The Attentional Bias to Emotion

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1 SUMMARY

Emotionally significant stimuli successfully compete for attentional resources with current, goal-directed behavior. This attentional bias entails an adaptive advantage and is particularly strong for negative, threat-related information, such as fearful facial expressions. Models of the attentional bias to threat, implicating the amygdala in the detection of emotionally significant (task-irrelevant) stimuli and the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) in the attentional control over those stimuli, have received large empirical support.

Temporal synchronization of neuronal activity indicates network interactions and may underlie the attentional threat bias. Synchronization in the theta and gamma band has been associated with the detection of emotionally significant, task-irrelevant stimuli in the amygdala and medial temporal lobe. Attentional selection in general has been reliably associated with frequency-specific synchronization of neuronal activity in frontal and parietal regions. However, it is unknown whether attentional control over emotional stimuli engages frequency-specific changes in the PFC. Individual differences, such as increased anxiety levels or genetic variants, are associated with elevated threat biases and modulate activation in this circuitry. Thus, it is expected that such individual differences are also associated with frequency-specific changes in those brain regions. The three studies of this thesis assessed attentional capture by emotional facial expressions in three domains of attention. Two of them investigated the role of synchronized neuronal activity by employing intracranial electroencephalography (iEEG; Study II) and magnetoencephalography (MEG; Study III).

Study I, a psychophysical study, investigated in seven successive experiments how emotional facial expressions modulated temporal fluctuation of attention in an attentional blink (AB) paradigm. The AB denotes a period of impaired attention when a second target briefly follows a first target in a stream of rapidly presented stimuli. It was expected that emotional facial expressions were more easily detected than neutral faces during the blink interval. Since the AB was absent or shallow in Experiments 1 and 2, respectively, the similarity between the two targets (Experiment 3), the similarity of targets and distractors (Experiment 4-6), and the task relevance of the emotional expression (Experiment 7) was manipulated. Increased similarity between targets and distractors resulted in a stronger AB for neutral faces relative to emotional faces. Task relevance of emotional expression in

Experiment 7 did not have a stronger impact on AB magnitude than increased target-distractor similarity.

Study II exploited the good spatial and temporal resolution of intracranial EEG (iEEG) to directly record from the fusiform gyrus, OFC, insula, and amygdala of patients with pharmaco-resistant epilepsy to uncover whether voluntary, endogenous attention (manipulated by the task) and reflexive, exogenous attention (manipulated by facial expressions) affect temporal synchronization in all regions equally (particularly in high frequencies > 30 Hz). Facial expressions were task-relevant in the first but task-irrelevant in the second task. When facial expressions were task-relevant, stronger changes in stimulus-induced high-frequency activity in all investigated regions were observed. The latencies revealed that the activation was temporally coordinated across the network, rather than serially proceeding along a processing hierarchy. Contrary to the initial hypothesis, differences between fearful and neutral faces were rarely observed. These results show that endogenous attention operates along the whole face-processing network, and that these effects are best captured by changes in high-frequency activity.

Finally, Study III employed MEG and a variant of a dot probe task to uncover whether frequency-specific neuronal activity was modulated by the allocation of attention towards task-irrelevant fearful face distractors. The participants were selected according to their genotype of the serotonin-transporter-linked polymorphic region (5-HTTLPR), as variation in this gene is associated with elevated anxiety levels. Lateralized attention effects to targets were found over parieto-occipital sensors in the theta, alpha, and gamma band. Interestingly, fearful face distractors led to an increase of gamma-band activity (GBA) in the right fronto-parietal attention network when presented at the same side as targets. Furthermore, those participants with a stronger genetic disposition (i.e., carriers of the 5-HTTLPR short allele) exhibited stronger activation in the theta band in regions involved in emotion processing. The current study provides first insight that the attentional bias to threat is exerted through dynamic interactions between frontal and parietal regions. In conclusion, the present work supports the hypothesis that the attentional bias to threat is reflected in temporal synchronization of neuronal activity and established important markers for further work on this topic, especially in the domain of clinical anxiety.

2 INTRODUCTION

From everyday life it seems intriguing that processing of emotionally significant events or objects is inextricably intertwined with attentional selection. Imagine that you let your mind wander while going for a walk in a nearby park. From the corner of your eye you notice a snake-like object lying on your path. You freeze and explore the object. Realizing that it is just a branch, you move on. This example illustrates that the encounter of a potential threat captures attention and mobilizes resources. In contrast to everyday life experience science has largely studied the processing of emotionally significant stimuli and attentional processing in isolation. In this chapter I will examine the efforts that have been undertaken to uncover how emotionally significant stimuli compete for attentional resources with current, goal-directed behavior. First, I will give a short introduction to emotion processing, mechanisms of attentional selection, and how both are implemented in the brain. Then, I will address how emotional meaning can bias selective attention, including a consideration of underlying neurocognitive mechanisms and individual differences. I will also discuss how and why the attentional bias to threat might be mediated by temporal synchronization of neuronal activity. Finally, evidence for the attentional bias to threat is reviewed. I will conclude with the research objectives of this thesis.

2.1 Emotion Processing

2.1.1 Emotion Processing and the Brain

Since the pioneering work of Charles Darwin (1872) considerable phylogenetic continuity in the expression of emotion in animals and humans has been established. Darwin sought to show this by carful observation of facial and bodily expressions of cats, dogs, and people in order to reveal cross-species similarities. He suggested that many emotional expressions in humans, such as baring the teeth when in rage, are remnants of our ancestral past. Darwin's work promoted the use of research in animals. Animal research has revealed findings that are partly transferable to humans, thus fostering the understanding of emotions in humans and having an important impact on affective neuroscience (Dalgleish, 2004).

The term "emotion" is usually not well defined and is often intermingled with the term "feeling". This becomes also evident in introductory books on the psychology of emotion (Meyer, Reisenzein, & Schützwohl, 2001). Those books typically provide an operational

definition of emotion because the exact specification of emotions is still a matter of investigation. However, it is agreed upon that emotions are phasic, multidimensional phenomena that include characteristic physiological changes and associated action tendencies (Adolphs, 2010a; Meyer et al., 2001). Such action tendencies are crucial in order to deal with significant changes in the environment that may posit a threat to survival. Emotions, in form of action tendencies, bear the advantage that they can flexibly guide behavior without relying on hard-wired, mandatory stimulus-response mappings. They provide coarse, behavioral guidelines but leave the individual with a set of options to choose. Therefore, emotions are "efficient modes of adaptation to changing environmental demands" (Levenson, 2003, p. 349). This adaptive advantage results in prioritized processing of emotionally significant stimuli, notably threat-related facial expressions (Öhman & Mineka, 2001).

Recently, LeDoux (2012) has stressed that emotional processes should be studied in the framework of survival circuits, e.g., which responses occur when an organism detects and reacts to a significant event in the course of survival. This circumvents the proper definition of emotion and emphasizes the phylogenetic continuity of adaptation. Survival circuits can be defined as "sensory-motor integrative devices that serve specific adaptive purpose", e.g. defense against harm (LeDoux, 2012, p. 655). The amygdala, consisting of several nuclei positioned bilaterally within the medial temporal lobes, is one part of a so-called defense system and detects potential threats in the environment (LeDoux, 1996; Zald, 2003). Facial expressions may communicate such threats. Observing for example the facial expression of fear in a conspecific signifies potential threat in the environment, whereas a counterpart with an angry expression indicates potential danger for oneself. In support of this notion, pictures of fearful facial expressions have been found to activate the amygdala (Breiter et al., 1996; Morris et al., 1996; Whalen et al., 2004). Hence, throughout this work emotionally significant stimuli refer to stimuli that have the potential to activate the defense system, one of these survival circuits.

2.1.2 Processing of Faces and Emotional Facial Expressions

Faces are salient stimuli regardless of their expression and provide crucial information for social interactions in everyday life. Thus, all faces are emotionally significant, even those with neutral facial expression. Still, fearful and angry facial expressions have dominated past research on preferential processing of facial expressions (Palermo & Rhodes, 2007) because

they signify threat and danger, respectively. Their rapid detection may posit an adaptive advantage (Vuilleumier, 2002).

Bruce and Young (1986) established an influential cognitive model of face perception. This model distinguishes several stages or units of face processing, from structural encoding of basic facial features (e.g., age or gender) to more elaborate processing of facial information (e.g., recall the person's name). Processing of facial expression already constituted one of the model's components. Its authors also recognized that selective visual attention may influence face perception and explicitly included selective attention as a distinct unit. This "directed visual processing" unit impacts the perception of facial expression indirectly via the cognitive system, a catch-all component including all sorts of cognitive functions such as memory. Further modifications of this model put more emphasis on the processing of facial expressions and associated specific brain areas to distinct aspects of face perception (Haxby, Hoffman, & Gobbini, 2000). The core system, dedicated to primary visual analysis, includes the inferior occipital gyri for early perception of facial features, the superior temporal sulci, and the lateral fusiform gyri for processing of changeable and invariant aspects of the face, respectively. More elaborate processing of faces (e.g., person identification or emotional analysis) depends on the given task demands or context. For that, other neuronal systems, referred to as the extended system, come into play. Haxby et al. (2000) suggested that all tasks necessitating spatially directed attention are served by the intraparietal sulcus. Perception of emotional facial expression engages the amygdala, insula, and the limbic system. Thus, face processing depends on the orchestrated activity of a large-scale cortical and subcortical network (Vuilleumier & Pourtois, 2007).

2.2 Mechanisms of Selective Attention

Based on the fact that the processing capacity of the visual system is limited (Broadbent, 1958), some form of selection is necessary for normal functioning. Attention represents the selection or filtering mechanism that enables selective processing the vast amount of information at the expense of unattended information. Different functions of attention have been identified, including alerting as a form of sustained vigilance, orienting to sensory events, and executive control to choose between conflicting options (Petersen & Posner, 2012; Posner & Petersen, 1990). Selective attention can operate overtly or covertly without moving the eyes. Covert visual attention has often been compared to a spotlight that enables the processing of stimuli

in the visual field. It has been elegantly shown that attentional shifts to a cued position in the visual field increased processing speed and were not related to eye movements (Posner, 1980; Posner, Snyder, & Davidson, 1980). Covert attention has been divided into active, voluntary and reflexive, involuntary attention, respectively referred to as endogenous and exogenous attention (Carrasco, 2011).

More recent approaches view attention as "an emergent property of many neuronal mechanisms working to resolve competition for visual processing and control of behavior" (Desimone & Duncan, 1995, p. 194). Based on the importance of selection for normal functioning and results from animal data, Desimone and Duncan (1995) advanced the biased competition model of attention. According to their model (Figure 1.1), incoming visual stimuli compete for cognitive resources and control of behavior. This competition can be biased by top-down control or by sensory-driven, bottom-up mechanisms. Top-down control mechanisms favor stimuli of relevance to the current behavior and rely on feedback from areas outside the visual cortex (Duncan, 2006; Miller & Cohen, 2001). Another way of biasing attention is bottom-up and sensory-driven. For example, highly salient stimuli, such as red apples on green grass, immediately capture attention and interrupt ongoing processing. Salient stimuli include colorful, moving, novel, or emotionally significant objects. Bottom-up processes seem to be highly automatic and independent of cognition or task demands. At the neuronal level, both processes enhance neuronal signals of currently attended objects or parts of the visual scene (Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Single cell recordings in monkeys revealed that the neuronal response to two stimuli in the same receptive field outside of the attentional focus reflected a weighted sum of the neuronal response to each stimulus alone. When attending to one of these stimuli, the neuronal response was comparable to that of the stimulus presented alone (Chelazzi, Duncan, Miller, & Desimone, 1998; Reynolds, Chelazzi, & Desimone, 1999). That is, attention eliminated the effect of the unattended stimulus. Comparable results have been found using functional magnetic resonance imaging (fMRI) in humans (cf. the following reviews: Kanwisher & Wojciulik, 2000; Kastner & Ungerleider, 2000). For example, suppression effects in V4 between simultaneously presented, competing visual stimuli were eliminated under directed attention (Kastner, De Weerd, Desimone, & Ungerleider, 1998). Top-down feedback mechanisms have later been related to fronto-parietal regions such as the intraparietal and superior frontal cortex (Corbetta & Shulman, 2002; Duncan, 2006; Miller & Cohen, 2001), whereas bottom-up mechanisms appear to involve the right temporo-parietal junction and

right inferior frontal cortex (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta & Shulman, 2002). Overall, the dorsal (top-down) and ventral (bottom-up) fronto-parietal attention networks can be related to endogenous and exogenous attention, respectively.

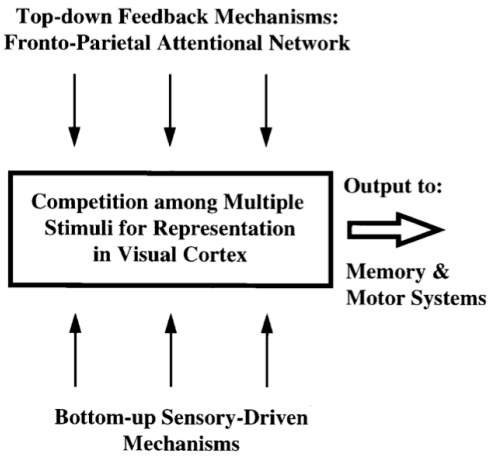

Figure 1.1. Biased competition model of selective attention in the visual system. Reproduced, with permission, from Kastner & Ungerleider, 2000, p. 333.

2.3 Attentional Bias to Threat

2.3.1 (Neuro-)Cognitive Models

Several lines of evidence corroborate the notion that emotionally significant, especially negative and threat-related stimuli such as fearful faces have a competitive advantage compared to neutral ones (Hartikainen, Ogawa, & Knight, 2000; Vuilleumier, Armony, Driver, & Dolan, 2001). Mathews, Mackintosh, and Fulcher (1997) proposed a cognitive model of how performance on selective attention tasks may be altered by threat-related, but task-irrelevant distractors. Specifically, both task-related neutral stimuli and task-irrelevant threat-related stimuli are initially processed in parallel to form a perceptual representation. Directed attention to the task-relevant stimulus as well as emotional significance boost the perceptual representations of the task-relevant and threat-related stimulus, respectively. Since both representations are connected by mutual inhibition, directed attention can usually minimize interference by the threat-related distractor. Nevertheless, a powerful emotional distractor may interfere with task execution resulting in impaired performance. The authors also suggested that this mechanism might be altered in people with heightened or clinical levels of

anxiety in favor of stronger representations for threat-related distractors resulting in greater interference.

At the neuronal level, face-selective neurons in superior temporal sulcus of the monkey fired stronger and more sustained in response to expressive compared to neutral monkey faces (Sugase, Yamane, Ueno, & Kawano, 1999), paralleling attentional effects in inferior temporal cortex (Chelazzi et al., 1998). Such effects have been attributed to the influence of top-down signals – fronto-parietal in case of attention and amygdalar in case of emotion – on the visual areas. All proposals of how emotionally significant stimuli bias competition in humans at the neuronal level are based on the assumption that attentional capture of threatening events in the environment provides an adaptive advantage for the organism. However, the prevailing view on the automaticity of such an attentional advantage differed. Some accounts assume that emotional significance, especially of faces (Palermo & Rhodes, 2007), is rapidly detected at a preconscious level by a subcortical circuit including the amygdala and is thereupon prioritized for further processing (Compton, 2003; Vuilleumier, 2005), while others argue that preferential processing of threat-related stimuli is not automatic and cannot occur in the absence of attention (Pessoa, Kastner, & Ungerleider, 2002; Pessoa & Ungerleider, 2004; Yiend, 2010). These conflicting positions can be reconciled if the perceptual load of the current task is considered (Lavie, 1995). The extent to which unattended objects are processed depends on the available resources of the visual system. Preferential processing of emotional stimuli may be suppressed if the attentional resources are completely consumed by a competing task. When the task load is low, however, this attentional bias may be reflected in both, behavior and the brain. Regarding the neuronal mechanism, all authors concurred that brain regions, which are partly distinct from the dorsal attention network, mediated attentional capture by threat-related stimuli (Compton, 2003; Pessoa, Kastner, et al., 2002; Pessoa & Ungerleider, 2004; Pourtois & Vuilleumier, 2006; Vuilleumier, 2005; Vuilleumier & Driver, 2007). The importance of the amygdala as a primary source for the threat bias has been a matter of conflict. Some attributed a central role to the amygdala executing direct and indirect top-down control on sensory visual pathways (Compton, 2003; Vuilleumier, 2005), while others put more emphasis on cortico-cortical connections as a primary source for feedback (Pessoa & Adolphs, 2010; Pessoa, Kastner, et al., 2002). In the latter case, top-down feedback signals by the amygdala might only arise indirectly via extrastriate visual areas. Experimental evidence for the attentional bias to threat will be discussed in 2.5.

2.3.2 The Attentional Bias to Threat and Anxiety Disorders

The attentional bias to threat is also thought to play an important role in the etiology and maintenance of anxiety disorders (Beck, 1976; J. A. Gray, 1985), since individuals suffering from anxiety disorders seem to exhibit an increased attentional bias to threat (MacLeod, Mathews, & Tata, 1986). It has been proposed that the key determinant in vulnerability to anxiety disorders is the subjective threat value (Broadbent & Broadbent, 1988; Mogg & Bradley, 1998). Individuals with low trait anxiety will only show an attentional bias to threat for highly threatening stimuli, while they tend to ignore stimuli with low or medium threat value. In contrast, the threshold to judge a stimulus as threatening may be lower in individuals with high trait anxiety. Thus, high-anxious individuals constantly over-estimate the actual threat value. A combination of high trait anxiety with a deficit in appraisal processes may lead to the development of anxiety disorders. Therefore, only attentional biases to stimuli with mild but not high threat value may signify anxiety-proneness (Mogg & Bradley, 1998). Anxiety also alters the outcome of performance in selective attention tasks in favor of task-irrelevant, threat-related distractors by a preattentive threat evaluation mechanism (Mathews & Mackintosh, 1998; Mathews et al., 1997). Although heightened levels of trait anxiety may not deterministically be associated with severe anxiety states, trait anxiety constitutes an analog for the presence of or vulnerability for an anxiety disorder in studies with healthy participants (Sylvester et al., 2012). Furthermore, the threat value of facial expressions or aversive scenes seems to be higher than that of word stimuli, so that these stimuli are more potent to capture attention in individuals with nonclinical anxiety levels (Mogg & Bradley, 1998).

Bishop (2007) criticized that the contribution of prefrontal control mechanisms to anxiety-related individual differences has been overlooked, as many studies focused on the amygdala, although the influence of the prefrontal cortex (PFC) has previously been recognized in cognitive models (Mathews & Mackintosh, 1998). According to Bishop (2007, 2008), biased competition in favor of threat-related, task-irrelevant stimuli in anxiety is determined by the relative strength of modulating signals from the PFC and the amygdala (Figure 1.2). The amygdala supports detection of threat-related stimuli, whereas the PFC exerts control by appraisal and regulation of aversive stimuli to ensure task-relevant processing. Anxiety is associated with hyperfunction of the amygdala and/or hypofunction of the prefrontal control signal in response to threat stimuli at the neuronal level and increased

attentional bias to threat at the behavioral level. The importance of load on moderating the effects of attentional capture by threat-related stimuli has also been incorporated into this model. Although it is well established that the attentional bias to threat is likely mediated by frontal and limbic brain areas, the underlying neuronal mechanism by which this bias is exerted remains unclear (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007).

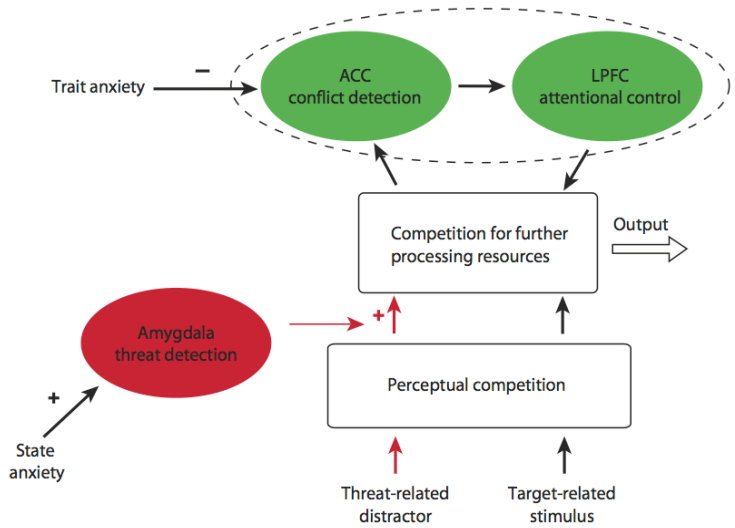

Figure 1.2. Neurocognitive model of selective attention to threat. Reproduced, with permission, from Bishop, 2007, p. 311. Abbreviations: ACC, anterior cingulate cortex; LPFC, lateral prefrontal cortex.

2.3.3 Genetic Markers of the Attentional Bias to Threat

Beside environmental factors, already Mathews (1998) hypothesized that genetic variation permanently influences thresholds of the threat evaluation mechanism underlying anxiety disorders. The study of neurobiological or psychological traits with a clear genetic correlate, referred to as intermediate phenotypes, is fruitful for advancing our understanding of the underlying mechanisms because the genetic impact may more readily be visible at the neurophysiological than the behavioral level (Bishop, 2008) and may be useful in tailoring treatments to more homogeneous patient groups (Domschke & Dannlowski, 2010).

