi, F., Goltser, T., Halfon, Y., Dobroborski, T. and Shalev, A. Y., 2002. Association between the dopamine transporter gene and posttraumatic stress disorder. Molecular Psychiatry. 7, 903-907.

Sehlmeyer, C., Schoning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V. and Konrad, C., 2009. Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS ONE. 4, e5865.doi:5810.1371/journal.pone.0005865.

Shin, L. M. and Liberzon, I., 2010. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology. 35, 169-191.

Shors, T. J., 2004. Memory traces of trace memories: neurogenesis, synaptogenesis and awareness. Trends in neurosciences. 27, 250-256.

Simon, N. M., Smoller, J. W., Fava, M., Sachs, G., Racette, S. R., Perlis, R., Sonawalla, S. and Rosenbaum, J. F., 2003. Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. Journal of psychiatric research. 37, 187-192.

Smith, J. L., Johnstone, S. J. and Barry, R. J., 2008. Movement-related potentials in the Go/NoGo task: the P3 reflects both cognitive and motor inhibition. Clinical Neurophysiology. 119, 704-714.

Somers, J. M., Goldner, E. M., Waraich, P. and Hsu, L., 2006. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Canadian journal of psychiatry. 51, 100-113.

Sotres-Bayon, F., Cain, C. K. and LeDoux, J. E., 2006. Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. Biological Psychiatry. 60, 329-336.

Sotres-Bayon, F., Bush, D. E. and LeDoux, J. E., 2007. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. Neuropsychopharmacology. 32, 1929-1940.

Spielberger, C. D., 1972. Anxiety. Current Trends in Theory and Research: vol 1 New York, NY, Academic Press.

Spielberger, C. D., 1979. Understanding Stress and Anxiety. London: Harper & Row Publishers.

Spielberger, C. D., 1983. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologists Press.

Stark, R., Zimmermann, M., Kagerer, S., Schienle, A., Walter, B., Weygandt, M. and Vaitl, D., 2007. Hemodynamic brain correlates of disgust and fear ratings. Neuroimage. 37, 663-673.

Stein, D. J., Arya, M., Pietrini, P., Rapoport, J. L. and Swedo, S. E., 2006. Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission tomography study. Metabolic brain disease. 21, 267-277.

Stocker, T., Kellermann, T., Schneider, F., Habel, U., Amunts, K., Pieperhoff, P., Zilles, K. and Shah, N. J., 2006. Dependence of amygdala activation on echo time: results from olfactory fMRI experiments. Neuroimage. 30, 151-159.

Stoppel, C., Albrecht, A., Pape, H. C. and Stork, O., 2006. Genes and neurons: molecular insights to fear and anxiety. Genes, brain, and behavior. 5 Suppl 2, 34-47.

Straube, T., Weiss, T., Mentzel, H. J. and Miltner, W. H., 2007. Time course of amygdala activation during aversive conditioning depends on attention. Neuroimage. 34, 462-469.

Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., Sato, K., Ono, S., Schormann, T., Zilles, K. and Fukuda, H., 2000. Correlation between human personality and neural activity in cerebral cortex. Neuroimage. 11, 541-546.

Svartdal, F., 2003. Extinction after partial reinforcement: predicted vs. judged persistence. Scandinavian journal of psychology. 44, 55-64.

Swick, D., Ashley, V. and Turken, A. U., 2008. Left inferior frontal gyrus is critical for response inhibition. BMC neuroscience. 9, 102.

Taake, I., Jaspers-Fayer, F. and Liotti, M., 2009. Early frontal responses elicited by physical threat words in an emotional Stroop task: Modulation by anxiety sensitivity. Biological Psychology. 81, 48-57.

Tabachnik, B. G. and Fidell, L. S., 2007. Using Multivariate Statistics. Pearson Education 5th Edition. .

Tabbert, K., Stark, R., Kirsch, P. and Vaitl, D., 2005. Hemodynamic responses of the amygdala, the orbitofrontal cortex and the visual cortex during a fear conditioning paradigm. International Journal of Psychophysiology. 57, 15-23.

Tabbert, K., Stark, R., Kirsch, P. and Vaitl, D., 2006. Dissociation of neural responses and skin conductance reactions during fear conditioning with and without awareness of stimulus contingencies. Neuroimage. 32, 761-770.

Timmann, D., Kolb, F. P., Baier, C., Rijntjes, M., Muller, S. P., Diener, H. C. and Weiller, C., 1996. Cerebellar activation during classical conditioning of the human flexion reflex: a PET study. Neuroreport. 7, 2056-2060.

Tottenham, N., Borscheid, A., Ellertsen, K., Marcus, D. J. and Nelson, C. A., 2002. Categorization of facial expressions in children and adults: Establishing a larger stimulus set Paper presented at the Cognitive Neuroscience Society annual meeting, San Francisco, CA.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B. and Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 15, 273-289.

Ursu, S., Stenger, V. A., Shear, M. K., Jones, M. R. and Carter, C. S., 2003. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. Psychological Science. 14, 347-353.

Volz, K. G., Schubotz, R. I. and von Cramon, D. Y., 2003. Predicting events of varying probability: uncertainty investigated by fMRI. Neuroimage. 19, 271-280.

Vuilleumier, P. and Pourtois, G., 2007. Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. Neuropsychologia. 45, 174-194.

Walther, S., Goya-Maldonado, R., Stippich, C., Weisbrod, M. and Kaiser, S., 2010. A supramodal network for response inhibition. Neuroreport. 21, 191-195.

Wang, M. H., Zhu, Y. H., Li, J. C. and Weng, X. C., 2007. [Functional magnetic resonance imaging of whole brain related to motor preparation and execution]. Zhonghua Yi Xue Za Zhi. 87, 971-974.

Weike, A. I., Schupp, H. T. and Hamm, A. O., 2007. Fear acquisition requires awareness in trace but not delay conditioning. Psychophysiology. 44, 170-180.

Weisbrod, M., Kiefer, M., Marzinzik, F. and Spitzer, M., 2000. Executive control is disturbed in schizophrenia: evidence from event-related potentials in a Go/NoGo task. Biological Psychiatry. 47, 51-60.

Williams, L. M., Barton, M. J., Kemp, A. H., Liddell, B. J., Peduto, A., Gordon, E. and Bryant, R. A., 2005. Distinct amygdala-autonomic arousal profiles in response to fear signals in healthy males and females. Neuroimage. 28, 618-626.

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S. and Zaudig, M., 1997. SKID-I. Struktiertes Klinisches Interview für DSM-IV Hogrefe, Göttingen.

Yaguez, L., Coen, S., Gregory, L. J., Amaro, E., Jr., Altman, C., Brammer, M. J., Bullmore, E. T., Williams, S. C. and Aziz, Q., 2005. Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. Gastroenterology. 128, 1819-1829.

Yoon, H. K., Yang, J. C., Lee, H. J. and Kim, Y. K., 2008. The association between serotonin-related gene polymorphisms and panic disorder. Journal of Anxiety Disorders. 22, 1529-1534.

Zinbarg, R. E., Uliaszek, A. A. and Adler, J. M., 2008. The role of personality in psychotherapy for anxiety and depression. Journal of personality 76, 1649-1688.

Zordan, L., Sarlo, M. and Stablum, F., 2008. ERP components activated by the "GO!" and "WITHHOLD!" conflict in the random Sustained Attention to Response Task. Brain and Cognition. 66, 57-64.

Zvolensky, M. J. and Schmidt, N. B., 2007. Introduction to anxiety sensitivity: recent findings and new directions. Behavior modification. 31, 139-144.