The attentional bias to threat is an example for such an intermediate phenotype. Genetic variation in the normal population (referred to as polymorphisms) in the serotonin transporter gene, the serotonin-transporter-linked polymorphic region (5-HTTLPR), has been associated with variation in the attentional bias to threat. Specifically, carriers of the short allele of 5-HTTLPR had higher anxiety-related traits and increased levels of extracellular

serotonin due to decreased transcriptional activity (Lesch et al., 1996). Reduced serotonergic transmission as in the short variant of 5-HTTLPR has been associated with a stronger attentional bias toward threat-related stimuli (reviewed by Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012). Importantly, carriers of the short allele exhibited alterations in the corticolimbic circuitry presented above (reviewed by Hariri & Holmes, 2006), including increased amygdala responses to threat-related faces, decreased coupling with the anterior cingulate cortex (ACC), and increased coupling with the ventral PFC. These changes seem to develop during adolescence probably due to chronic decrease in serotonergic neurotransmission (Wiggins et al., 2012).

These lines of evidence are in good agreement with the neurobiological biased competition model (Bishop, 2007) suggesting that genetic variations mediating vulnerability to anxiety disorders impact the balance between amygdalar threat detection and prefrontal control.

2.4 Functional Implications of Synchronized Neuronal Activity on the Threat Bias

2.4.1 Temporal Synchronization of Neuronal Activity

The temporal synchronization of neuronal activity has been assigned a fundamental role in integration of information in sensory systems. This idea was derived from the so-called temporal correlation hypothesis, postulating that feature integration into a coherent percept is achieved by the temporal correlation of neuronal discharges of cell assemblies in different parts of the cortex in a millisecond time range (Engel, König, Kreiter, Schillen, & Singer, 1992; Singer & Gray, 1995; von der Malsburg & Schneider, 1986). According to this framework, stimulus processing is implemented neuronally on the backbone of existing anatomical connections (Uhlhaas et al., 2009). In particular, synchronization can occur locally (e.g., feature integration solving the binding problem; Donner & Siegel, 2011) or globally, involving long-range interactions between higher and lower cortical areas (Engel, Fries, & Singer, 2001; Siegel, Donner, & Engel, 2012). Consequently, entraining other neuronal populations to already synchronized assemblies enhances the salience of the objects encoded by the synchronized cell assembly and thereby exert top-down control (Engel et al., 2001). This mechanism does not require a processing hierarchy but enables flexible and context-dependent selection of relevant information and efficient routing of signals through processing pathways (Fries, 2005; Salinas & Sejnowski, 2001; Womelsdorf et al., 2007).

Temporal synchronization of neuronal activity has been attributed an important role in top-down driven attention (Engel et al., 2001; Jensen, Kaiser, & Lachaux, 2007; Tallon-Baudry, 2009). The temporal correlation of neuronal activity hypothesis has also been subject to criticism (Ghose & Maunsell, 1999; Shadlen & Movshon, 1999).

Temporal synchronization of neuronal activity has been divided into different frequency bands: delta (0.5-3.5 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (> 30 Hz). These have been associated with various different functions. Activity in the delta band has been related to motivational processes and deep sleep (Greene & Frank, 2010; Knyazev, 2007). Synchronization in the theta band has been associated with the processing of emotionally salient stimuli, fear-related arousal and working memory (Jensen & Lisman, 2005; Knyazev, 2007; Pare, Collins, & Pelletier, 2002). Alpha-band oscillations seem to play an important role in attention processes and task-related disengagement (Klimesch, 2012; Palva & Palva, 2007), while responses in the beta band have been linked to sensorimotor control and maintenance of the current cognitive state (Engel & Fries, 2010; Pfurtscheller, Stancak, & Neuper, 1996). Finally, synchronization in the gamma band has received a lot of attention in recent years and serves sensory processing in multiple modalities (Bauer, Oostenveld, Peeters, & Fries, 2006; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Siegel, Donner, Oostenveld, Fries, & Engel, 2007), multisensory processing (Senkowski, Schneider, Foxe, & Engel, 2008), and various cognitive functions, including feature binding (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996), attention (Fries, Reynolds, Rorie, & Desimone, 2001; Jensen et al., 2007; Siegel, Donner, Oostenveld, Fries, & Engel, 2008), and awareness (Engel & Singer, 2001; Wyart & Tallon-Baudry, 2009).

Early work in animals demonstrated that the activity of single neurons synchronized within visual cortex but also across remote brain areas to form a unique percept (Engel, König, Kreiter, & Singer, 1991; Engel, Kreiter, König, & Singer, 1991; C. M. Gray, König, Engel, & Singer, 1989). Such bottom-up driven coding of stimulus properties was particularly prominent in the gamma band, but synchronized firing of neurons also reflected top-down control. For example, two neurons in the secondary somatosensory cortex of a monkey, a region previously associated with attention, increased their synchronization, when the animal attended a tactile but not a visual stimulus (Steinmetz et al., 2000). Another study reported synchronization between neurons in the visual and parietal cortex of the cat to go but not to no-go stimuli in the theta- and alpha-frequency range (von Stein, Chiang, & König, 2000). Consistent with its role in top-down control, the phase relationships suggested a lead of the

parietal cortex. Gamma-band synchronization increased instead for novel stimuli between short-range connections, substantiating a role in stimulus-driven processing. This early work also demonstrated that multi-unit recordings could reliably detect synchronous activity of a neuronal population (C. M. Gray et al., 1989), which is important for the transfer to noninvasive electrophysiological techniques in humans.

Noninvasive techniques such as electro- or magnetoencephalography (EEG or MEG, respectively) are well suited to detect synchronized neuronal activity in humans, since they preferentially register averaged activity from large populations of neurons, while asynchronous activity cancels out. The EEG, recorded from the scalp surface, measures postsynaptic currents of synchronized pyramidal neurons (Luck, 2005). The MEG detects magnetic fields produced by cerebral electrical activity with extremely sensitive devices (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Consistent with the findings from animal experiments, Tallon-Baudry, Bertrand, Delpuech, and Pernier (1997) found an enhancement of high-frequency components 200 ms poststimulus during visual search that was not phase-locked to the stimulus onset. This response was related to top-down control. Results from animal and human studies converge that oscillatory brain dynamics play a pivotal role in information processing and communication in the brain.

2.4.2 Synchronized Neuronal Activity in Attention

Electrophysiological studies in monkeys and humans tackled the neuronal mechanism by which selective attention might operate. Gamma-band synchronization increased and alpha- and beta-band synchronization decreased, when macaque monkeys attended to behaviorally relevant stimuli and ignored distractors (Fries et al., 2001). Source reconstruction of MEG data in humans could show that this pattern of synchronized oscillations operates along the whole dorsal visual pathway including the frontal eye field and the intraparietal sulcus (Siegel et al., 2008). The gamma-band coupling between neurons in the frontal eye field and visual area V4 in monkeys increased when attention was directed to a behaviorally relevant stimulus in their joint receptive fields (Gregoriou, Gotts, Zhou, & Desimone, 2009). Moreover, the coupling originated in the frontal eye field, which was interpreted as a source of top-down control. Altogether, these studies highlight the role of temporal synchronization of neuronal activity in attentional selection.

2.4.3 Synchronized Neuronal Activity in Emotion Processing

Animal data support the notion that synchronization of neuronal activity is involved in processing of emotionally significant stimuli. In particular, synchronization in the theta band seems to be relevant for the establishment of conditioned fear memory in the amygdala (Pare & Collins, 2000; Pare et al., 2002; Seidenbecher, Laxmi, Stork, & Pape, 2003). In humans, stimulus-induced theta- and gamma-band responses have been reported in several MEG studies using affective priming or face discrimination paradigms (Garolera et al., 2007; Luo, Holroyd, Jones, Hendler, & Blair, 2007). Gamma-band power was also enhanced in response to threat-related facial expressions such as anger and fear (Balconi & Lucchiari, 2008) and in response to pleasant and unpleasant stimuli over frontal and temporal electrodes (Keil et al., 2001; Müller, Keil, Gruber, & Elbert, 1999). Recently, it has been demonstrated that distinct features of facial expressions (eyes or mouth) are encoded across different frequency bands (Schyns, Thut, & Gross, 2011). These results implicate temporal synchronization in the theta and gamma band in processing of emotionally significant stimuli.

2.4.4 Does Synchronized Neuronal Activity Mediate the Attentional Bias to Threat?

Although amygdala and PFC appear to mediate the attentional bias to threat (Bishop, 2007, 2008), these brain regions also show consistent activation in other mental phenomena (Adolphs, 2010b; Lindquist & Barrett, 2012; Miller & Cohen, 2001). The idea that identical brain regions are important for numerous aspects of emotion, cognition, or perception has been formalized in constructionism (Lindquist & Barrett, 2012). Specifically, emotional processing, such as the threat bias, emerges from basic psychological operations accomplished by distributed networks in the human brain. These networks are not uniquely dedicated to emotional processing. The advantage of such versatile networks is that the absence of a one-to-one correspondence between behavior and anatomical site allows distributed and rapid computation of complex cognitive operations (Mesulam, 1990). Existing anatomical connections constrain and guide possible network interactions (Mesulam, 2012). Lindquist and Barrett (2012) state that the specific mechanism of "how proposed basic psychological operations emerge from the interplay of these neurons" (p. 538) is yet unknown.

However, as reviewed in in the above paragraphs, temporal correlation of neuronal discharges provides a flexible means for routing of neuronal information through processing pathways and mediates basic psychological operations such as object perception, top-down

directed attention, and emotion processing. Furthermore, dynamic interactions of cell assemblies, reflected in synchronized neuronal activity, provide indices of network interactions (Engel et al., 2001; Siegel et al., 2012). The importance of temporal synchronization for routing of information has been shown in animal studies at the single cell level (Steinmetz et al., 2000), in multi-unit recordings (C. M. Gray et al., 1989), for local field potentials (von Stein et al., 2000), and in noninvasive electrophysiological methods in humans (Hipp, Engel, & Siegel, 2011; Siegel et al., 2008). For example, a recent EEG study revealed that large-scale beta synchronization in frontal, parietal, and extrastriate visual areas predicted the percept of an ambiguous audiovisual stimulus at the single-trial level (Hipp et al., 2011). Thus investigating temporal synchronization of neuronal activity with noninvasive techniques, such as EEG and MEG, can provide a promising tool to bridge the gap between the cell and the systems level of neuroscience, especially because methodological advances allow the estimation of neuronal sources underlying electrophysiological data (Cornwell et al., 2008; Gross et al., 2001; Luo et al., 2007; Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997).

Therefore, MEG and (intracranial) EEG are well suited to uncover the fine temporal structure of correlated neuronal activity underlying the attentional bias to threat. Moreover, it is hypothesized that the threat bias will evolve in regions of the dorsal and ventral fronto-parietal attention, limbic, and salience networks that neither are involved exclusively in the processing of emotion or attention (Lindquist & Barrett, 2012). Furthermore, high levels of trait anxiety and anxiety disorders have been associated with network dysfunction (Sylvester et al., 2012). If temporal synchronization of neuronal activity mediates the attentional bias to threat, then alterations in the threat bias at the behavioral level should be accompanied by changes at the neuronal level. Thus, it is expected that elevated vulnerability to anxiety in carriers of the short allele of 5-HTTLPR is associated with alterations in temporal synchronization of neuronal activity.

2.5 Evidence for the Attentional Bias to Threat

2.5.1 How Does the Attentional Bias to Threat Impact Behavior?

A variety of behavioral paradigms have been used to examine whether emotionally significant stimuli automatically draw attention and receive privileged processing. All these paradigms have in common that they investigate the effect on attentional processing by manipulating the emotional content of the information being processed. The appliance of these paradigms to

subgroups with increased vulnerability to anxiety, pathological levels of anxiety, or to patients with brain lesions provided further insights into the mechanism of the threat bias.

In the emotional Stroop task, participants have to name the color of ink in which a word is printed. The meaning of the word interferes with the speed of color naming, i.e. participants take longer to name words with negative compared to neutral valence (J. M. G. Williams, Mathews, & MacLeod, 1996). This paradigm has primarily been administered to clinical populations, in which interference effects are greatest when the emotional word stimuli match the participants' specific concerns (Yiend, 2010). Stimuli presented below the threshold of awareness also elicit interference in anxious participants (Mogg, Bradley, Williams, & Mathews, 1993), suggesting a preattentive mechanism. Algom, Chajut, and Lev (2004) have criticized the interpretation of the emotional Stroop as being caused by a selective attention mechanism by showing that it appears to originate from a threat-related generic slowdown.

Visual search tasks have been employed to determine whether emotional facial expressions preattentively draw attention. Participants are required to detect a face with a discrepant facial expression in an array of faces as quickly as possible. Detection of angry faces was faster and more accurate than that of happy faces (Frischen, Eastwood, & Smilek, 2008; Hansen & Hansen, 1988; Öhman, Lundqvist, & Esteves, 2001). Frischen et al. (2008) argued that results in visual search tasks could easily be confounded by visual low-level features of the stimuli, the choice of distractors, or the set size. A recent study (Becker, Anderson, Mortensen, Neufeld, & Neel, 2011) questioned both the superiority effect of angry faces and the assumption of preattentive, parallel search. Instead, those authors reported that happy faces are detected more efficiently than angry faces, and that attention was allocated consciously in a serial search process. These results are consistent with the contention that emotional facial expressions are processed more efficiently than neutral ones, but they do not capture attention automatically. A patient with bilateral amygdala lesion performed equally well to healthy controls in a speeded visual search for fearful faces despite impaired categorization of fearful faces (Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009). This result suggests that the amygdala might not be necessary for attentional capture by threat-related stimuli.

Affective priming studies assume that the encoding of emotionally significant primes impact the subsequent processing of target stimuli, i.e. participants are faster in categorizing the target stimulus (e.g., the word "ugly") after the presentation of an emotionally congruent (e.g., the word "hate") compared to an incongruent prime stimulus (e.g., the word "flower").

This effect has also been observed for subliminally presented primes (Hermans, Spruyt, De Houwer, & Eelen, 2003). However, affective priming seems to occur only when the categorization task for the target demands attentional allocation to the affective content of that stimulus (Spruyt, De Houwer, Hermans, & Eelen, 2007).

Among the most popular paradigms to investigate the attentional capture by emotional stimuli are cueing paradigms such as the dot probe paradigm (MacLeod et al., 1986; Mogg & Bradley, 1998). Two stimuli of different valence, often faces, are presented simultaneously and immediately followed by an emotionally neutral target stimulus at one of the two locations. The task requires speeded detection or identification of the target stimulus (e.g., dot or arrow). Response times to probes are faster when attention is allocated to the same spatial location. One advantage of this paradigm, in contrast to the emotional Stroop or visual search tasks, is that it requires a response to a neutral target in the absence of any other emotional information. Hence, effects can be attributed to the spatial allocation of attention rather than to some general interference (Yiend, 2010). A bias to the threat-related stimulus has been observed in individuals with clinical anxiety (MacLeod et al., 1986; Mogg & Bradley, 1999a), heightened anxiety scores (Mogg & Bradley, 1999b; Mogg, Bradley, de Bono, & Painter, 1997), increased vulnerability due to their 5-HTT genotype (Pergamin-Hight et al., 2012), but also in healthy individuals (Cooper & Langton, 2006; Hartikainen et al., 2000; Koster, Crombez, Verschuere, & De Houwer, 2004). This effect is also present for subliminally presented stimuli (Mogg & Bradley, 1999a). Other cue paradigms involve only a single cue, similar to the Posner paradigm (Posner, 1980), that can validly and invalidly cue the subsequent target position (Fox, Russo, Bowles, & Dutton, 2001; Fox, Russo, & Dutton, 2002). Both dot probe and single cue paradigms concur that the threat bias originates from difficulty to disengage attention from rather than from stronger vigilance to threat (Fox et al., 2001; Fox et al., 2002; Koster et al., 2004; Salemink, van den Hout, & Kindt, 2007).

Temporal allocation of attention can be measured with the attentional blink (AB) paradigm. The AB reflects a period of impaired attention, when two sequential targets in a stream of rapidly succeeding task-irrelevant distractors have to be reported. The second target (T2) is often missed when it follows the first (T1) with a temporal delay of 100-400 ms (Broadbent & Broadbent, 1987; Raymond, Shapiro, & Arnell, 1992; Weichselgartner & Sperling, 1987). A seminal study demonstrated that healthy controls reported more emotional compared to neutral T2 stimuli during the AB interval, but this advantage for emotional T2 was absent in a patient with bilateral amygdala lesion (Anderson & Phelps, 2001). This result

substantiates the important role of the amygdala for attentional capture by emotional stimuli. Remarkably, the preferential processing of emotional stimuli on the AB does not only have a beneficial effect by attenuating the AB (Milders, Sahraie, Logan, & Donnellon, 2006; Müsch, Engel, & Schneider, 2012), since emotional stimuli presented as T1 also capture attention and prolong the AB duration (Most, Chun, Widders, & Zald, 2005; Stein, Zwickel, Ritter, Kitzmantel, & Schneider, 2009). These findings show that emotional information captures attention more easily and has facilitated entry into awareness.

Pavlovian fear conditioning studies also provide a means to manipulate the emotional significance of stimuli by associating positive or negative valence to a stimulus. It can then be examined whether stimuli alter attention due to prior learning. This has been done in a variety of different paradigms showing that previously punished stimuli equally bias attention under low load and facilitate audiovisual integration (T. H. Lee, Lim, Lee, Kim, & Choi, 2009; Maiworm, Bellantoni, Spence, & Röder, 2012; Pischek-Simpson, Boschen, Neumann, & Waters, 2009; Yates, Ashwin, & Fox, 2010).

2.5.2 The Anatomical Network Mediating the Attentional Bias to Threat

A major part of neuroimaging research on the threat bias focused on the amygdala, mainly because its ambiguous role in the preattentive and automatic capture of attention by threat-related stimuli (Bishop, 2007; Compton, 2003; Pessoa, Kastner, et al., 2002; Pessoa & Ungerleider, 2004; Vuilleumier, 2005). Some of the first positron emission tomography (PET) and fMRI studies observed amygdala activation to masked presentations of threat-related faces that were not consciously perceived by the participants (Morris, Öhman, & Dolan, 1998; Whalen et al., 1998). These findings have led researchers to assume that the amygdala's response to threat-related facial expressions is automatic and operates at a subconscious level. Subsequent studies selectively manipulated attention to facial expressions and showed activation of the amygdala to fearful faces even when attention was directed away from faces (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Vuilleumier et al., 2001; M. A. Williams, McGlone, Abbott, & Mattingley, 2005). Vuilleumier et al. (2001) presented a pair of houses and a pair of faces simultaneously. Face pairs depicted neutral or fearful expressions. The participants attended to either the vertical or horizontal stimulus pair and judged whether the pair depicted the same or different stimuli (i.e., match vs. nonmatch). Fearful compared to neutral faces slowed down reaction times. In addition, the presentation of fearful

faces resulted in enhanced hemodynamic responses in the fusiform gyrus and the amygdala when face processing was task-relevant. This effect vanished in the fusiform gyrus but not in the amygdala when face processing was task-irrelevant. A control experiment in an independent group of participants verified that they did not pay attention to faces when asked to match houses. The amygdala's sustained response to fearful relative to neutral faces outside the attentional focus was replicated in a slightly different task, while activity in the fusiform gyrus decreased during inattention to faces (Anderson et al., 2003). Some authors emphasized that stimuli presented in the periphery might be more efficient to drive amygdala responses via the magnocellular pathway (M. A. Williams et al., 2005). In summary, these results suggested that threat-related stimuli are processed automatically, irrespective of the focus of attention.

On the contrary, other studies have cast doubt on the assumption that the processing of threat-related stimuli does not require attention. Pessoa, McKenna, Gutierrez, and Ungerleider (2002) also measured hemodynamic responses when attention was directed to and away from facial expressions. In one condition, participants had to match the orientation of two peripherally presented bars, while ignoring centrally presented fearful or neutral faces. In the second condition, they had to discriminate the faces' sex while ignoring the bars. Increased responses to fearful compared to neutral faces were only observed in the calcarine, the fusiform gyrus, superior temporal sulcus, the amygdala, the nucleus accumbens, the insula, and the medial frontal pole, when attention was directed to faces. When attention was directed to bars instead, fearful faces did not elicit stronger activation in those areas. The authors argued that their competing task was more demanding than that of Vuilleumier et al. (2001) and that the task demanded all attentional resources, so that task-irrelevant faces failed to elicit responses in the amygdala and the other brain regions. These results could be replicated in a follow-up study that parametrically manipulated attention by varying the difficulty of the bar matching task (Pessoa, Padmala, & Morland, 2005). The bar matching task recruited the dorsal fronto-parietal attention network, whereas the sex discrimination task recruited the fusiform gyrus, the superior temporal sulcus, the orbitofrontal cortex (OFC), and the amygdala. The amygdala response significantly differed between fearful and neutral faces only when discrimination of peripheral bar orientation was easy. Likewise, no differential responses for fearful compared to neutral faces in the amygdala during difficult task conditions were observed for peripherally presented faces (Silvert et al., 2007) and neither for faces, whose threat value was incremented by prior fear conditioning (Lim, Padmala, &

Pessoa, 2008). Altogether, these findings demonstrate that the amygdala response is under cortical top-down control and its activation depends on the availability of attentional resources, when the competing task is very demanding.

Empirical work in individuals with heightened anxiety scores shed further light on the anatomical network underlying the threat bias and on the automaticity of the amygdala response to threat. Participants with high levels of state anxiety showed altered activity in the cortical circuitry implicated in top-down control of threat (Bishop, Duncan, Brett, & Lawrence, 2004). Enhanced activity in the rostral ACC and the lateral PFC reflected increased attentional control over threat-related distractors in low state-anxious individuals, whereas participants scoring high on state anxiety showed less activity in those regions suggesting less attentional control (Bishop, Duncan, Brett, et al., 2004). Likewise, high state-anxious in contrast to low state-anxious individuals did not show a reduced amygdala response to unattended compared to attended fearful faces (Bishop, Duncan, & Lawrence, 2004), supporting the notion that the preattentive amygdala response was determined by the nature of the (threat) stimulus and by the individual sensitivity to those stimuli (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998). Differential amygdala responses to threat in high and low anxious individuals were further qualified by perceptual load (Bishop, Jenkins, & Lawrence, 2007). During low load, elevated state anxiety was associated with increased activity in the amygdala and superior temporal sulcus, whereas elevated trait anxiety was accompanied by reduced lateral PFC responses to fearful face distractors, corroborating reduced attentional control over task-irrelevant threat-related distractors. Under high load, neither group exhibited increased threat responses in the amygdala. Altogether, these results demonstrate increased sensitivity to and reduced attentional control over threat-related stimuli in individuals with heightened anxiety scores, manifested in enhanced amygdala and reduced ACC and PFC activations, respectively.

To date, few imaging studies examined whether 5-HTTLPR as a marker of increased vulnerability to anxiety disorders modulates the attentional bias to threat, albeit previous work consistently showed elevated amygdala activity to negative facial expressions in S-carriers compared to homozygous carriers of the long allele (Dannlowski et al., 2010; Hariri et al., 2002; Munafò, Brown, & Hariri, 2008). Still, two studies investigated the modulation of the threat bias by 5-HTTLPR with a dot probe paradigm. Stronger biased attention to emotional facial expressions in S-carriers was associated with smaller volumes of the lateral PFC (Beevers, Pacheco, Clasen, McGeary, & Schnyer, 2010) and resulted in greater neuronal responses in

fronto-parietal regions as well as the insula in a sample of healthy children and adolescents (9-17 yrs.), even when face cues were presented below the threshold of awareness (Thomason et al., 2010). These results provide mounting evidence that increased vulnerability to anxiety disorders is associated with altered prefrontal control functions and stronger attentional bias toward threat.

fMRI studies in brain lesioned patients substantiated the role of the above-mentioned brain regions in the attentional bias toward threat. For example, a neglect patient with parietal damage exhibited robust amygdala and OFC activity to presentation of unseen fearful faces in the neglected hemifield (Vuilleumier et al., 2002). Similarly, fearful faces presented in the blind hemifield of a patient with a lesion in left striate cortex evoked increased responses in the bilateral amygdala during a sex discrimination task (Morris, DeGelder, Weiskrantz, & Dolan, 2001). Moreover, the amount of amygdala but not hippocampal sclerosis was inversely related to activation of the ipsilateral visual cortex (including the fusiform gyrus) to fearful versus neutral faces (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). This result supports the claim that reentrant projections of the amygdala to the visual cortex enhance sensory processing of emotional stimuli.

Other studies mapped the anatomical network of the attentional bias to threat by utilizing emotional cueing or dot probe paradigms. A pioneering study identified exogenous cueing effects by fear-conditioned faces in the familiar fronto-parietal attention network (including the supplementary motor area, the ACC, the intraparietal sulcus, and the frontal eye fields) as well as the lateral OFC (Armony & Dolan, 2002). The activation of the lateral OFC was unexpected but accords well with its role in mediating emotional conflict (Bishop, Duncan, Brett, et al., 2004; Vuilleumier et al., 2001). The results in the dorsal fronto-parietal attention network were confirmed and extended by Pourtois, Schwartz, Seghier, Lazeyras, and Vuilleumier (2006), who presented bilateral, exogenous face cues of different expression before a matching-orientation task. Laterally presented fearful but not happy faces proved to be potent exogenous cues and modulated activation within the intraparietal sulcus in a spatially selective manner during valid compared to invalid trials, respectively. Deactivation in invalid trials likely reflected higher disengagement costs. Trials, in which only the face cue was present without being followed by a target, elicited greater responses to fearful compared to happy faces in the inferior temporo-parietal and temporo-occipital cortex, previously associated with the ventral fronto-parietal attention network (Corbetta & Shulman, 2002). Using bilateral cue and target displays, differential responses to fearful face cues appeared to

be lateralized (Noesselt, Driver, Heinze, & Dolan, 2005). That is, only increased, right-hemispheric activity in visual cortex and amygdala were observed when the fearful faces were presented in the left visual field but no increase in left-hemispheric activity for fearful faces presented in the right visual field. Furthermore, covert shifts of attention yielded reduced processing of task-irrelevant faces in the amygdala and fusiform gyrus (Brassen, Gamer, Rose, & Büchel, 2010). In line with results reported earlier, this study also observed amygdala responses to fearful faces under a wide attentional focus (i.e., uninformative cues).

Finally, manipulating the awareness of threat-related stimuli by backward masking or binocular rivalry procedures substantiated the role of the amygdala in mediating the attentional bias to threat. One study reported amygdala responses to briefly presented (33 ms) and masked fearful relative to neutral faces (Carlson, Reinke, & Habib, 2009), whereas two others failed to observe amygdala activation under similar conditions of reduced awareness (Pessoa, Japee, Sturman, & Ungerleider, 2006; Phillips et al., 2004). Binocular rivalry exploits the fact that when two different stimuli are dichoptically presented to the two eyes the percept is typically dominated by the stimulus presented to the dominant eye, while the other one is suppressed. In contrast to the backward masking results, a number of studies employing binocular rivalry consistently showed increased amygdala activity (Jiang & He, 2006; Troiani, Price, & Schultz, 2012; M. A. Williams, Morris, McGlone, Abbott, & Mattingley, 2004) and suppression of left parietal cortex (Troiani et al., 2012) for fearful faces despite suppression from awareness.

Altogether, the review of neuroimaging data consistently implicated the ventral fronto-parietal attention network, amygdala, and OFC in the detection and the dorsal fronto-parietal attention network, PFC, and ACC in the attentional control of threat-related facial expressions, respectively. Perceptual load was found to be a crucial modulating factor of the preattentive amygdala response to threat. Visual processing areas, such as the fusiform gyrus and the superior temporal sulcus, appear to be recruited more for processing threat-related compared to neutral stimuli. The importance of those brain regions in mediating the attentional bias to threat is underpinned by alterations in this circuitry in individuals with heightened anxiety levels and increased vulnerability due to their genetic disposition.

2.5.3 The Timing of the Attentional Bias to Threat

Akin to the PET and fMRI literature, several EEG and MEG studies investigated whether threat-related stimuli modulated event-related potentials (ERP) when attention was directed toward or away from those stimuli. In doing so, several components were identified that reflected processing of emotional significance.

Results on emotional modulation of the well-known face-sensitive N170, a negative deflection over posterior temporal sensors induced by face presentations (Bentin, Allison, Puce, Perez, & McCarthy, 1996), are inconsistent. The amplitude of the N170 was enhanced when attention was directed to faces but was unaffected by facial expression (Eimer, Holmes, & McGlone, 2003; Holmes, Vuilleumier, & Eimer, 2003). Yet, others reported larger N170 amplitudes for emotional facial expressions (Monroe et al., 2013; Rellecke, Sommer, & Schacht, 2012) or when attention had to be directed to facial expressions (Streit et al., 1999). Still, the N170 does not appear to be a reliable marker of the attentional bias to threat.

Another EEG study (Holmes et al., 2003) used the same house- vs. face-matching task described earlier (Vuilleumier et al., 2001). Fearful compared to neutral faces reduced the N1 amplitude over frontal sensors at very short latencies (100-120 ms), and that reduction later spread across central and parietal electrodes (180-300 ms). However, the reduced N1 to fearful faces disappeared when attention was directed to houses, suggesting that processing of emotional expression is strongly modulated by selective attention (Holmes et al., 2003). Reduction of N1 amplitudes generalizes to other facial expressions (Eimer et al., 2003), and partially remains when unattended faces are presented foveally (Holmes, Kiss, & Eimer, 2006). The early, frontal effect has been attributed to rapid detection of emotional information, while the sustained, centro-parietal effect has been related to higher level processing of emotional information, respectively (Eimer & Holmes, 2007). Higher order cortical brain regions, such as the OFC, ACC, or medial PFC, have been suggested as generators of the reduced N1 (Eimer & Holmes, 2007). Remarkably, these findings highlight that emotionally relevant information is available within less than 200 ms after stimulus onset.

Early modulations were also obtained when pleasant, unpleasant, and neutral stimuli instead of faces were used. Typically, processing pleasant and unpleasant pictures is associated with an increased early (150-300 ms) negative potential over temporo-occipital sensors (Schupp, Junghöfer, Weike, & Hamm, 2003), labeled early posterior negativity (EPN). This component has been related to sources in occipito-temporo-parietal areas (Schupp, Flaisch,

Stockburger, & Junghöfer, 2006). It was investigated whether the EPN, as a marker of preattentive processing of emotional information, could still be elicited under increased perceptual load (Schupp, Stockburger, Bublatzky, et al., 2007). Pleasant, unpleasant, and neutral stimuli were consecutively presented, while participants performed a concurrent attention task. The participants had to count vertical or horizontal grids overlaid at varying proportion on the visual stimuli. When none or few stimuli contained grids (low load), the emotional content modulated the EPN. However, emotional modulation, even to the most arousing exemplars of the stimulus set, was absent when attentional resources were scarce (Schupp, Stockburger, Bublatzky, et al., 2007). In contrast, the EPN was not attenuated when the concurrent task exploited auditory instead of visual processing channels, suggesting that emotional modulation of the EPN involves independent processing resources for the two modalities (Schupp et al., 2008). Interestingly, emotional modulation and attention had additive effects on the EPN, when attention was directed to the emotional content of the presented stimuli (Schupp, Stockburger, Codispoti, et al., 2007). Hence, although the EPN reflects emotion processing as early as the N1, the assumption that this processing occurs automatically does not receive empirical support, which is consistent with the literature reviewed so far.

Although the N1 and EPN inform about the processing depth of emotional information in the absence of focal attention, the impact of task-irrelevant, emotional distractors on target processing of the concurrent attention task would allow more direct inferences on the attentional threat bias. The N2pc seems to be a good indicator of attentional selection of task-relevant items and inhibition of task-irrelevant distractors. The N2pc is a relative negativity between 180-350 ms over occipital sensors contralateral to the target item such as a target in visual search. Task-irrelevant fearful faces presented in the visual periphery elicited an N2pc, while participants performed a task requiring the detection of occasional luminance changes at fixation (Eimer & Kiss, 2007). Likewise, the N2pc emerged earlier for angry compared to happy facial expressions, reflecting prioritized threat processing (Holmes, Bradley, Kragh Nielsen, & Mogg, 2009), predicted subsequent behavioral ratings of faces, suggesting a bi-directional influence of attention and emotion (Kiss et al., 2007), and was affected by trait anxiety (Fox, Derakshan, & Shoker, 2008). A recent MEG study elegantly showed that task-irrelevant fearful faces elicited a (magnetic counterpart of the) N2pc that was completely independent to the target-related N2pc but similar in terms of size, latency, and underlying occipito-temporal sources (Fenker et al., 2010). In other words, task-irrelevant

fearful faces mandatorily modulated neuronal activity around 240 ms poststimulus in extrastriate cortex. In two visual search experiments, participants had to report the location or orientation of a predefined target (colored bars) overlaid on fearful or neutral faces. Since the bilateral stimulus display contained all possible pairings of the two facial expressions, the target-related N2pc could be assessed unbiased by emotion (same bilateral expression displays) and the expression-related N2pc could be estimated under equal attentional conditions of target search (different bilateral expression displays). Behavioral effects only paralleled the N2pc effects when the perceptual load of the search task was reduced. The authors attributed the N2pc evoked by fearful faces to late, but automatic top-down influences from the amygdala to extrastriate cortex (for similar thoughts, see Holmes et al., 2009) that only transfers to measurable behavioral output unless perceptual demands are sufficiently low. In accordance, similar latencies to fearful faces have also been recorded with intracranial EEG (iEEG) directly in the amygdala (Krolak-Salmon, Hénaff, Vighetto, Bertrand, & Mauguiere, 2004). Taken together, the N2pc seems to be a reliable marker for the withdrawal of attention from current processing by emotional distractors, appearing around 250 ms poststimulus.

Emotional distractors also modulate target processing, as reflected by the P1 component. Typically, increased P1 amplitudes evoked by attended visual stimuli have been interpreted as evidence for a selective sensory gating mechanism by spatial attention (Hillyard, Vogel, & Luck, 1998). Using the same emotional variant of the dot probe paradigm as the previously described fMRI study (Pourtois et al., 2006), the lateral occipital P1 component (100-200 ms), generated in extrastriate areas, was selectively enhanced to lateralized visual targets replacing a fearful compared to a neutral face (Pourtois, Grandjean, Sander, & Vuilleumier, 2004). This effect was selective to fearful faces and did not occur for happy faces. These results show that task-irrelevant fearful faces are potent exogenous cues that can impact with target processing, extending findings from earlier studies (Stormark, Nordby, & Hugdahl, 1995). A re-analysis of the 2004 data with topographic analysis of surface potentials revealed that the topographic maps preceding the P1 time range (40-80 ms) differed for valid (i.e., fearful faces presented in same visual hemifield as targets) compared to invalid (i.e., fearful faces in opposite hemifield) trials with fearful faces (Pourtois, Thut, Grave de Peralta, Michel, & Vuilleumier, 2005). In other words, those dissimilar topographic maps reflected different functional neuronal generators. Estimated sources were posterior parietal and inferior temporal cortex for valid and medial frontal and ACC for invalid trials. ACC activation might reflect interference during invalid trials when fearful faces in the opposite hemifield captured

attention, whereas temporo-parietal sources suggest an enhancement of spatial orienting mechanisms during valid trials. Similar P1 effects have been demonstrated for angry face cues (Fox et al., 2008). In addition, P1 amplitude was differentially modulated by trait anxiety with high and low anxious individuals showing threat bias and avoidance, respectively (Li, Li, & Luo, 2005). In summary, the P1 also seems to be a reliable marker for the withdrawal of attention from current processing by emotional distractors, appearing around 100 ms earlier than the N2pc.

Steady-state visual evoked potentials (ssVEP) offer a different approach to study the interaction of attention and emotion. The ssVEP is generated in occipital cortex by a visual stimulus flickering at a fixed rate. This results in an oscillatory brain response with the same frequency as the driving stimulus (for an alternative explanation, see Capilla, Pazo-Alvarez, Darriba, Campo, & Gross, 2011). Using this approach, it was shown that emotional (pleasant and unpleasant) pictures interfered with a concurrent attentionally demanding task (Hindi Attar, Andersen, & Müller, 2010; Keil, Moratti, Sabatinelli, Bradley, & Lang, 2005; Müller, Andersen, & Hindi Attar, 2011; Müller, Andersen, & Keil, 2008). An increased or reduced ssVEP either reflects facilitation or competition, respectively. Paralleling behavioral findings, the ssVEP to emotional words presented during the AB interval was enhanced, suggesting that affective content facilitates processing during periods of reduced awareness (Keil, Ihssen, & Heim, 2006). Moreover, by superimposing two stimuli with varying flicker frequencies, ssVEP amplitude and phase modulation to each stimulus can be assessed separately. This procedure revealed that task-irrelevant facial expressions yielded opposite competition effects in a concurrent task in high and low anxious groups (Wieser, McTeague, & Keil, 2012). Specifically, angry and happy faces were the most potent distractors in high and low anxious participants most, respectively. The ssVEP to the target superimposed on angry faces was reduced in the high anxious group, demonstrating a direct processing cost of the threat bias. Thus, ssVEPs are well-suited to assess competition between task-irrelevant emotional distractors and ongoing target processing.

Consistent with the fMRI literature, differential ERPs to fearful faces were found even when they were presented subliminally (33 ms in Bayle, Hénaff, & Krolak-Salmon, 2009; 8 ms in Kiss & Eimer, 2008). These components, have been localized to originate from the amygdala in a recent MEG study (Bayle et al., 2009). The importance of subcortical brain regions in mediating responses to emotional facial expressions has also been highlighted in experiments on a patient with extensive lesion in the striate visual cortex. Although the gender

discrimination for faces in the "blind" hemifield opposite to the lesion was at chance level, comparable P1 and N1 components to fearful and happy faces in the blind and intact hemifield were recorded over the central occipital sensor (de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999). This result emphasizes that facial expressions can activate the ventral visual pathway via anatomical routes bypassing V1.

The investigation of attentional capture by non-visual emotional stimuli or between modalities contributed to the field by showing that emotional effects on attentional allocation are not restricted to one modality. Similar facilitation effects on the P1 to visual targets were observed (as in Pourtois et al., 2004) in a cross-modal dot probe paradigm (Brosch, Grandjean, Sander, & Scherer, 2009) when the target was preceded by a threat-related auditory cue. The bilateral cue consisted of angry and neutral prosody instead of fearful and neutral faces (Pourtois et al., 2004). Furthermore, fear-conditioned auditory stimuli manipulated attention processing as reflected by changes in the ERPs (Pauli & Röder, 2008) and event-related fields (Bröckelmann et al., 2011). In addition, olfactorily fear-conditioned faces elicited early changes in frontal and occipito-temporal regions as measured with MEG (Steinberg et al., 2012).

In summary, ERP studies substantiate that task-irrelevant emotional distractors bias competition quite early between 100-250 ms poststimulus, as reflected in the P1 and N2pc. The N1 and EPN are reliable markers of emotion processing in a similar time range that depend, however, on the availability of processing resources.

2.5.4 Frequency-Specific Neuronal Activity and the Attentional Bias to Threat

Compared to the abundance of fMRI and ERP results reviewed above, the investigation of temporal synchronization underlying the attentional bias to threat is still in its infancy. Consistent with results on emotion processing in general, activity in the theta and gamma have been implicated in the threat bias.

In line with enhanced gamma-band power in response to threat-related stimuli (Balconi & Lucchiari, 2008; Keil et al., 2001; Müller et al., 1999), increased gamma-band synchronization between 30-50 Hz has also been found in a MEG study investigating the time course of processing threat-related expressions (Luo et al., 2007). Source reconstruction revealed that all facial expressions elicited synchronization in the gamma band in the occipito-temporal cortex between 40-300 ms peaking at 140 ms, while fearful faces increased gamma-

band responses in the amygdala as early as 20 ms and angry faces around 140 ms. Activation in frontal areas was observed around 200 ms. As activity in occipito-temporal cortex and amygdala preceded that in the frontal areas, these results were interpreted as evidence for a subcortical route via the amygdala for fear processing and a cortical route for anger processing. The attentional bias to threat-related and neutral distractor faces has been investigated under different load conditions of a concurrent orientation-matching task (Luo et al., 2010). Facial expressions did not interfere with behavioral performance in the two load conditions. However, early gamma-band synchronization around 30-60 ms in the amygdala was increased in response to fearful but not neutral faces irrespective of task load. Late amygdala responses were modulated by task load at 280-340 ms, i.e., fearful face distractors elicited gamma-band activity (GBA) in the amygdala only under low load conditions. These findings suggest that the degree of amygdala activation to threat-related, task-irrelevant distractors is a function of time. Accordingly, previous iEEG studies also reported increased gamma-band power in the amygdala in response to fearful faces and unpleasant stimuli (Oya, Kawasaki, Howard, & Adolphs, 2002; Sato et al., 2011b), albeit at different latencies. Pessoa (2010) critically commented on the results of the MEG study by Luo et al. (2010), questioning that the task load might not have been demanding enough to exploit all attention resources and that the timing of the early amygdala response did not confirm with response latencies in the visual system. Furthermore, spatial resolution of MEG beamformer solutions might be afflicted with a certain level of uncertainty.

Differences in gamma-band synchronization were also found in other experiments. In an auditory-visual distraction paradigm, distractibility by novel compared to standard sounds increased, when participants had to match unpleasant relative to neutral pictures. This was paralleled by increased gamma-band synchronization at 40 Hz for novel sounds and unpleasant pictures compared to neutral ones (Garcia-Garcia, Yordanova, Kolev, Dominguez-Borras, & Escera, 2010). In contrast, another study reported gamma-band suppression between 50-250 ms poststimulus in response to angry face distractors in left extrastriate cortex in a concurrent letter detection task (Maratos, Senior, Mogg, Bradley, & Rippon, 2012). Such early responses are in agreement with Luo et al. (2007). However, this finding reflected active suppression of neuronal activity in response to negative information.

Theta-band activity plays an important role in fear conditioning (Pare & Collins, 2000; Pare et al., 2002; Seidenbecher et al., 2003) and has been altered in 5-HTT deficient mice (Narayanan et al., 2011). Consistent with this notion, the analysis of the same data set of

Maratos et al. (2012) yielded substantial theta desynchronization 50-250 ms poststimulus in response to threat-related compared to neutral faces in the visual cortex, frontal cortex, and amygdala, when the face stimuli contained low spatial frequency information (Maratos, Mogg, Bradley, Rippon, & Senior, 2009). Since the suppression in frontal areas lasted longer than in the amygdala, theta desynchronization might mediate effortful control in response to threat-related stimuli. Furthermore, theta suppression might also integrate activity within the emotion-processing network. In contrast, another study observed stronger theta synchronization to threatening relative to neutral cues in a dot probe paradigm over posterior sensors, which likely reflected evaluation of emotional significance (Sun, Sun, Wang, & Gong, 2012).

Experiments investigating temporal synchronization of neuronal activity add to the wealth of present literature as they allow the investigation of neuronal communication in various frequency bands. Previous findings, albeit not consistent with regard to the direction of effects, demonstrated that threat-related distractors modulated activity in the theta and gamma band. Yet, given the important role of the PFC, ACC, and parietal regions in attentional control of threat-related stimuli, it is surprising that the attentional bias to threat has not been associated with frequency-specific changes in those regions. The impact of individual differences, such as genetic disposition to anxiety disorders, on temporal synchronization of neuronal activity has also not yet been investigated. In addition, it remains unclear whether other frequency bands play a role in the attentional bias to threat (e.g., the alpha band as an important marker of attention processing).

2.6 Research Objectives

The results of the literature reviewed so far concur in the contention that emotionally significant stimuli are processed more efficiently than neutral ones. The attentional bias to emotionally significant stimuli, measurable in a variety of different paradigms, is mediated by distributed network of cortical and subcortical structures. The ventral fronto-parietal attention network, the amygdala, and the OFC have consistently been implicated in the detection of emotionally significant (task-irrelevant) stimuli, while the dorsal fronto-parietal attention network, the PFC, and the ACC exert attentional control over those stimuli. Individual differences, such as increased vulnerability to anxiety disorders due to genetic disposition, are associated with heightened threat biases and affect activation in this circuitry.

Emotionally significant, task-irrelevant distractors bias competition and interfere with ongoing behavior quite early around 100-250 ms, best represented by the N2pc and P1 components. Less is known about the frequency-specific responses of the attentional bias to threat. Synchronization in the theta and gamma band in the medial temporal lobe, including the amygdala, has been associated with the detection of emotionally significant (task-irrelevant) stimuli. However, drawing on the important role of the ventral and dorsal fronto-parietal attention network, the PFC, and ACC for the control over threat-related stimuli on the one hand and on the role of alpha- and gamma-band synchronization for attentional selection on the other, the attentional bias to threat should also be associated with frequency-specific changes in those brain regions.

The present work assessed attentional capture by emotional, including threat-related, facial expressions in three different studies. Each of these studies independently manipulated attention and emotion and investigated a different domain of attention. The first, a behavioral study, investigated in seven successive experiments how emotional facial expressions modulated temporal fluctuations of attention with an AB paradigm. It was expected that emotional facial expressions were more easily detected than neutral faces during the blink interval. The second study exploited the good spatial and temporal resolution of iEEG to directly record from the amygdala, fusiform gyrus, OFC, and insula of patients with pharmaco-resistant epilepsy during two simple detection tasks. Facial expressions were task-relevant in the first but task-irrelevant in the second task. It was hypothesized that exogenous attention to fearful faces and endogenous attention to task-relevant faces was reflected in stronger temporal correlation of neuronal activity, particularly in the gamma band. Finally, the third study investigated the impact of task-irrelevant distractor faces on spatial attention in an attentional probe task using MEG in for 5-HTTLPR genetically predefined participants. It was expected that processing threat-related distractors elicited stronger synchronization, preferably in the gamma or theta band, in the ventral fronto-parietal attention network and/or visual and limbic areas, including the fusiform gyrus. Attentional control over threat-related distractors should instead be reflected in stronger synchronization in the dorsal fronto-parietal attention network, preferably in the alpha and gamma band. Furthermore, it was assumed that elevated vulnerability to anxiety in carriers of the short allele of 5-HTTLPR was associated with alterations in temporal synchronization of neuronal activity in those regions.

3 STUDY I[1]: SIMILARITY OF DISTRACTOR AND TARGET IMPACTS THE ATTENTIONAL BLINK WITH FACES

3.1 Introduction

When we allocate attention to a flux of incoming stimuli, awareness for these stimuli is not constant over time but instead fluctuates from moment to moment. In order to study how visual awareness is changing over time during a stream of quickly succeeding information, rapid serial visual presentation (RSVP) paradigms are widely used. In these paradigms, one or more targets have to be reported in a stream of rapidly succeeding stimuli. If two task-relevant targets appear in close temporal proximity within a stream of irrelevant distractors, a period of limited awareness for the second target, the AB, is often observed. The AB reflects a deficit in reporting the second target (T2) in case it follows the first task-relevant target (T1) with a temporal delay of 100-400 ms (Broadbent & Broadbent, 1987; Raymond et al., 1992; Weichselgartner & Sperling, 1987). Single task control conditions in this type of experiments suggest an attentional rather than perceptual cause of the AB (Raymond et al., 1992). In single task conditions physical stimulation remains the same (presentation of T1 and T2) but attentional demands are decreased, as only the second stimulus is task-relevant. In single task conditions the AB is usually absent (Raymond et al., 1992).

Traditional models have attributed the AB to attentional capacity limitations at a late processing stage (Chun & Potter, 1995; Potter, Staub, & O'Connor, 2002; Shapiro, Arnell, & Raymond, 1997; Shapiro, Raymond, & Arnell, 1994). In particular, these models suggested that the perceptual representation for the second target (i.e. T2), formed during an early processing stage, cannot be transferred into working memory, and thus will not be reported until the system has successfully transferred the first target (i.e., T1) into working memory at a late processing stage. However, limited capacity models cannot account for some recent findings of the AB (Martens & Wyble, 2010). More recent accounts suggest that the AB results from active control of attentional resources (Bowman & Wyble, 2007; Vul, Nieuwenstein, &

[1] A substantial part of this work (Experiments 2-7) has previously been published in: Müsch K, Engel AK, Schneider TR (2012) On the Blink: The Importance of Target-Distractor Similarity in Eliciting an Attentional Blink with Faces. PLoS ONE 7(7): e41257. doi:10.1371/journal.pone.0041257. Please note that this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. The experiments have been conducted and analyzed by Kathrin Müsch. Till R. Schneider and Andreas K. Engel assisted in conceiving and designing the experiments and in writing the manuscript.

Kanwisher, 2008; Wyble, Bowman, & Nieuwenstein, 2009). These models are able to explain why salient stimuli can outlive the AB: the encoding of salient stimuli needs fewer resources due to increased bottom-up strength, and thus less allocation of attentional resources is necessary (Bowman & Wyble, 2007; Wyble et al., 2009). Salience can either be driven by perceptual features, such as discernability of targets from distractors, or by contents (e.g., emotional vs. neutral stimuli).

Several studies employed neutral face stimuli for probing the AB achieving mixed results. Most studies found an AB for faces (Table A1), whereas others did not with famous faces (Jackson & Raymond, 2006), low T1 load (Landau & Bentin, 2008), upright faces (Darque, Del Zotto, Khateb, & Pegna, 2011), or when T1 and T2 were faces (Awh et al., 2004; Serences, Scolari, & Awh, 2009). Landau and Bentin (2008) suggested that the salience of faces among nonface distractors was an important factor in determining the susceptibility of face targets to be blinked. However, they did not specifically investigate this claim. Taken together, these results suggest that face processing requires attentional resources, since faces can be blinked, and that the perceptual salience of faces among distractors is critical for eliciting an AB.

The AB magnitude can be modulated by manipulating the allocation of attention toward T1 or T2 (Martens & Wyble, 2010). For example, AB magnitude was reduced by task-irrelevant mental performance in an additional memory task or by focusing less on the AB task (Olivers & Nieuwenhuis, 2006). The AB was also extinguished when highly familiar or famous faces were used (Jackson & Raymond, 2006). In addition, emotional target stimuli seem to modulate blink magnitude as well. Several studies have demonstrated an influence of emotional information on the extent of the blink magnitude by using a variety of emotional stimuli including words (Anderson, 2005; Anderson & Phelps, 2001; Keil & Ihssen, 2004), photographs of objects or scenes (Most, Chun, Johnson, & Kiehl, 2006; Most et al., 2005; Reinecke, Rinck, & Becker, 2008; Trippe, Hewig, Heydel, Hecht, & Miltner, 2007) and emotional faces (de Jong & Martens, 2007; De Martino, Kalisch, Rees, & Dolan, 2009; Fox, Russo, & Georgiou, 2005; Milders et al., 2006; Stein et al., 2009). Interestingly, the AB is differentially modulated depending on whether T1 or T2 is emotionally salient. The AB is increased following an emotional T1, possibly due to a longer attentional dwell time on T1, leaving less capacity for the processing of T2 (Huang, Baddeley, & Young, 2008; Stein et al., 2009). In contrast, the AB is attenuated when emotional compared to nonemotional stimuli are presented as T2, which suggests stronger attentional capture by emotional stimuli

(Anderson & Phelps, 2001; Milders et al., 2006). Importantly, several studies found a robust AB for neutral compared to realistic (De Martino et al., 2009; Stein et al., 2009) or schematic emotional faces (Maratos, Mogg, & Bradley, 2008; Miyazawa & Iwasaki, 2010).

In contrast to studies reporting an emotional modulation of the AB in healthy individuals (Anderson & Phelps, 2001; Milders et al., 2006; Trippe et al., 2007), several studies reported an emotional modulation of the AB only in individuals with high anxiety scores (Arend & Botella, 2002; Fox et al., 2005), with dysphoria (Koster, De Raedt, Verschuere, Tibboel, & De Jong, 2009), or with posttraumatic stress symptoms (Amir, Taylor, Bomyea, & Badour, 2009), yet failed to find an effect in healthy participants. Such an absence of the AB is unlikely to be caused by the type of stimulus material because similar stimuli were used as in experiments, which found an AB in healthy individuals (e.g., words in Amir et al., 2009; Arend & Botella, 2002; Koster et al., 2009; and faces in Fox et al., 2005). Amir et al. (2009) suggested that this absence might be related to the lower depth of target processing (e.g., no semantic processing or explicit emotion processing). Accordingly, in a series of experiments semantic processing (Huang et al., 2008) or emotion processing (Stein et al., 2009) were shown to be a necessary condition for an increased AB following emotional stimuli as T1. For emotional T2 it has not yet been investigated systematically whether explicit emotion processing is required to decrease AB magnitude.

The aim of the present study was to systematically investigate the influence of target-distractor similarity. In total, seven experiments were conducted in different groups of participants in order to investigate how emotional valence modulates the temporal allocation of attention. As the AB was absent or only shallow in Experiments 1 and 2, respectively, we selectively manipulated the T1 and T2 similarity (Experiment 3), similarity of targets and distractors (Experiment 4-6), and the task relevance of the emotional expression (Experiment 7). Manipulating experimentally the similarity between targets and distractors revealed a strong effect of the type of distractors accounted for the shallow and missing AB effect of the previous experiments. The final experiment demonstrated that the type of task (whether the emotional expression was explicitly or implicitly task-relevant) did not have an impact over and above the effect of target-distractor similarity in Experiments 4 and 5.

3.2 Experiment 1 and Experiment 2

Experiment 1 and Experiment 2 are reported together because both did not elicit a robust AB. Since performance at ceiling accounted for the absent AB in Experiment 1, the stimulus duration was increased and the T2 task was changed in order to resolve a putative confound in the T2 task (i.e. discrimination between face detection and emotion detection).

3.2.1 Methods

Participants. Fifteen participants were recruited from the University Medical Center Hamburg-Eppendorf each for Experiment 1 (7 female, $M \pm SD$ = 23.7 ± 2.9 years) and for Experiment 2 (10 female, $M \pm SD$ = 24.0 ± 2.3 years), who were paid for participation. All participants had normal or corrected to normal vision and reported no history of psychiatric or neurological illness. One female participant had to be excluded from Experiment 1 and one male participant had to be excluded from Experiment 2 due to performance at chance level. The participants of these and the subsequent experiments provided written, informed consent. The ethics committee of the Hamburg Medical Association approved all procedures.

Stimuli. Emotional and neutral faces were embedded among distractors in a RSVP stream (Figure 3.1). Faces of 12 males and 12 females with neutral, fearful, and happy expressions from the Karolinska Directed Emotional Faces (Lundqvist, Flykt, & Öhman, 1998) served as targets. These faces were selected for highest gender discernability as determined in a pilot rating. Distractors were phase-scrambled versions of 54 neutral faces. All stimuli were converted to gray-scale, matched for luminance and masked by an oval shape to remove hair, neck and background information. T1 faces were presented in red tint (each pixel value of the red color channel multiplied by 1.75 in Experiment 1 and 2.25 in Experiment 2, respectively) in order to distinguish it from the other stimuli in the stream.

Design and Procedure. Each trial consisted of a stream of 25 visual stimuli including scrambled distractors and target faces, starting with a 500 ms fixation period. Each stimulus was displayed for 100 ms in Experiment 1 and 70 ms in Experiment 2 at the center of the monitor, resulting in a stimulation frequency of 10.0 and 14.3 Hz, respectively (Figure 3.1). The first face (T1) always had a neutral expression whereas the expression of the second face (T2) was systematically varied (fearful, happy, and neutral expression 31.7% each; remaining 5% scrambled distractor). In Experiment 1, the temporal interval between T1 and T2 varied between lag 1 (100 ms, no intervening item between T1 and T2), lag 2 (200 ms, one

intervening item and so forth), lag 3 (300 ms), lag 4 (400 ms), lag 5 (500 ms), lag 6 (600 ms), and lag 7 (700 ms) in order to cover the whole AB interval. In Experiment 2, the temporal interval between T1 and T2 varied between lag 1 (70 ms, no intervening item between T1 and T2), lag 2 (140 ms, one intervening item and so forth), lag 3 (210 ms), lag 4 (280 ms), lag 5 (350 ms), lag 6 (420 ms), and lag 8 (560 ms) in order to cover the whole AB interval. The gender of the two targets was counterbalanced and two targets never had the same identity in a given trial. T1 appeared equally often at positions 9 to 15 of each stream in both experiments.

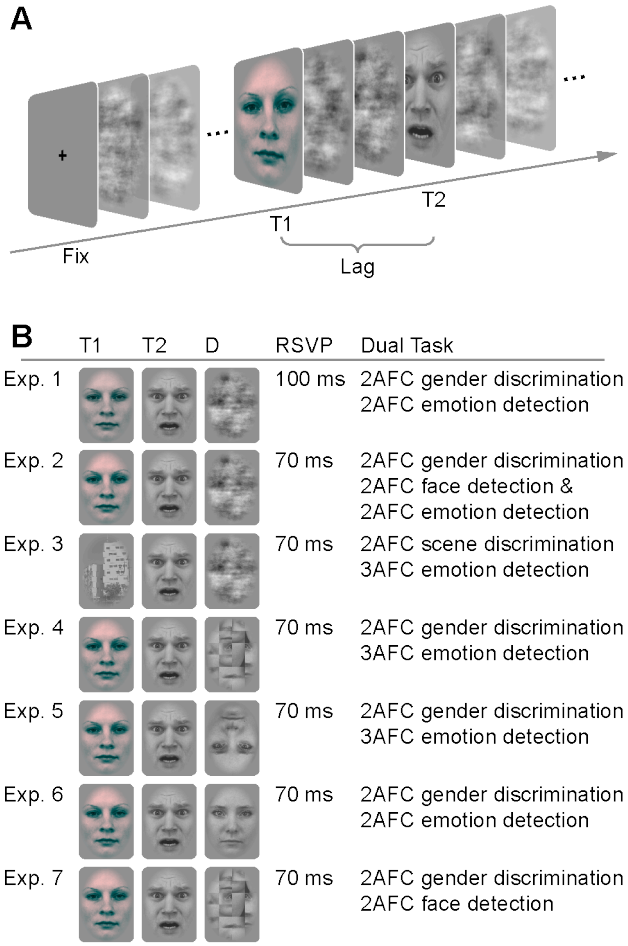

Figure 3.1. Schematic illustration of a single trial and overview of AB experiments. (A) After 500 ms fixation period, 25 stimuli including the two targets with a variable lag (lag 3 in this example) were rapidly presented. The first *and* the second target were task-relevant. T1 was presented between position 9 and 15 in a stream of distractors followed by T2 at lags 1, 2, 3, 4, 5, 6, 7 (Experiment 1) or 1, 2, 3, 4, 5, 6, 8 (Experiments 2-7). (B) The experiments differed with regard to stimuli used as T1, T2, and distractors, stimulus presentation duration, and dual task demands. Abbreviations: T1, first target; T2, second target; D, distractors; RSVP, rapid serial visual presentation; 2AFC, two-alternative forced-choice.

In Experiment 1 after each trial, participants were first requested to report the gender of T1 ("male", "female") and then whether they had seen an emotional face (T2; "emotion present", "emotion absent") by button-press on the keyboard with the left or right index

finger, respectively. Please note, that this design did not allow the discrimination of face detection versus emotion detection of T2.

This concern was addressed in Experiment 2. In Experiment 2, participants were first requested to report the gender of T1 ("male", "female") and then whether they had seen a second face (T2; "face", "no face") by button-press on the keyboard with the left or right index finger, respectively. In case of a "face", participants were asked to indicate whether the face was emotional or neutral ("emotional face", "neutral face"). This two-step procedure allowed discriminating different levels of processing: face detection versus emotion detection of T2.

The response button mapping was counterbalanced across participants. Seven blocks with 60 trials each were presented in random order. In total, 19 trials per condition were presented (7 lags x 3 emotions = 399 trials). In 5% of the trials T2 was not present and replaced by a scrambled distractor. To familiarize participants with the experimental procedure, 10 practice trials were presented before each experiment. No speeded responses were demanded and participants received no feedback during the experiment. Stimuli were presented on a 20" TFT monitor at a refresh rate of 60 Hz and a viewing angle of approximately 9° in Experiment 1 and on a 22" CRT monitor at a refresh rate of 100 Hz and a viewing angle of approximately 5.4° in Experiment 2 using the Psychophysics Toolbox (3rd version) (Brainard, 1997; Pelli, 1997) and MATLAB 7 (The MathWorks Inc, Natick, MA, USA).

Data Analysis. Mean accuracy was calculated for T1 and T2, respectively. T2 report was analyzed contingent on correct T1 report. For the T2 task in Experiment 1 the percentage of correct responses was calculated as the proportion of correctly detected emotional and neutral faces relative to the total number of trials presenting a face as T2, separately for fearful, happy, and neutral expressions. For the T2 task in Experiment 2 the percentage of correct responses was calculated as the proportion of detected relative to the total number of trials presenting a face as T2, separately for fearful, happy, and neutral faces. The detection of T2 was considered more relevant to the AB than the emotion detection because the amount of misses per lag directly reflects the impairment of visual awareness, i.e. the attentional blink. In addition, false alarms were defined as the proportion of "emotion present" and "face" responses to the number of T2-absent trials contingent on correct T1 report in Experiment 1 and Experiment 2, respectively. Low values of false alarms indicate that participants were able to perform the task correctly. The percentage of correct responses on T1 and T2 report were subjected to a repeated measures analysis of variance (ANOVA) with lag (1, 2, 3, 4, 5, 7 in

Experiment 1; 1, 2, 3, 4, 5, 6, 8 in Experiment 2) and emotion (fearful, happy, neutral) as within-subject factors. Due to technical problems, trials with lag 6 were not included in the analysis of Experiment 1. In order to check for a possible confusion between T1 and T2 in the gender discrimination task at each lag, T1 error rates of Experiment 2 were compared for trials in which both targets had the same versus the opposite gender. For all experiments, estimates were Greenhouse-Geisser-corrected whenever appropriate. Original degrees of freedom are reported. Five planned orthogonal contrasts were conducted as follow-up analysis: (1) the linear effect of lag; (2) neutral vs. emotional faces; (3) fearful vs. happy faces; (4) the interaction between lag and neutral vs. emotional faces (4), and (5) the interaction between lag and fearful vs. happy faces. Effect sizes were reported as eta-squared, representing the proportion of accounted variance ($\eta^2 < 0.1$ = small effect size; $0.1 < \eta^2 < 0.25$ = medium effect size; $\eta^2 > 0.25$ = large effect size).

Table 3.1. Results of the repeated measures ANOVA for each experiment.

	T1				T2			
	df	*F*	*p*	η^2	*df*	*F*	*p*	η^2
Experiment 1 (N = 14)								
Lag (6)	**5, 65**	**75.62**	**< 0.001**	**0.85**	5, 65	0.32	0.91	0.02
Emotion (3)	2, 26	1.99	0.157	0.13	**2, 26**	**16.33**	**< 0.001**	**0.56**
Lag x Emotion	**10, 130**	**2.73**	**0.04**	**0.17**	10, 130	0.44	0.93	0.03
Experiment 2 (N = 14)								
Lag (7)	**6, 78**	**43.21**	**< 0.001**	**0.77**	**6, 78**	**11.58**	**0.002**	**0.47**
Emotion (3)	2, 26	0.03	0.975	0.00	**2, 26**	**15.50**	**0.001**	**0.54**
Lag x Emotion	12, 156	0.88	0.565	0.06	**12, 156**	**2.80**	**0.041**	**0.18**
Experiment 3 (N = 13)								
Lag (7)	6, 72	0.57	0.756	0.05	6, 72	0.67	0.672	0.05
Emotion (3)	2, 24	0.624	0.454	0.05	2, 24	0.46	0.640	0.04
Lag x Emotion	12, 144	0.98	0.470	0.08	12, 144	0.54	0.884	0.04
Experiment 4 (N = 21)								
Lag (7)	**6, 120**	**32.49**	**< 0.001**	**0.62**	6, 120	2.65	0.092	0.12
Emotion (3)	2, 40	1.31	0.280	0.06	**2, 40**	**18.50**	**< 0.001**	**0.48**
Lag x Emotion	12, 240	1.51	0.175	0.07	12, 240	0.80	0.567	0.04
Experiment 5 (N = 15)								
Lag (7)	**6, 84**	**13.28**	**< 0.001**	**0.49**	**6, 84**	**6.88**	**0.003**	**0.33**
Emotion (3)	2, 28	0.11	0.893	0.01	**2, 28**	**8.89**	**0.001**	**0.39**
Lag x Emotion	12, 168	1.25	0.292	0.08	12, 168	1.54	0.191	0.10
Experiment 6 (N = 20)								
Lag (7)	6, 114	1.77	0.110	0.09	6, 114	0.41	0.738	0.02
Emotion (2)	**1, 19**	**17.03**	**0.001**	**0.47**	**1, 19**	**44.18**	**< 0.001**	**0.70**
Lag x Emotion	6, 114	0.94	0.471	0.05	6, 114	0.11	0.995	0.01
Experiment 7 (N = 16)								
Lag (7)	**6, 90**	**28.01**	**< 0.001**	**0.65**	**6, 90**	**3.73**	**0.038**	**0.20**
Emotion (3)	2, 30	2.26	0.121	0.13	**2, 30**	**13.07**	**0.001**	**0.47**
Lag x Emotion	12, 180	0.62	0.707	0.04	**12, 180**	**2.01**	**0.026**	**0.12**

Abbreviations: T1, first target, T2, second target; *df*, degrees of freedom; *F*, *F*-value; *p*, *p*-value; η^2, effect size; N, sample size.

3.2.2 Results

For Experiment 1, T1 performance and T2 performance were separately compared in a 6 x 3 (lag x emotion) within-subjects ANOVA. The ANOVA on T2 performance resulted in a main effect of emotion (Table 3.1, Figure 3.2A). The contrast analysis revealed that performance differed for all facial expressions and was best for fearful, intermediate for happy, and lowest for neutral faces (Table 3.2). The ANOVA on T1 resulted in a main effect of lag and a lag by emotion interaction (Table 3.1, Figure 3.2A). The contrast analysis on the interaction effect revealed that performance for fearful faces at lag 1 was better than for the other two categories (Table 3.2). The percentage of false alarms was low ($M \pm SD$ = 4.9 ± 8.1). These results indicate that no AB was found, which would be reflected in main effect of lag or an interaction lag by emotion. Inspection of Figure 3.2A also reveals that performance was at ceiling.

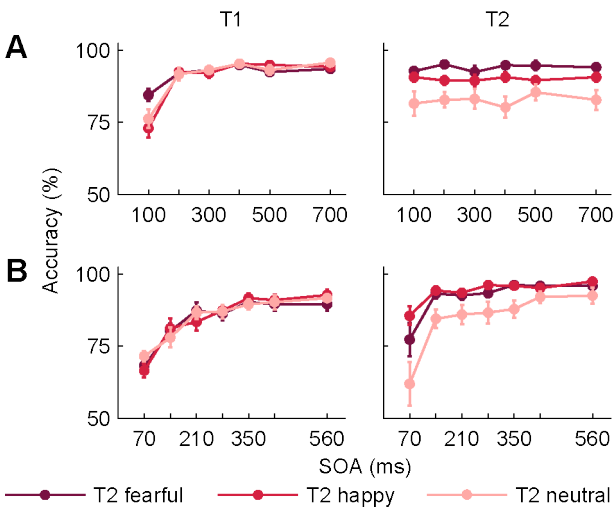

Figure 3.2. Mean accuracy for first and second targets (T1, T2) in Experiments 1 and 2. Stimuli were presented for (A) 100 ms in Experiment 1 or (B) 70 ms in Experiment 2. Performance is depicted separately for the different facial expressions of T2. T2 detection is conditional on T1 performance. Error bars represent standard errors of the means (SEM). Abbreviations: T1, first target; T2, second target; SOA, stimulus onset asynchrony.

For Experiment 2, T1 performance and T2 performance were separately compared in a 7 x 3 (lag x emotion) within-subjects ANOVA. The ANOVA on T2 performance resulted in main effects of lag and emotion and a lag by emotion interaction (Table 3.1, Figure 3.2B). The contrast analysis on the interaction effect revealed that the effect of lag was more pronounced for neutral faces compared to emotional faces, while the effect of lag was only a trend for the difference of fearful and happy faces (Table 3.2). Correct report of T1 was dependent on the lag (Table 3.1, Figure 3.2B), which was reflected by a linear increase across lags (Table 3.2). The percentage of false alarms was quite low ($M \pm SD$ = 10.5 ± 13.4). T1 error rates for trials

in which T1- and T2-faces had opposite sex were higher compared to trials in which T1- and T2-faces were the same sex only at lag 1 (opposite sex $M \pm SD = 14.5 \pm 11.0$, same sex $M \pm SD = 46.7 \pm 12.3$; $t[13] = 6.34$, $p < 0.001$) but not at any other lag (all ts < 1.33, all ps > 0.205; except for lag 3, $t[13] = 2.20$, $p = 0.046$, not significant following Bonferroni correction). Therefore, it cannot be ruled out that T1 and T2 stimuli were confused in the gender classification task of Experiment 2. Taken together, these results suggest a temporal impairment of visual awareness modified by emotional expression solely in Experiment 2.

3.2.3 Discussion

Surprisingly, no AB was found in Experiment 1. Given the high T2 performance, the absence of an AB was likely due to a ceiling effect. T2 performance depended on the emotional content of T2 suggesting a facilitated processing of fearful and happy faces over neutral faces. These results are in line with the assumption of enhanced attention for emotional stimuli (Vuilleumier, 2005; Yiend, 2010).

The decreased performance on T2 in Experiment 2 could be interpreted as a genuine AB, which additionally was modulated by emotional expression. However, the profile of the AB was very shallow. Performance on T1 in Experiment 2 was also reduced in the first two lags. Participants may have confused T1 and T2 at shorter lags, especially when there was no distractor in between. An additional analysis on T1 errors revealed preliminary evidence for this assumption: error rates for opposite-sex compared to same-sex trials were only higher at lag 1 but not at any other lag. Thus, it seems likely that participants confused T2 and T1 in the gender classification task. Earlier studies using letters also found increased order inversion effects for T1 at the first lag (Chun, 1997a, 1997b; Chun & Potter, 1995). According to the 2-stage competition model (Potter et al., 2002) there is a trade-off between T1 and T2 performance when the lag between the targets is less than 100 ms. Hence, it seems inherent in the AB that correct report of T1 is compromised by correct report of T2 at the first lag (Chun, 1997a). However, the present results merely reflect a globally diminished performance for T1 and T2 instead of a trade-off between targets.

Table 3.2. Results of the planned contrast analysis for each experiment.

	T1				T2			
	df	*F*	*p*	η^2	*df*	*F*	*p*	η^2
Experiment 1 (N=14)								
C1: Lag	**1, 13**	**109.37**	**< 0.001**	**0.89**	1, 13	0.36	0.560	0.03
C2: NE vs. EMO	**1, 13**	**0.06**	**0.805**	**0.01**	**1, 13**	**15.45**	**0.001**	**0.56**
C3: FE vs. HA	1, 13	5.41	0.037	0.29	**1, 13**	**15.42**	**0.002**	**0.54**
C4: Lag x (NE vs. EMO)	**1, 13**	**0.76**	**0.399**	**0.06**	1, 13	0.05	0.836	0.00
C5: Lag x (FE vs. HA)	1, 13	11.55	0.005	0.47	1, 13	0.12	0.734	0.01
Experiment 2 (N=14)								
C1: Lag	**1, 13**	**129.84**	**< 0.001**	**0.91**	**1, 13**	**22.18**	**< 0.001**	**0.63**
C2: NE vs. EMO	1, 13	0.05	0.826	0.00	**1, 13**	**16.48**	**0.001**	**0.56**
C3: FE vs. HA	1, 13	0.00	0.958	0.00	**1, 13**	**6.03**	**0.029**	**0.32**
C4: Lag x (NE vs. EMO)	1, 13	1.64	0.223	0.11	**1, 13**	**8.16**	**0.013**	**0.39**
C5: Lag x (FE vs. HA)	1, 13	1.16	0.301	0.08	1, 13	3.49	0.084	0.21
Experiment 3 (N=13)								
C1: Lag	1, 12	2.15	0.168	0.15	1, 12	0.96	0.347	0.07
C2: NE vs. EMO	1, 12	1.93	0.190	0.14	1, 12	0.25	0.625	0.02
C3: FE vs. HA	1, 12	0.51	0.489	0.04	1, 12	0.58	0.460	0.05
C4: Lag x (NE vs. EMO)	1, 12	1.93	0.190	0.14	1, 12	0.04	0.837	0.00
C5: Lag x (FE vs. HA)	1, 12	0.38	0.549	0.03	1, 12	2.30	0.155	0.16
Experiment 4 (N=21)								
C1: Lag	**1, 20**	**183,49**	**< 0.001**	**0.90**	1, 20	3.26	0.086	0.14
C2: NE vs. EMO	1, 20	0.29	0.594	0.01	**1, 20**	**23.86**	**< 0.001**	**0.54**
C3: FE vs. HA	1, 20	2.15	0.159	0.10	**1, 20**	**5.01**	**0.037**	**0.20**
C4: Lag x (NE vs. EMO)	1, 20	0.07	0.793	0.00	1, 20	1.34	0.260	0.06
C5: Lag x (FE vs. HA)	1, 20	3.30	0.084	0.14	1, 20	0.10	0.756	0.01
Experiment 5 (N=15)								
C1: Lag	**1, 14**	**31.24**	**< 0.001**	**0.69**	**1, 14**	**9.62**	**0.008**	**0.41**
C2: NE vs. EMO	1, 14	0.00	0.954	0.00	**1, 14**	**13.30**	**0.003**	**0.49**
C3: FE vs. HA	1, 14	0.20	0.661	0.01	1, 14	1.71	0.213	0.11
C4: Lag x (NE vs. EMO)	1, 14	0.97	0.341	0.07	**1, 14**	**6.97**	**0.019**	**0.33**
C5: Lag x (FE vs. HA)	1, 14	0.01	0.935	0.00	1, 14	1.53	0.236	0.10
Experiment 6 (N=20)								
C1: Lag	1, 19	1.63	0.217	0.08	1, 19	0.29	0.598	0.02
C2: NE vs. EMO	-	-	-	-	-	-	-	-
C3: FE vs. HA	**1, 19**	**17.03**	**0.001**	**0.47**	**1, 19**	**44.18**	**< 0.001**	**0.70**
C4: Lag x (NE vs. EMO)	-	-	-	-	-	-	-	-
C5: Lag x (FE vs. HA)	**1, 19**	**4.38**	**0.05**	**0.19**	1, 19	0.16	0.691	0.01
Experiment 7 (N=16)								
C1: Lag	**1, 15**	**82.45**	**< 0.001**	**0.85**	**1, 15**	**6.72**	**0.020**	**0.31**
C2: NE vs. EMO	1, 15	4.19	0.059	0.22	**1, 15**	**22.74**	**< 0.001**	**0.60**
C3: FE vs. HA	1, 15	0.59	0.453	0.04	1, 15	0.001	0.972	0.00
C4: Lag x (NE vs. EMO)	1, 15	0.00	0.968	0.00	1, 15	3.65	0.075	0.20
C5: Lag x (FE vs. HA)	1, 15	0.02	0.885	0.00	1, 15	0.71	0.413	0.05

Note: Contrast 1 (C1) tests for a linear trend on the factor lag. Contrast 2 (C2) compares neutral vs. emotional faces and contrast 3 (C3) fearful to happy faces. Contrasts 4 (C4) and 5 (C5) investigate a linear trend on the factor lag for neutral vs. emotional and fearful vs. happy faces, respectively. Abbreviations: T1, first target, T2, second target; *df*, degrees of freedom; *F*, *F*-value; *p*, *p*-value; η^2, effect size; N, sample size; NE, neutral expression; EMO, fearful or happy expression; FE, fearful expression; HA, happy expression.

3.3 Experiment 3

To rule out the possibility that participants confused T2 with T1 stimuli in the gender classification task, indoor and outdoor scenes in Experiment 3 replaced neutral T1-faces.

3.3.1 Methods

Participants. Thirteen students (8 female, $M \pm SD = 24.1 \pm 1.5$ years), none of whom participated in the previous experiments, were recruited from the same pool and were paid for participation. All participants had normal or corrected to normal vision and reported no history of psychiatric or neurological illness.

Stimuli. Stimuli were identical to those of Experiment 2 except that gray-scale indoor and outdoor scenes instead of neutral faces were presented as T1. T1 scenes were not tinted because they could easily be discriminated from T2 faces (compare De Martino et al., 2009). Visual scenes (equal in mean luminance) were selected according to highest discrimination performance and matched for visual complexity according to a pilot rating.

Design and Procedure. Unlike in Experiment 2, the task on T2 consisted of only one question. An additional response option for "no face" was included, thus resulting in three response possibilities ("emotional face", "neutral face", "no face") for each trial.

Data Analysis. Data analysis was identical to Experiment 2 except for the following changes. False alarms in Experiments 3, 4, and 5 were defined as the proportion of "emotional face" or "neutral face" responses to the number of T2-absent trials contingent on correct T1 report.

3.3.2 Results

T1 performance and T2 performance were separately subjected to a 7 x 3 (lag x emotion) within-subjects ANOVA. There were no significant effects on T1 performance and on T2 performance (Table 3.1, Table 3.2, Figure 3.3). As in the previous experiments, the percentage of false alarms was low ($M \pm SD = 2.2 \pm 4.2$).

3.3.3 Discussion

There were no effects of lag or emotion in Experiment 3 thus suggesting that the transient performance decrease in Experiment 2 resulted from a confusion of the target faces (Chun, 1997a, 1997b; Chun & Potter, 1995; Potter et al., 2002; Wyble et al., 2009). The absence of an AB is in direct contrast to the study by De Martino et al. (2009) who reported an AB also using scenes as T1, faces as T2, and scrambled distractors. In their experiment performance for fearful T2 faces was higher than for neutral T2 faces only at lag 5 (350 ms), which was,

however, the only lag tested in this experiment. The distractors in the experiment by De Martino et al. (2009) differed from the ones in the present Experiments 1, 2, and 3. The role of distractors in eliciting an AB for faces was addressed in the following three experiments.

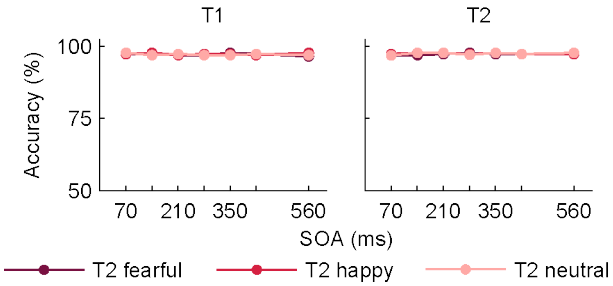

Figure 3.3. Mean accuracy for first and second targets (T1, T2) in Experiment 3. Performance is depicted separately for the different facial expressions of T2. T2 detection is conditional on T1 performance. Error bars represent SEM.

3.4 Experiment 4, Experiment 5, and Experiment 6

In contrast to previous studies using upright neutral faces (Fox et al., 2005), 180° rotated neutral faces (de Jong & Martens, 2007), or randomly rearranged quadrants of face or scene images (De Martino et al., 2009; Milders et al., 2006) as distractors, the distractors in the previous experiments were phase-scrambled versions of the face stimuli and contained no meaningful high-level information. A previous study using letters reported that the AB could be eliminated when targets were embedded in highly discriminable distractors (Chun & Potter, 1995). To investigate whether the shallow AB profile in Experiment 2 might have resulted from insufficient masking and from dissimilarity between targets and distractors, the similarity of the distractors with the target faces was varied in the following three experiments. They are reported together because every participant took part in two of the experiments.

3.4.1 Methods

Participants. Twenty-eight participants (15 female, $M \pm SD = 26.5 \pm 4.0$ years), none of whom participated in the previous experiments, were recruited from the same pool and were paid for participation. All participants had normal or corrected to normal vision and reported no history of psychiatric or neurological illness.

Stimuli. Target stimuli were identical to those of Experiment 2. Phase-scrambled distractors were replaced by three different types of distractors of the same 54 neutral faces

resulting in three experiments. In Experiment 4, faces were divided into 20 randomly rearranged parts of 75 x 70 pixels and masked by an oval shape to remove hair, neck and background information. These distractors will be referred to as mosaic-scrambled faces. In Experiment 5, distractors consisted of 180° rotated faces with neutral expression. In Experiment 6, distractors were upright faces with neutral expression.

Design and Procedure. Design and procedure were identical to that of Experiment 2 except for the following specifications: each participant took part in two experiments. The order of the experiments was counterbalanced across subjects resulting in final samples of 21 participants in Experiment 4 (12 female, $M \pm SD$ = 26.6 ± 4.2 years), 15 participants in Experiment 5 (8 female, $M \pm SD$ = 26.8 ± 2.9 years), and 20 participants in Experiment 6 (10 female, $M \pm SD$ = 26.0 ± 4.5 years). In Experiments 4 and 5 the task on T2 was identical to that of Experiment 3 providing three response options in each trial ("emotional face", "neutral face", or "no face"). In Experiment 6, T2 was always present resulting in a total of 399 trials (7 lags x 3 emotion, 19 trials per condition). The T2 task remained an emotion detection task. However, since distractors were upright neutral faces, the option "no face" was inappropriate for Experiment 6 and only two of the previous response options were provided ("emotional face", "neutral face"). Hence, participants replied with "neutral face" when they did not see an emotional face in a given trial.

Data Analysis. Data analysis for the three experiments was identical to that of Experiment 2 except for Experiment 6 using neutral face distractors, in which the percentage of correct responses for the T2 task was calculated as the proportion of correct emotion detection. Only fearful and happy T2 were analyzed, as neutral T2 could not be differentiated from distractors and faces were always present as distractors. In Experiment 6, false alarms were calculated as the proportion of "emotional face" responses to the number of trials depicting neutral T2 faces contingent on correct T1 report. In addition, these false alarm rates were compared to hit rates for "emotional face" responses in order to clarify whether the absent AB was due to a floor effect.

3.4.2 Results

For Experiment 4 using mosaic-scrambled face distractors, T1 performance and T2 performance were separately compared in a 7 x 3 (lag x emotion) within-subjects ANOVA. The ANOVA on T2 performance resulted in main effects of lag and emotion (Table 3.1,

Figure 3.4A). The contrast analysis showed that the difference between neutral and emotional faces was larger than that between the two emotional faces (Table 3.2). Correct report of T1 depended on lag (Table 3.1, Figure 3.4A), which was reflected by a linear increase across lags (Table 3.2). These results indicate that an AB was found for faces, which was not modulated by emotional expression. Independently, performance for emotional faces was better than for neutral faces across all lags.

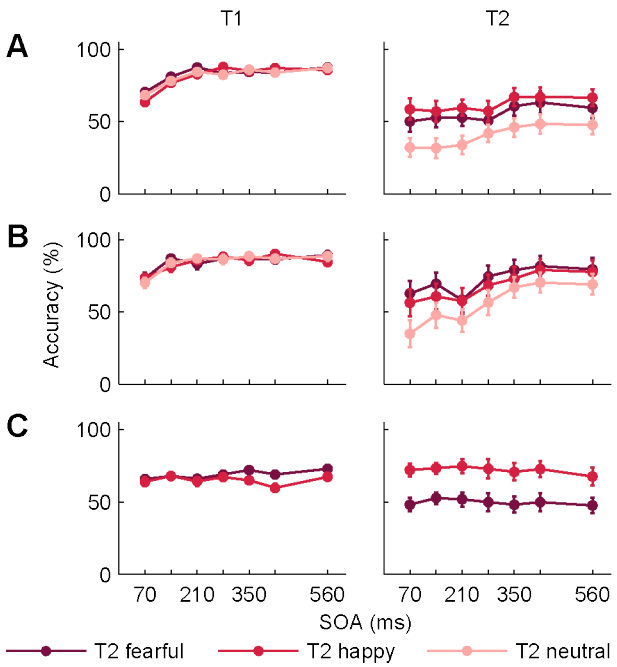

Figure 3.4. Mean accuracy for first and second targets (T1, T2) in Experiment 4, 5, and 6. Target stimuli were identical to Experiment 1. Distractors were either (A) mosaic-scrambled faces, (B) inverted faces with neutral expression, or (C) upright faces with neutral expression. Performance is depicted separately for the different facial expressions of T2. T2 performance is conditional on T1 performance. Error bars represent SEM.

For Experiment 5 presenting inverted face distractors, T1 performance and T2 performance were separately subjected to a 7 x 3 (lag x emotion) within-subjects ANOVA. Comparison of T2 performance resulted in a main effect of lag and emotion (Table 3.1, Figure 3.4B). Follow-up analysis suggested a linear increase across lags and easier detection of emotional compared to neutral faces (Table 3.2). Notably, although the interaction effect did not reach statistical significance, the planned interaction contrast for the comparison of neutral to emotional faces was significant (Table 3.2), reflecting that the AB for neutral faces was more pronounced relative to emotional faces. Correct report of T1 depended on lag (Table 3.1, Figure 3.4B) reflected by a linear increase across lags (Table 3.2). These results

suggest a transient impairment of visual awareness and an advantage for the detection of emotional faces.

For Experiment 6 using neutral face distractors, T1 performance and T2 performance were separately subjected to a 7 x 2 (lag x emotion) within-subjects ANOVA. Only effects of emotion were found which were opposite for T1 and T2 performance (Table 3.1, Table 3.2, Figure 3.4C): T1 was reported correctly more often when it was followed by a fearful instead of a happy face, while T2 performance was higher for happy faces compared to fearful faces. These results indicate that performance differed according to the emotional expression, but no AB was found in Experiment 6.

The percentage of false alarms for T2 was $M \pm SD = 10.5 \pm 13.3$ in Experiment 4 and $M \pm SD = 12.2 \pm 14.4$ in Experiment 5. For Experiment 6, the percentage of false alarms, reflected by the proportion of "emotional face" responses to the number of T2 trials containing neutral faces, was $M \pm SD = 18.9 \pm 12.3$. This rate was significantly lower than the average number of correct responses for emotional T2 ($M \pm SD = 60.3 \pm 17.0$; $t[19] = 9.54$, $p < 0.001$).

3.4.3 Discussion

As expected, increasing the similarity of distractors and targets in terms of facial features decreased the overall T2 performance. Importantly, the use of more similar distractors resulted in an AB when distractors were mosaic-scrambled and inverted faces, hence containing more feature information than the abstract phase-scrambled distractors used before. Therefore we conclude that dissimilarity between targets and distractors can account for the missing AB in Experiments 2 and 3.

There was no AB when distractors were upright faces. The absence of an AB with upright face distractors is in direct contrast to the experiment by Fox et al. (2005) using upright neutral faces as distractors. Longer stimulus duration (110 ms) could account for the higher performance. However, T1 performance in Experiment 6 was lower than that of Experiments 4 and 5 and of Fox et al. (2005). In addition, performance for fearful faces in the T2 task was almost at chance level. In addition, T1 stimuli and T1 task were different (Table A1): flower T1 had to be discriminated from mushroom T1 (Fox et al., 2005), thus facilitating the T1 differentiation from T2 stimuli as well as from distractors. These results suggest that the task of Experiment 6 was more demanding than that of the previous experiments and that of Fox et al. (2005). However, participants were able to reliably detect emotional faces from

the stream of neutral distractors, as reflected by significantly more hits than false alarms for "emotional face" responses. Thus, results of Experiment 6 corroborate the finding that faces with emotional expressions are spared the AB.

In line with results from Experiments 1 and 2, T2 performance depended on the emotional content of T2 suggesting a facilitated processing of fearful and happy faces over neutral faces. A superiority effect for happy faces was found except for the inverted face experiment, in which fearful faces tended to be better recognized than neutral faces. These results are in line with the assumption of enhanced bottom-up attention for emotional stimuli (Vuilleumier, 2005; Yiend, 2010).

As in Experiment 2, a decreased T1 performance at lag 1 in the mosaic-scrambled and the inverted face experiment reflected the competition for attentional resources of T1 with T2 at lag 1 (Chun, 1997a, 1997b; Chun & Potter, 1995). T1 performance in the experiment with upright face distractors was greatly reduced across all lags. In this case upright T1 faces differed from the distractors only in color (red tint) and therefore may have been more difficult to extract from the RSVP stream. Thus, it is likely that participants reported the gender of neighboring faces instead that of T1.

3.5 Experiment 7

This final experiment investigated whether the specific attentional set, i.e. the allocation of attentional resources that is adjusted by the observer (top-down control), had an additional impact on the AB over and above the effect of target-distractor similarity. In contrast to all previous experiments, in which emotion recognition was explicitly demanded by the T2 task, in Experiment 7 the emotional expression of faces was irrelevant to the T2 task. For emotionally expressive T2, the influence of the type of task has never directly been investigated so far. Milders et al. (2006) successfully elicited an AB with a very similar design but an implicit emotion recognition task.

3.5.1 Methods

Participants. Seventeen participants (10 female, $M \pm SD = 28.4 \pm 4.1$ years), none of whom participated in the previous experiments, were recruited from the same pool and were paid for participation. All participants had normal or corrected to normal vision and reported

no history of psychiatric or neurological illness. One female subject had to be excluded due to performance at chance level.

Stimuli. Stimuli were identical to Experiment 4.

Design and Procedure. Design and procedure were identical to that of Experiment 2 except for the task on T2. Participants were solely requested to report whether they had seen an upright second face ("yes", "no").

Data Analysis. Data analysis was identical to that of Experiment 2.

3.5.2 Results

The comparison of T2 performance in a 7 x 3 (lag x emotion) within-subjects ANOVA resulted in main effects of lag, emotion, and an interaction between lag and emotion (Table 3.1, Figure 3.5). Follow-up contrast analysis on the interaction revealed a trend in that the linear effect of lag was more pronounced for neutral compared to emotional faces (Table 3.2). The percentage of false alarms was $M \pm SD = 7.6 \pm 9.7$. These results indicate that an AB was found for faces, which was modulated by emotional expression.

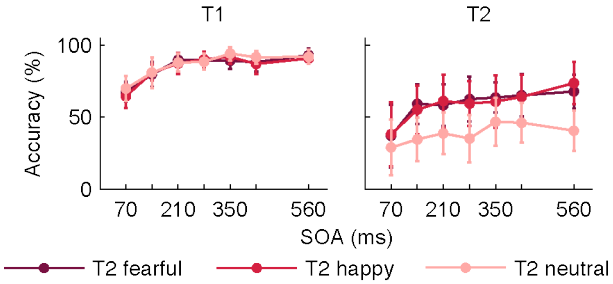

Figure 3.5. Mean accuracy for first and second targets (T1, T2) in Experiment 7. Performance is depicted separately for the different facial expressions of T2. T2 detection is conditional on T1 performance. Error bars represent SEM.

The 7 x 3 (lag x emotion) within-subjects ANOVA on T1 performance revealed a significant effect of lag (Table 3.1, Figure 3.5), which was reflected by a linear increase across lags (Table 3.2).

3.5.3 Discussion

Unlike in the previous experiments, the detection of the emotional facial expression of T2 was not relevant to solve the task in Experiment 7. In line with results from Milders et al. (2006) an AB was observed. The trend of the interaction contrast suggested that the AB was attenuated

for happy and fearful faces. Somewhat surprisingly, T2 performance for neutral faces did not recover to baseline level. Reasons for this might be twofold. First, AB patterns in the individual participants were highly heterogeneous. Second, T2 performance for neutral faces seemed to drop particularly from lag 6 to lag 8, which most likely reflects an expectation effect: because lag 7 was omitted, participants might not have expected a second face anymore. Emotional but not neutral T2s at lag 8 were detected due to increased salience. Results of Experiment 7 suggest that the attentional set or the demands of top-down control in the specific task do not have an incremental effect on eliciting the AB beyond the effect of target-distractor similarity of the previous experiments.

3.6 General Discussion

The major goal of the present study was to systematically investigate the impact of target-distractor similarity under conditions of high attentional demands in a RSVP stream in which two targets were embedded. The results of the experiments yielding an AB are summarized in Figure 3.6. Contrary to our expectation, the AB was absent in Experiment 1, presumably due to a ceiling effect, and only a shallow AB was found in Experiment 2. However, this effect could not be replicated when we replaced neutral T1 faces by indoor and outdoor scenes in Experiment 2. To investigate whether the absence of an AB resulted from target-distractor dissimilarity and insufficient masking, Experiments 4-6 selectively manipulated the distractors' similarity to the target faces. An AB was revealed in Experiment 4 using mosaic-scrambled distractors and Experiment 5 using inverted face distractors. Thus, similarity between targets and distractors seems to account for the strength of the AB in the present experiments. No AB was found, however, in Experiment 6, when targets were emotional faces and distractors were neutral faces. This result supports the notion that faces with emotional expression tend to be less likely to be blinked. Moreover, in Experiments 5 and 7 emotional faces were found to be less susceptible to the AB, further confirming the attentional advantage for emotional faces.

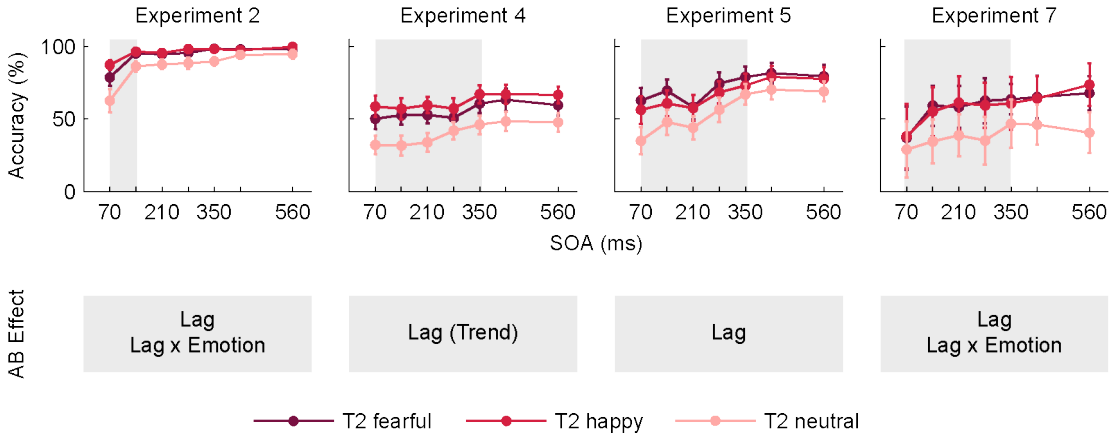

Figure 3.6. Summary of experiments yielding an AB for T2. Error bars represent SEM. Gray shading approximately indicates the AB.

In the first three experiments, the nature of the abstract phase-scrambled distractors and their featural dissimilarity to the targets may have diminished appropriate masking of the target faces. Phase-scrambled distractors may not be sufficiently meaningful or may not contain enough high-level pattern information to function as effective masks. However, previous studies revealed that masks neither have to be meaningful (Giesbrecht & Di Lollo, 1998) nor have to contain pattern information (Grandison, Ghirardelli, & Egeth, 1997) to be effective. Landau and Bentin (2008) suggested that the salience of faces among nonface distractors was an important factor in determining the susceptibility of face targets to be blinked. Previous studies showing an AB effect on emotional T2 faces used a stream of neutral faces (Fox et al., 2005), 180° rotated neutral faces (de Jong & Martens, 2007), or mosaic-scrambled distractors (De Martino et al., 2009; Milders et al., 2006) consisting of randomly rearranged squares of faces or scenes. Therefore, the masking effect on T1 by the subsequent distractors may have been stronger in previous studies using faces as targets (de Jong & Martens, 2007; De Martino et al., 2009; Fox et al., 2005; Milders et al., 2006) resulting in larger attentional impairments for processing of T2 compared to our Experiments 1-3. This assumption is consistent with a series of AB experiments investigating the role of T1 and its subsequent item in the RSVP stream (Seiffert & Di Lollo, 1997). The authors reported a correlation between T1 performance and AB magnitude using letters as targets and concluded that masking influenced the AB deficit indirectly by increasing the processing load of T1. Furthermore, Jannati, Spalek, and Di Lollo (2011; Experiment 2) successfully elicited an AB for letters by increasing target-distractor similarity relative to a report using the same experimental design (Giesbrecht & Di Lollo, 1998), when pseudoletters instead of digits were used as distractors. Our Experiments 4 and 5 also provide support for the role of target-

distractor dissimilarity as causes for the missing AB in our first three experiments. The experiments using mosaic-scrambled and inverted face distractors successfully elicited an AB. Using upright neutral faces as distractors resulted in a drop in T1 and T2 performance except for happy faces. However, we did not observe an AB under conditions of minimal target salience with upright neutral face distractors that were maximally similar to emotionally target faces, supporting the finding that emotional faces tend to outlive the AB. A similar finding of reduced performance without significant AB has also been reported by Awh et al. (2004; Experiment 5) when faces were masked by other faces. Taken together, the results from Experiments 4 and 5, specifically, corroborate the role of insufficient masking as a cause for the missing and the shallow AB in our first three experiments.

Furthermore, results from Experiment 7 suggest that the nature of the (emotion recognition) task does not play a crucial role in shaping the AB over and above the role of target-distractor similarity. Similar to the results of Experiment 4 using an explicit emotion detection task and mosaic-scrambled distractors, an AB was also found in Experiment 7 when participants had to engage in a face detection task on T2, in which the emotional expression of T2 was task-irrelevant. Our result is in line with several other studies reporting an AB with an implicit face detection task (Jackson & Raymond, 2006; Landau & Bentin, 2008; Milders et al., 2006). Previous work demonstrated that increasing the task load and changing the instruction had an impact on AB magnitude (Ferlazzo, Lucido, Di Nocera, Fagioli, & Sdoia, 2007; Nieuwenstein & Potter, 2006; Olivers & Nieuwenhuis; Taatgen, Juvina, Schipper, Borst, & Martens, 2009), suggesting that attentional set or top-down control of the specific task plays a role in the elicitation of the AB. However, it did not seem to make a difference for the present experiments, whether the emotional expression was relevant to the task or not.

Face stimuli in the RSVP may be more salient than letters or words and therefore require adequate masks to transiently impair awareness. Faces convey relevant information for social interactions. Several lines of research suggest that face processing differs from processing of other stimuli. Already newborns show increased attention to face compared to nonface stimuli (e.g. Morton & Johnson, 1991). Furthermore, face recognition in contrast to word or object recognition seems to be holistic and configural (Farah, Wilson, Drain, & Tanaka, 1998). Therefore it was hypothesized that faces are processed automatically by a pre-attentive mechanism as they pop out of visual search arrays with different distractors (Hershler & Hochstein, 2005). In addition, faces may be processed with little attentional resources, which is supported by studies showing that faces can be processed in the near-

absence of attention (Reddy, Reddy, & Koch, 2006) or outside of awareness (Morris et al., 1998; Whalen et al., 1998). A recent study found that faces receive mandatory processing during a change detection task (Weaver & Lauwereyns, 2011). This attentional advantage for faces was still present when additional semantic information was given where to expect the change. These results suggest that even neutral T2 faces receive enhanced attention due to their salience when presented during the AB interval. Support for this notion comes from several AB studies, which failed to find an AB for neutral faces masked either with nonface stimuli (Awh et al., 2004; Darque et al., 2011; Landau & Bentin, 2008; Serences et al., 2009) or with other neutral faces (Awh et al., 2004). The amygdala has been suggested to be a neuroanatomical key region for the processing of emotionally and socially relevant stimuli (for review see Adolphs, 2010b) and is assumed to contribute to the modulating effect of emotional words on the AB (Anderson & Phelps, 2001). However, even neutral faces are highly salient and result in increased amygdala activity, and therefore attentional resources may be sufficient to process both target face stimuli irrespective of the emotional expression of T2 in Experiments 1-3. Although the majority of studies employing faces as T2 actually found an AB for faces, it is evident that the experimental paradigms reported in the literature are very heterogeneous. Currently it does not seem possible to isolate a single factor or a combination of factors that is able to predict the occurrence or absence of an AB in experiments using face stimuli as targets (Table A1).

In conclusion, our experiments demonstrate that the AB for faces is minimal or absent when targets can be easily discriminated from distractors. When distractors are more similar to target faces, an AB for faces can be reliably obtained. In addition, our results support the notion that the AB is modulated by emotional expression in that neutral faces tend to be blinked more likely than emotional faces.

4 STUDY II: SELECTIVE ATTENTION MODULATES HIGH-FREQUENCY ACTIVITY IN THE FACE-PROCESSING NETWORK

4.1 Introduction

Emotionally and socially significant stimuli in our environment receive prioritized perceptual processing. This processing bias has been attributed to the engagement of reflexive, exogenous, selective attention (Vuilleumier, 2005) and entails an adaptive advantage for the organism (Öhman & Mineka, 2001). Facial expressions are one of the most emotionally and socially significant visual stimuli in the human environment because they signify intentions and emotional states of our conspecifics, making them essential for social communication. This has led to the hypothesis that a processing bias for emotional facial expressions is hard-wired into the human brain (Palermo & Rhodes, 2007).

Processing of faces in general and emotional facial expressions in particular depend on the orchestrated activity of large-scale neuronal networks (Gobbini & Haxby, 2007; Haxby et al., 2000; Vuilleumier & Pourtois, 2007). The visual perception of faces has been attributed to occipital and temporal regions including the inferior occipital, the fusiform, and the inferior temporal gyri (Kanwisher, McDermott, & Chun, 1997; Parvizi et al., 2012; Pourtois, Spinelli, Seeck, & Vuilleumier, 2010a; Tsuchiya, Kawasaki, Oya, Howard, & Adolphs, 2008). However, the face-processing network can be dynamically extended with regions recruited for the extraction of specific aspects of a face depending on the task or context at hand. Consequently, the terms "core system" and "extended system" have been coined to describe networks involved in basic visual perception and subsequent, context-related analysis of faces, respectively (Gobbini & Haxby, 2007; Haxby et al., 2000). Processing of facial expressions involves the core system and additional parts of the extended system such as the amygdala, the insula, and the OFC. The amygdala contributes especially to processing of fearful faces but slightly less also to faces with neutral expression and other salient stimuli (Adolphs, 2010b; Adolphs, Tranel, Damasio, & Damasio, 1994; Cornwell et al., 2008; Fusar-Poli et al., 2009; Krolak-Salmon et al., 2004; Morris et al., 1996; Pourtois, Spinelli, Seeck, & Vuilleumier, 2010b; Rutishauser et al., 2011; Vuilleumier et al., 2004). The OFC is involved in identification of facial expressions and their associated meaning (Adolphs, 2002; Rolls, 2004). The anterior portion of the insula has been associated with the perception of facial disgust (Fusar-Poli et al., 2009; Phillips et al., 1998) and salience detection (Menon & Uddin, 2010). In summary, the ventral occipito-temporal cortex (VOTC), the amygdala, the OFC, and the insula form a

network that mediates both perceptual processing and cognitive control related to the analysis of facial expressions.

Although some studies show that emotional facial expressions capture attention automatically (Fenker et al., 2010; Vuilleumier, 2002), the activity of the face-processing network can be modulated by voluntary, endogenous attention such as task demands or the specific context at hand. For example, Monroe et al. (2013) reported larger amplitudes of event-related fields for fearful than for happy or neutral faces in the fusiform gyrus around 150 ms, but only when attention had to be directed to the faces' expression and not to their age. The authors concluded that a valence modulation in the fusiform gyrus is more likely under conditions of directed attention to facial expressions. Likewise, larger ERPs in the amygdala were observed specifically for fearful faces in an iEEG study, but only when the patients had to pay attention to the facial expression and not to gender (Krolak-Salmon et al., 2004). Results from a meta-analysis of fMRI data further support the notion that directed attention to facial expression boosts activity within the core and extended face-processing network. Specifically, explicit compared to implicit processing of facial expressions was associated with stronger responses in the fusiform gyrus, the amygdala, and inferior frontal regions (Fusar-Poli et al., 2009).

iEEG recordings allow the investigation of face processing with precise information on the temporal structure (e.g., latency, duration) of neuronal responses. This precise temporal information is obtained with high spatial precision, as electrodes are directly placed within neuronal populations. Specifically, the effects of exogenous and endogenous attention can be compared in the exact same region of the same participant. Furthermore, the neuronal responses recorded with iEEG can be divided into their constituent spectral components, reflecting different processes. It has been suggested that dynamic interactions of cell assemblies, reflected in temporal synchronization of neuronal activity, provide indices of network interactions (Engel et al., 2001; Siegel et al., 2012). High-frequency GBA (> 30 Hz) in particular has been related to population level spiking activity on the one hand (Lachaux, Axmacher, Mormann, Halgren, & Crone, 2012; Manning, Jacobs, Fried, & Kahana, 2009; S. Ray & Maunsell, 2011) and the hemodynamic responses measured with fMRI on the other (Lachaux et al., 2007; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Directed attention reliably increases GBA and concomitantly decreases lower frequencies in the alpha (8-12 Hz) and beta (13-30 Hz) band (Fries et al., 2001; Jensen et al., 2007; Ossandón et al., 2012; Siegel et al., 2008). Studies using either iEEG or electrocorticography (ECoG) with

subdural grids or strips revealed that (emotional) face processing has been associated with specific ERP components (Allison, McCarthy, Nobre, Puce, & Belger, 1994; Allison, Puce, Spencer, & McCarthy, 1999; Halgren et al., 1994; Krolak-Salmon et al., 2004; McCarthy, Puce, Belger, & Allison, 1999; Pourtois et al., 2010a, 2010b; Puce, Allison, & McCarthy, 1999). Few intracranial studies investigated modulation of frequency-specific neuronal responses in the face-processing network (Engell & McCarthy, 2010, 2011; Lachaux et al., 2005; Tsuchiya et al., 2008; Vidal et al., 2010). Only one research group examined synchronization of GBA in response to neutral (Sato et al., 2012) and fearful facial expressions (Sato et al., 2011b). However, these experiments were confined to the amygdala and did not investigate attentional modulation. Here we investigated whether directing attention toward or away from facial expressions is associated with fast changes of neuronal activity in the face-processing network.

To address this question, we exploited the high temporal and spatial resolution of iEEG and recorded from depth electrodes implanted in patients undergoing resective neurosurgical treatment for drug-resistant epilepsy, to uncover the fast dynamics of emotional face processing. We investigated frequency-specific neuronal activity and ERPs in different regions of the face-processing network: the VOTC (including the posterior fusiform gyrus) and ventral temporal cortex (VTC; including the anterior inferior temporal gyrus), the amygdala, the OFC, and the insula. We compared neuronal responses between faces and control stimuli (nonfaces) and between two facial expressions (fearful vs. neutral) under two different detection tasks. Spatial attention was always directed toward centrally presented face and nonface stimuli. However, the attentional focus on facial expressions was manipulated by the task. The tasks demanded either to focus on the facial expressions (explicit task) or on low level features of the image (implicit task). We predicted that neuronal activity in the face-processing network can be modulated by two factors: 1) by reflexive, exogenous attention driven by stimulus salience (face > nonface, fearful > neutral) and 2) by voluntary, endogenous attention driven by task demands (explicit > implicit). We expected that task demands and facial expressions modulate the increase and duration of GBA and concomitant decreases of alpha- and beta-band activity (ABBA). Furthermore, we investigated whether task demands and stimulus salience globally affect the face-processing network, or whether regions of the core and the extended system are recruited differently.

4.2 Methods

4.2.1 Participants

We obtained intracranial recordings from 12 right-handed patients with drug-resistant epilepsy (6 males, mean age: 32.3 ± 10.0 years) who were evaluated for possible surgery at the Epilepsy Department of the Grenoble University Hospital (Grenoble, France). Table 4.1 summarizes medical history, pathological information, current medication at the time of experiment and resected tissue for each patient. Recording sites were solely determined according to clinical considerations with no reference to the current experiment. All patients provided written informed consent. The Institutional Review Board and the French Science Ethical Committee approved the experimental procedures. The experiments were carried out according to the Declaration of Helsinki. All patients had normal or corrected to normal vision.

4.2.2 Stimuli and Experimental Design

Twenty-seven male and 27 female faces with neutral, fearful, and happy expressions were taken from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998). All stimuli were converted to gray-scale, matched for luminance, and masked by an oval shape to remove hair, neck and background information. Phase-scrambled versions of neutral and fearful faces served as perceptual control conditions and will be referred to as nonfaces in the following. To manipulate the allocation of attention, we ran two versions of the task (Figure 4.1) differing solely in whether facial expression was task-relevant or not, hence referred to as explicit vs. implicit task, whose presentation was blocked. Targets of the implicit task were fearful faces, neutral faces, or nonfaces with a red tint in order to distinguish them from the other stimuli in the stream, while targets of the explicit task were gray-scale faces with happy expressions. In both tasks, fearful and neutral faces, nonfaces and targets were presented randomly for 400 ms with a jittered interstimulus interval (1100-2650 ms). In the implicit task, patients had to detect the stimuli with the red tint, whereas in the explicit task faces with happy expressions had to be detected and reported by a button press. Only 10 percent of the trials consisted of targets to maintain attention throughout the task. Target stimuli were discarded from further analysis. In each block, 180 trials consisting of 54 nonfaces, half fearful-scrambled and half neutral-scrambled, 54 neutral, 54 fearful faces and 18 targets were presented. Implicit task

Table 4.1. Medical history and pathological information of the sample.

	Epileptic focus			Seizure information							
Pat	**Lat**	**Reg**	**Etiology**	**Frequency**	**Age of onset**	**Clinical manifestations**	**LOC**	**Current drugs**	**Medical history**	**Surgery or EC information**	**PO deficit**
P1	RH	MTL (HS)	C	MSM	3	Epigastric sensation, throat discomfort, ictal dysphonia	Y	CBZ, LTG	Major depression, anxiety disorders (panic attack)	AMTL	NR
P2	LH	FL	D	MSW	8	Speech arrest, motor sensation	N	ZNS, LCS, PHT	NR	FOPC	Anarthria
P3	RH	TPL	HE	MSW	12	Aura, déjà-vu, out-of-body sensation	Y	VPA, CBZ	NR	EC	NR
P4	LH	AMTL (A/H)	C	MSM	18	Speech arrest, gestural automatisms	Y	ZNS, LCS, CLB	West syndrome (at the age of one)	AMTL	NR
P5	LH	MTL	C	MSD	5	Hypomotor seizure	Y	LTG, LCS	NR	ATL (H)	Transitory anomia
P6	RH	BFC	C	MSM	10	Epigastric sensation, ictal dysphonia, vocal automatisms	Y	LEV, LCS, OXC	NR	PFP, MPFC	NR
P7	LH	MTL	C	MSW	17	Hot sensation spreading from thorax to face	Y	LCS, CLB, LTG	Interictal anomia	TC	Transitory anomia
P8	LH	BTL	C	MSW		Inconstant rotatory vertigo, vocal automatisms	Y	OXC, CLE	NR	ATL	NR
P9	LH	FTC	C	MSW	26	Partial loss of consciousness, happy sensation	Y	LEV, LTG, LCS	NR	ATL, FP-OC	Anomia
P10	RH	BTL	C	MSM	16	Warm feeling	Y	OXC, LCS	NR	EC	NR
P11	LH	MTL (A/ET)	P	S	56	Olfactory and gustatory hallucinations	N	CBZ, LTG	NR	NR	NR
P12	LH	MTL	C	MSM	17	Speech arrest and automatisms	Y	LCS, LTG	NR	TPJ	Anomia

Abbreviations: A, with amygdala; AMTL, anterio-medial temporal lobe; ATL, anterior temporal lobe; BFC, basal frontal cortex; BTL, basal temporal lobe; C, cryptogenic; CBZ, carbamazepine; CLB, clobazam; CLE, clonazepam; D, cortical dysplasia; EC, electrocoagulation; ET, entorhinal cortex; FL, frontal lobe; FOPC, fronto-opercular cortex; FP, frontal pole; FTL, fronto-temporal lobe; H, with hippocampus; HE, heterotopia; HS, hippocampal sclerosis; Lat, lateralization; LCS, lacosamide; LEV, levetiracetam; LH, left hemisphere; LOC, loss of control; LTG, lamotrigine; MPFC, medial prefrontal cortex; MSD, multiple seizures daily; MSM, multiple seizures monthly; MSW, multiple seizures weekly; MTL, middle temporal lobe; N, no; NR, nothing to report; OC, orbital cortex; OXC, oxcarbazepine; P, psychogenic; Pat, patient; PFP, prefrontal pole; PHT, phenytoin; PO, post-operative; Reg, brain regions; RH, right hemisphere; S, sporadic; TC, temporal cortectomy; TPJ, temporo-parietal junction; TPL, temporo-parietal lobe; VPA, sodium valproate; Y, yes; ZNS, zonisamide;

blocks always preceded explicit task blocks to minimize bias for facial expression. The whole set of implicit and explicit task blocks was repeated when possible. In total, every patient performed each task twice, except for two patients (P2, P11). Visual stimuli were displayed on a 19" TFT monitor at a refresh rate of 60 Hz and a viewing distance of approximately 60 cm using Presentation (Neurobehavioral Systems, Albany, CA, USA). Of note, two patients (P4, P11) participated in a more difficult pilot version of the experiment, wherein the targets of the explicit task consisted of happy, surprised, and disgusted facial expressions. In this version, the patients considered fearful faces also as targets and mistakenly responded by button press.

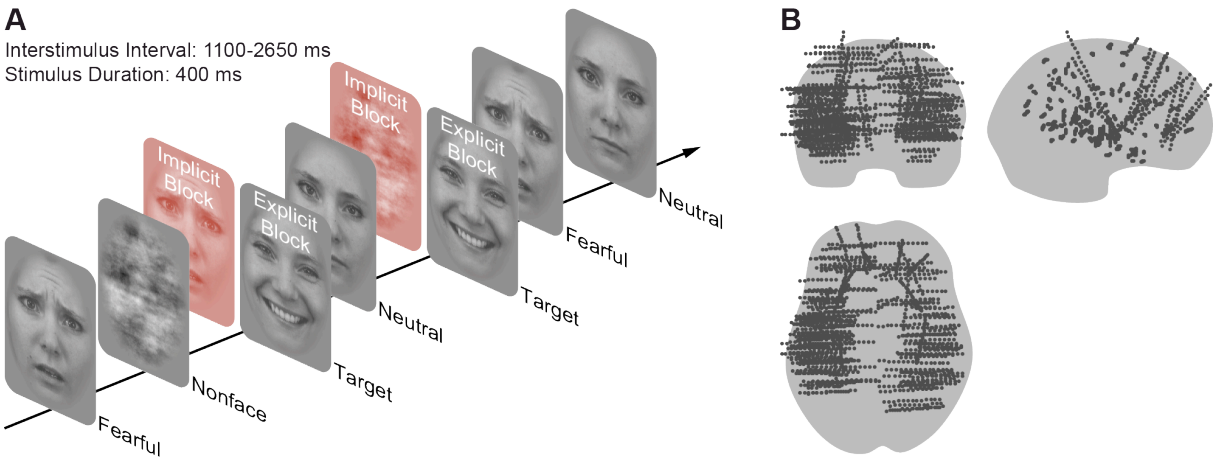

Figure 4.1. Experimental design and electrode coverage. (A) Schematic of implicit and explicit tasks. Tasks differed solely in the type of target and the task instructions. Patients had to detect stimuli with the red tint and happy faces in implicit and explicit tasks, respectively. (B) Electrode coverage of the entire brain across all patients in a MNI glass brain.

4.2.3 Electrode Implantation and Localization

Ten to 16 semirigid, multilead electrodes were stereotactically implanted in each patient. All electrodes had a diameter of 0.8 mm with 5-18 contacts, each of 2 mm length and 1.5 mm apart (Dixi, Besançon, France). Sites in the left cerebral hemisphere were denoted by a prime, i.e., the contact a'1 was the most medial contact from the electrode a in the left hemisphere.

The experiment was conducted four to seven days ($M \pm SD = 5.9 \pm 0.7$) following electrode implantation. The location of each site was determined by coregistration of the individual pre- to postimplantation structural MRI and normalization of the preimplantation MRI to the International Consortium for Brain Mapping template (Montreal Neurological Institute [MNI], Montreal, Canada). Electrode localization was performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and nutmeg (http://nutmeg.berkeley.edu). Anatomical

regions were identified with the automated anatomical labeling atlas (AAL; Tzourio-Mazoyer et al., 2002) with MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). All coordinates (x, y, z in mm) are given in MNI space (Evans et al., 1993).

4.2.4 Stereotactic EEG Recordings and Preprocessing

The iEEG was recorded using a 128-channel video-EEG acquisition and monitoring system (Micromed, Treviso, Italy). Data were bandpass filtered online between 0.1 and 200 Hz and sampled at 512 Hz. A monopolar reference in the white matter was used for all contact sites during data acquisition and for analyses of the ERPs. For the spectral analyses, each contact was re-referenced offline to its adjacent neighbor on the same electrode. In the following, these data will be referred to as "sites". This bipolar reference montage increases local specificity by suppressing signal artifacts from adjacent recording sites and effects due to volume conduction (Jerbi, Freyermuth, et al., 2009; Jerbi, Ossandón, et al., 2009; Lachaux, Rudrauf, & Kahane, 2003). Spatial resolution after bipolar referencing is below inter-contact spacing (i.e., 3.5 mm). Data were systematically screened for epileptiform activity using visual and semiautomatic inspection. Any trial containing epileptiform activity was discarded from further analysis. Bipolar referenced data were high-pass filtered at 0.5 Hz and low-pass filtered at 170 Hz for spectral analysis. For computation of ERPs, monopolar referenced data were high-pass filtered offline at 0.5 Hz and low-pass filtered at 25 Hz. The recorded signal was epoched into segments of –500 to 1000 ms around stimulus onset. Data analysis was performed with custom MATLAB (The Mathworks, Natick, MA, USA) routines and FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011).

4.2.5 Data Analysis

Behavioral Data. The percentage of hits was calculated as the proportion of detected targets relative to the total number of targets. The percentage of false alarms was defined as the proportion of nontargets followed by button presses. Low values of false alarms indicate that participants were able to perform the task correctly. Hits and false alarms were computed separately for implicit and explicit tasks. In order to assess the sensitivity, d' was calculated according to signal detection theory as d' = Z(hit rate) – Z(false alarm rate) with Z being the inverse of the cumulative Gaussian distribution (Macmillan & Creelman, 1991). In cases of

perfect performance, d' was estimated assuming that 1/100th of the performance was wrong (Wickens, 2002). Mean reaction times were computed for explicit and implicit tasks. Paired *t* tests compared the d' scores and reaction times of both tasks.

Site Selection. Visually responsive sites were determined based on the GBA responses because the high frequency range has been previously associated with visual processing of complex stimuli (Lachaux et al., 2012; Lachaux et al., 2005; Ossandón et al., 2012; Tsuchiya et al., 2008; Vidal et al., 2010). First, the instantaneous amplitude between 50-150 Hz was estimated using the Hilbert transform (for further details, please see below). Second, the GBA of trials from all conditions (fear, neutral, nonface) and tasks (explicit, implicit) was collapsed. Third, each poststimulus sample point of this average response was compared to the mean of the prestimulus baseline (–400 to –100 ms) with a running Wilcoxon signed rank test. To account for multiple testing, the obtained *p* values were corrected with the false discovery rate (FDR) at $p < 0.05$. In addition, at least three subsequent sample points had to be significant after FDR correction to reflect a meaningful visual response. Finally, visually responsive sites were selected in a-priori defined regions of interest (ROI). Based on meta-analytic, functional neuroimaging data on processing of facial expressions or emotion (Fusar-Poli et al., 2009; Phan, Wager, Taylor, & Liberzon, 2002), these included the VOTC, the VTC anterior to the VOTC, the amygdala, the OFC, and the insula. Only sites matching the selection criterion described above were considered for subsequent analysis including ABBA power profiles and ERPs. Since contacts in the amygdala were rare, those sites were considered irrespectively of exceeding the selection threshold.

Spectral Analysis. Spectral analysis included computation of time-frequency representations (TFR) using a sliding-time-window Fourier transformation and an estimation of the instantaneous amplitude using the Hilbert transform (Le Van Quyen et al., 2001). Hanning windows and multitapers (Mitra & Pesaran, 1999) were used as sliding time windows for low and high frequencies, respectively. For the multitaper approach, the data in each sliding time window were multiplied by a set of orthogonal tapers. Subsequently, the Fourier transformation was calculated for each of the tapers, and the spectra for each individual taper were magnitude squared. Finally, the power for each tapered data segment was averaged. Each trial was zero padded up to 2 s of length. The length of the sliding time window ΔT and the amount of spectral smoothing Δf determines the number of tapers k = $((\Delta T * \Delta f)-1)$. For the analysis of low (2.5 to 30 Hz in steps of 2.5 Hz) and high frequencies (30 to 150 Hz in steps of 10 Hz), sliding time windows of fixed length (ΔT = 400 ms and ΔT =

200 ms, respectively) with a step size of 20 ms and fixed frequency smoothing (Δf = 2.5 Hz and Δf = 20 Hz, respectively) were used, resulting in one taper for low and three tapers for high frequency ranges. Therefore, frequencies below and above 30 Hz were analyzed separately. For frequencies above 30 Hz, orthogonal Slepian tapers were used. These tapers optimally concentrate the spectral energy over the frequency range of interest (Mitra & Pesaran, 1999). For frequencies below 30 Hz, a single Hanning taper was used instead. For total power, frequency decomposition was performed on single-trial data, and power values of single trials were then averaged. These power estimates can include signal components that are phase-locked and non phase-locked to the stimulus onset (Tallon-Baudry & Bertrand, 1999). Furthermore, responses were characterized as the percentage of signal change according to the formula:

$$\text{Total power} = \text{poststimulus}_{\text{total}} - \text{prestimulus}_{\text{total}}$$

In order to avoid an overlap of the baseline window with the poststimulus window, the baseline period spanned from–500 ms to [stimulus onset $-\frac{1}{2}\Delta T$], with ΔT = 400 ms for low and ΔT = 200 ms for high frequencies, respectively. Thus, the baseline period differed for high and low frequencies. For visualization, the poststimulus period of each condition and frequency range was separately tested against the mean prestimulus period with a dependent samples *t* test, and the resulting *t* values were transformed into z-scores. In addition, the difference between faces and nonfaces of each task and frequency range was separately assessed by means of an independent samples *t* test, and the resulting *t* values were transformed into z-values. These z-values were then plotted. The TFRs were used for visualization and to verify that the main responses were in the frequency bands of interest (cf. below).

Based on previous research on visual and attentional responses (Lachaux et al., 2005; Ossandón et al., 2012; Tsuchiya et al., 2008; Vidal et al., 2010), we restricted our analysis of ABBA to frequencies between 8 to 24 Hz and GBA to frequencies between 50 to 150 Hz, respectively. Tsuchiya et al. (2008) utilized a decoding approach to identify the frequency bands best describing the differences between faces and control stimuli instead of a-priory specifying a frequency band of interest. This decoding approach revealed that exactly the frequency range between 50 and 150 Hz best described the differences between faces and control stimuli. Applying the Hilbert transform to continuous recordings splits the data into instantaneous amplitude (i.e., envelope) and phase components in the frequency ranges of

interest (Le Van Quyen et al., 2001). The continuous iEEG signal was bandpass-filtered in multiple successive frequency bands (from 50 to 150 Hz in steps of 10 Hz or from 8 to 24 Hz in steps of 4 Hz for high and low frequencies, respectively) using a zero phase shift, noncausal, finite impulse filter with 0.5 Hz roll-off. Then, the envelopes, i.e., the time-varying amplitude, for each bandpass-filtered signal were computed with the standard Hilbert transform. The envelope of each frequency band was divided by its mean across the entire recording session and multiplied by 100, yielding responses expressed in percentage of the mean (%). This normalization procedure accounted for a bias toward lower frequencies due to the power law. Finally, the envelopes of all multiple successive frequency bands were averaged providing one single time series across the entire session. For data reduction, the final Hilbert envelopes were down-sampled to 64 Hz. Similar to the TFRs, these power profiles were characterized as the percentage of signal change relative to baseline according to the following formulas:

$$GBA = poststimulus_{GBA} - prestimulus_{GBA}/prestimulus_{GBA}$$

$$ABBA = poststimulus_{ABBA} - prestimulus_{ABBA}/prestimulus_{ABBA}$$

The baseline period spanned from –400 ms to –100 ms before stimulus onset. As an additional level of confidence, the power profile computation using the Hilbert transform was also used to confirm the TFRs obtained by the sliding window approach. However, all statistical analyses were performed on the power profiles because they provide a lower degree of complexity and thus higher statistical power. For visualization on the population level, the average power profile for a specific time window of interest (e.g., 100 to 300 ms) was computed separately for faces and nonfaces for all bipolar, visually responsive sites in a given ROI across all patients. Then the difference between faces and nonfaces was plotted at the corresponding location in the MNI brain.

Event-Related Potentials. The segmented, monopolar-referenced signal was averaged for each condition and baseline corrected between –500 and 0 ms before stimulus onset. The ERP signal was resampled to 64 Hz to assure comparable resolution to the Hilbert envelopes for statistical analysis.

Statistical Analysis. Statistical analysis of electrophysiological data was performed at the single site level (Lachaux et al., 2012; Lachaux et al., 2005) for all selected contacts. A running two-way ANOVA with the factors task and condition was performed separately for each neuronal marker (GBA, ABBA, ERP). Since differences between faces, i.e., the average of fearful and neutral faces, and nonfaces dominated and occluded differences between fearful

and neutral faces, when all three conditions were included as levels of the experimental factor condition, two separate ANOVAs were calculated to disentangle the influence of the face per se from that of the emotional expression. The first ANOVA compared task (explicit, implicit) with condition (face, nonface), whereas the second ANOVA contrasted task (explicit, implicit) with condition (fear, neutral). Specifically, separate two-way ANOVAs including the two experimental factors (task by condition) were computed for each poststimulus sample point (each 15.625 ms) of the baseline-corrected, single-trial data. The resulting *p* values for the main effects of task and condition and of their interaction were then each FDR-corrected across all poststimulus sample points to account for multiple comparisons.

4.3 Results

4.3.1 Behavioral Performance

The mean hit and false alarm rates (mean, *M* ± standard deviation, *SD*) were 89.6 % ± 13.1 and 8.2 % ± 16.5 for the explicit task and 96.8 % ± 7.0 and 0.5 % ± 1.6 for the implicit task, when all participants were considered. The exclusion of the two patients (P4 and P11) with the pilot version resulted in a drop of false alarms during explicit tasks (hits: $M \pm SD$ = 87.8 % ± 13.8; false alarms: $M \pm SD$ = 1.2 % ± 1.3), whereas results during implicit tasks were unaffected (hits: $M \pm SD$ = 96.1 % ± 7.6; false alarms: $M \pm SD$ = 0.7 % ± 1.7). This pattern is consistent with the fact that these patients erroneously considered fearful faces as targets. This was also reflected in the sensitivity index d' for all patients, which was smaller in explicit ($M \pm SD$ = 3.5 ± 1.0) than implicit tasks ($M \pm SD$ = 4.3 ± 0.5; $t_{11} = -2.79$, $p = 0.018$). However, when P4 and P11 were excluded, d' did not differ between tasks (explicit: $M \pm SD$ = 3.7 ± 0.9; implicit: $M \pm SD$ = 4.3 ± 0.6; $t_9 = -2.02$, $p = 0.074$). Patients responded faster to red-tinted targets in the implicit task ($M \pm SD$ = 460.8 ms ± 45.1) than to happy face targets in the explicit task ($M \pm SD$ = 584.3 ms ± 80.9; $t_{11} = 7.02$, $p < 0.001$). These results confirm that patients were able to perform the task, and that the implicit task was easier than the explicit one, as reflected in the reaction times but not in the performance scores.

4.3.2 Ventral Occipito-Temporal cortex

In order to select sites from the VOTC, only visually responsive sites labeled as fusiform gyrus with the y coordinate ≤ –35 and the x coordinate < |45| were considered (within Brodmann

areas [BA] 19 and 37). In total, 47 sites in VOTC from nine patients (P1, P3, P5, P7, P8, P9, P10, P11, P12) were considered.

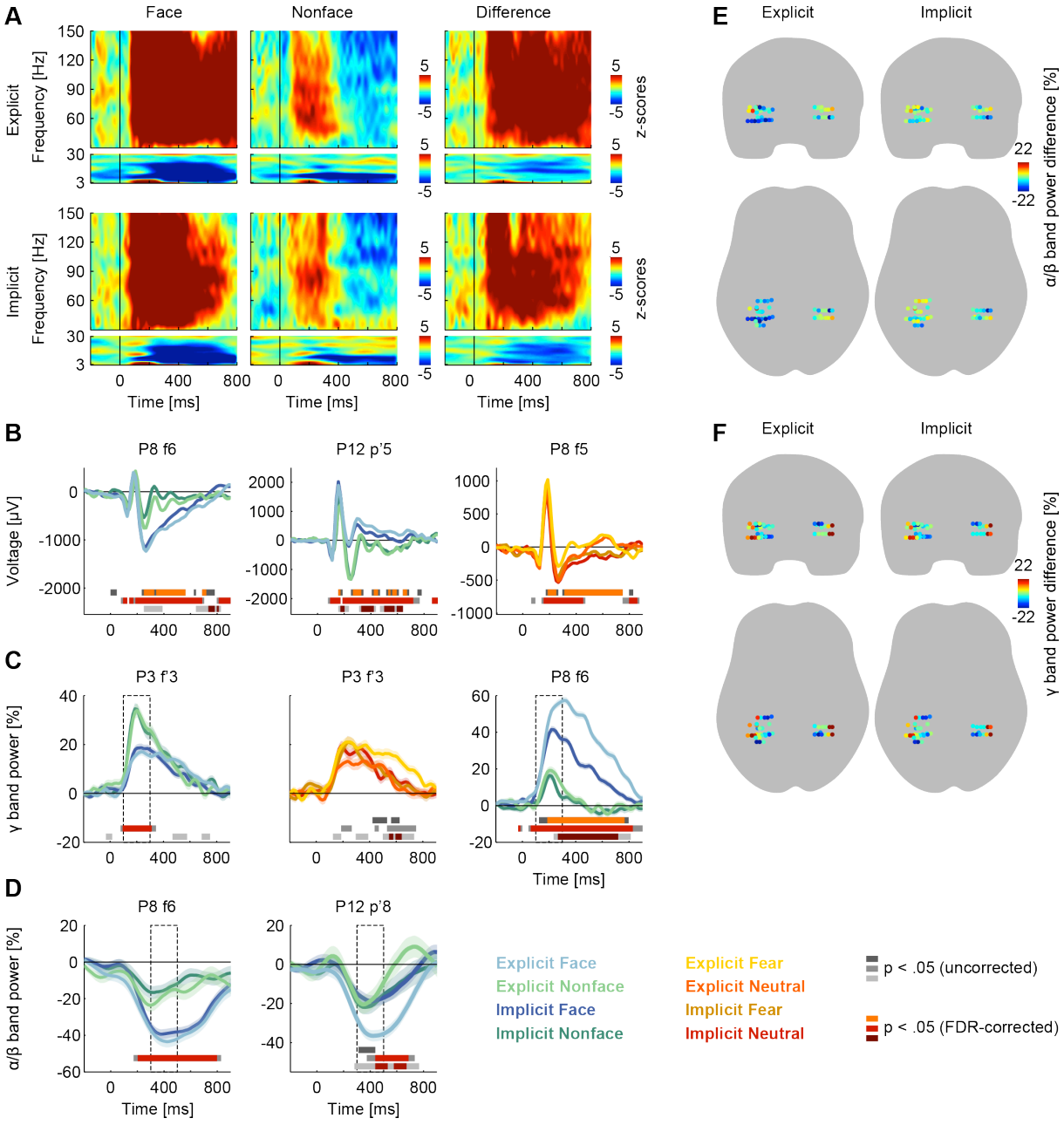

Figure 4.2. Results for the VOTC. (A) TFR example from patient P8, site f6, for the conditions face, nonface, and their difference for explicit (upper panel) and implicit tasks (lower panel). (B) The ERPs are shown for three sites of two patients. The bars illustrate the uncorrected and FDR-corrected results of the running ANOVA, color-coded for the main effect of task (top), condition (middle), and their interaction (bottom). Face vs. nonface condition effects are indicated in the two leftmost plots and fearful vs. neutral condition effects in the rightmost one. (C) Power profiles for GBA are depicted for three sites of two patients. The shading reflects the SEM. Face vs. nonface condition effects are indicated in the two outer plots and fearful vs. neutral condition effects in the middle one (statistics as described above). (D) Power profiles for ABBA are shown for two different patients. The shading reflects the SEM. Face vs. nonface condition effects are indicated (statistics as described above). (E) Mean ABBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 300-500 ms after stimulus onset (cf. dashed rectangles in D). Depicted are all visually responsive sites in the grey matter of the VOTC from all patients. (F) Mean GBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 100-300 ms after stimulus onset (cf. dashed rectangles in C) for the same sites.

In most recording sites within the VOTC (43/47), the presentation of visual stimuli resulted in a prompt, strong, and sustained GBA increase after 80 ms (Figure 4.2A). Initial GBA peaks between 100-200 ms were generally stronger for faces than nonfaces in the lateral VOTC (11/43), and stronger for nonfaces than faces in the medial VOTC (20/43; Figure 4.2F), resulting in a condition effect emerging after 100 ms or even earlier (cf. P3 f'3 and P8 f6, Figure 4.2C). After the initial peak beyond 250 ms, the GBA response to faces in the explicit task was more sustained than to nonfaces resulting in a significant interaction after 250 ms and lasting up to 700 ms (cf. P8 f6, Figure 4.2C). Enhanced GBA to fearful compared to neutral faces was observed in two sites (300-500 ms), which was very robust at the single-trial level (cf. P3 f'3, Figure 4.2C).

In most sites (40/43), the enhancement of GBA co-occurred with an ABBA suppression, starting at 100 ms and peaking around 400 ms (Figure 4.2A). ABBA suppression (500-700 ms) was stronger for faces than nonfaces in the majority of sites (23/40; cf. P8 f6, Figure 4.2D and E). In seven out of 40 sites, stronger ABBA suppression for faces compared to nonfaces was only present in the explicit task (cf. P12 p'8, Figure 4.2D). Task effects occurred beyond 700 ms. Differential processing for fearful and neutral faces could not be observed for ABBA.

Across all recording sites, presentation of visual stimuli was associated with a very sharp onset response 100 ms poststimulus in the ERP. Figure 4.2B shows a typical P1/N1-like complex following the first negative deflection. ERPs differentiated faces and nonfaces, although the direction of this effect differed (compare f6 of P8 with p'5 of P12). Furthermore, task effects (explicit vs. implicit) were observed at later latencies than the condition effects (face vs. nonface). Interaction effects did not exhibit a consistent pattern. Only three sites exhibited a differential response for the two facial expressions (cf. f5 of P8, Figure 4.2B).

4.3.3 Ventral Temporal Cortex

Recording sites in the VTC were selected to probe face processing at a higher level along the ventral visual stream. Only visually responsive sites were considered whose y coordinate was > –35 (BA 20, 35, or 36). All sites sufficing these criteria were within BA 20, 35, or 36. In total, 50 sites from nine patients (P1, P3, P4, P5, P7, P8, P9, P11, P12) were considered.

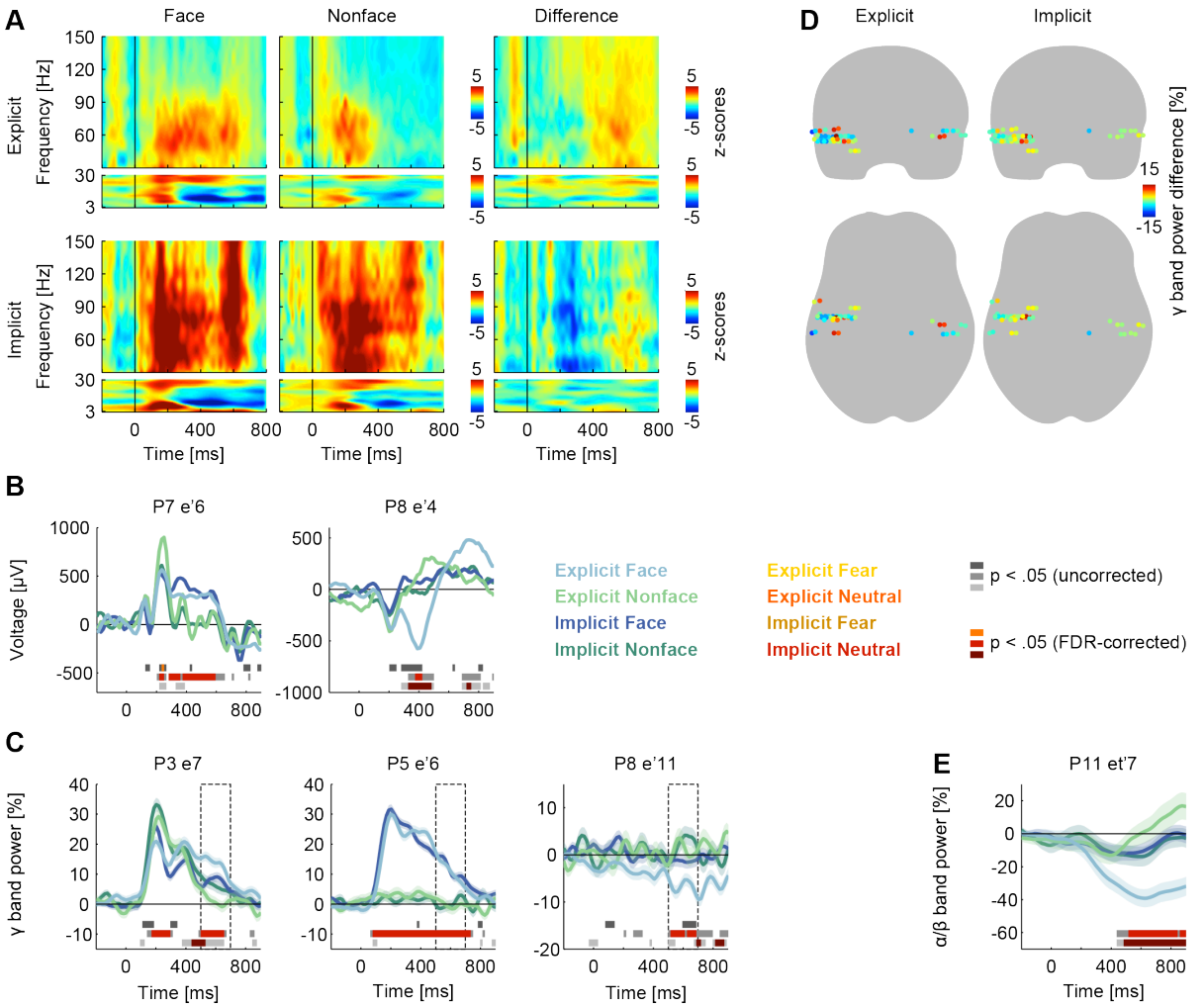

Figure 4.3. Results for the VTC. (A) TFR example for P3, site e7, for the conditions face, nonface, and their difference for explicit (upper panel) and implicit tasks (lower panel). (B) The ERPs are shown for two patients. The bars illustrate the uncorrected and FDR-corrected results of the running ANOVA, color-coded for the main effect of task (top), condition (middle), and their interaction (bottom). Face vs. nonface condition effects are depicted. (C) Power profiles for the GBA are shown for three patients (legend and statistics as described above). The shading reflects the SEM. Face vs. nonface condition effects are depicted. (D) Mean GBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 500-700 ms after stimulus onset (cf. dashed rectangles in C). Depicted are all visually responsive sites in the grey matter of the VTC from all patients. (E) Power profiles for ABBA are shown for one site of P11 (legend and statistics as described above). The shading reflects the SEM. Face vs. nonface condition effects are depicted.

Five out of 50 sites in the VTC exhibited enhanced GBA in response to faces compared to nonfaces in the same time range (100-200 ms) as in the VOTC (Figure 4.3A; cf. P5 e'6, Figure 4.3C), one out of 50 sites showed the opposite pattern of stronger GBA to nonfaces compared to faces (P3 e7, Figure 4.3C). The remaining responses in this ROI were lower in amplitude and later in latency than in the VOTC. Additionally, GBA was more sustained in response to faces compared to nonfaces after 500 ms poststimulus during the explicit task (6/50, Figure 4.3D), although the direction of this effect varied (compare P3 e7 with e'11 of P8, Figure 4.3C). GBA did not differ between fearful and neutral faces.

Similar to results in the VOTC, a decrease in ABBA following visual stimulation was occasionally observed in the VTC (14/50). Almost no differences between experimental conditions on ABBA suppression were found in VTC (for an exception, see Figure 4.3E). Furthermore, ABBA did not differentiate between fearful and neutral faces.

ERPs in this ROI were more heterogeneous than in the VOTC. Paralleling the results in the GBA, faces compared to nonfaces elicited a more positive sustained potential 300-600 ms after stimulus onset in most of the patients (Figure 4.3B). We did not observe substantial differences between explicit and implicit tasks and between fearful and neutral faces.

4.3.4 Insula

Sites in the posterior insula ($y < 0$) were excluded because they included auditory and motor responsive sites in P4 and P11 who participated in the pilot version of the task. Recording sites in the inferior frontal gyrus (pars triangularis) were included because they exhibited the same response profile. In total, this ROI comprised 33 visually responsive sites (BA 45, 47, 48) in seven patients (P1, P2, P5, P6, P8, P9, P11).

The presentation of visual stimuli yielded an early-onset, strong, and broadband increase in GBA at the majority of sites (24/33) that started around 100 ms (19/33) or 250 ms (5/33) and receded much slower for faces during explicit tasks than for any other condition (8/33; Figure 4.4A, C, D). Of the remaining insular sites, three exhibited a GBA decrease after 250 ms for faces compared to nonfaces irrespectively of task (cf. P5 g'10, Figure 4.4C). Differences between fearful and neutral faces paralleled the preferential processing of faces during explicit tasks (except for q'2 of P9, Figure 4.4C). No condition effects for ABBA were observed in this ROI.

Three patients exhibited a positive component around 200 ms in the ERP that was more pronounced for faces than nonfaces only during explicit tasks (Figure 4.4B). In addition, there were differences between tasks after 400 ms. The comparison of fearful and neutral facial expressions yielded differential responses for explicit and implicit tasks, although none survived the FDR correction (P9 q'3, Figure 4.4B).

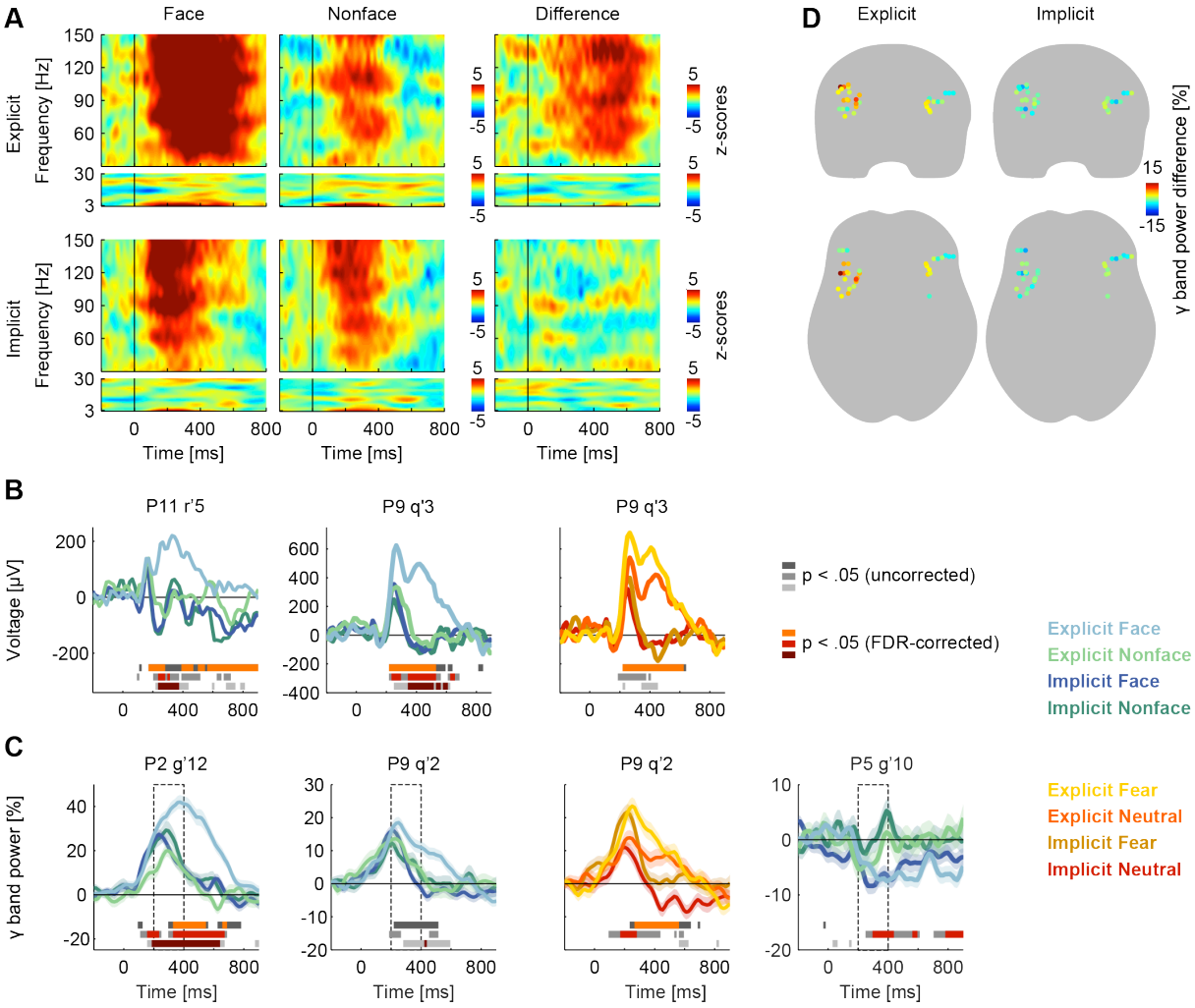

Figure 4.4. Results for the insula. (A) TFR example for P2, site g'12, for the conditions face, nonface, and their difference for explicit (upper panel) and implicit tasks (lower panel). (B) The ERPs are shown for three patients. The bars illustrate the uncorrected and FDR-corrected results of the running ANOVA, color-coded for the main effect of task (top), condition (middle), and their interaction (bottom). Face vs. nonface condition effects are indicated in the two leftmost plots and fearful vs. neutral condition effects in the rightmost one. (C) Power profiles for GBA are shown for four sites of three patients (legend and statistics as described above). The shading reflects the SEM. Face vs. nonface condition effects are indicated in all plots except for the third from the left, for which fearful vs. neutral condition effects are depicted. (F) Mean GBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 200-400 ms after stimulus onset (cf. dashed rectangles in C). Depicted are all visually responsive sites in the grey matter of the insula from all patients.

4.3.5 Orbitofrontal Cortex

We recorded from 68 sites in eight patients (P1, P4, P5, P6, P7, P9, P11, P12) within the OFC (BA 10, 11, 47). Most sites (32/68) showed stronger suppression of GBA for faces compared to nonfaces between 200-800 ms (Figure 4.5A; cf. P5 p'3, Figure 4.5C), which survived multiple comparison correction in only seven sites.

At the group level, differential responses for faces compared to nonfaces were more pronounced during the explicit task (Figure 4.5D). Interestingly, we found an early GBA enhancement exclusively for faces during the explicit task resulting in a significant interaction

between 130 and 200 ms in a single patient (P6 x2, Figure 4.5C). The comparison of fearful and neutral faces did not yield any systematic effects in GBA. No effects were observed for ABBA in the OFC.

ERPs in the OFC revealed task and condition effects with varying polarity (Figure 4.5B). Face processing was sustained during the explicit task in a single patient between 300-550 ms (P5 o'8). The ANOVA on fearful and neutral facial expressions revealed differences between explicit and implicit tasks between 200 and 800 ms (P9 o'7, Figure 4.5B).

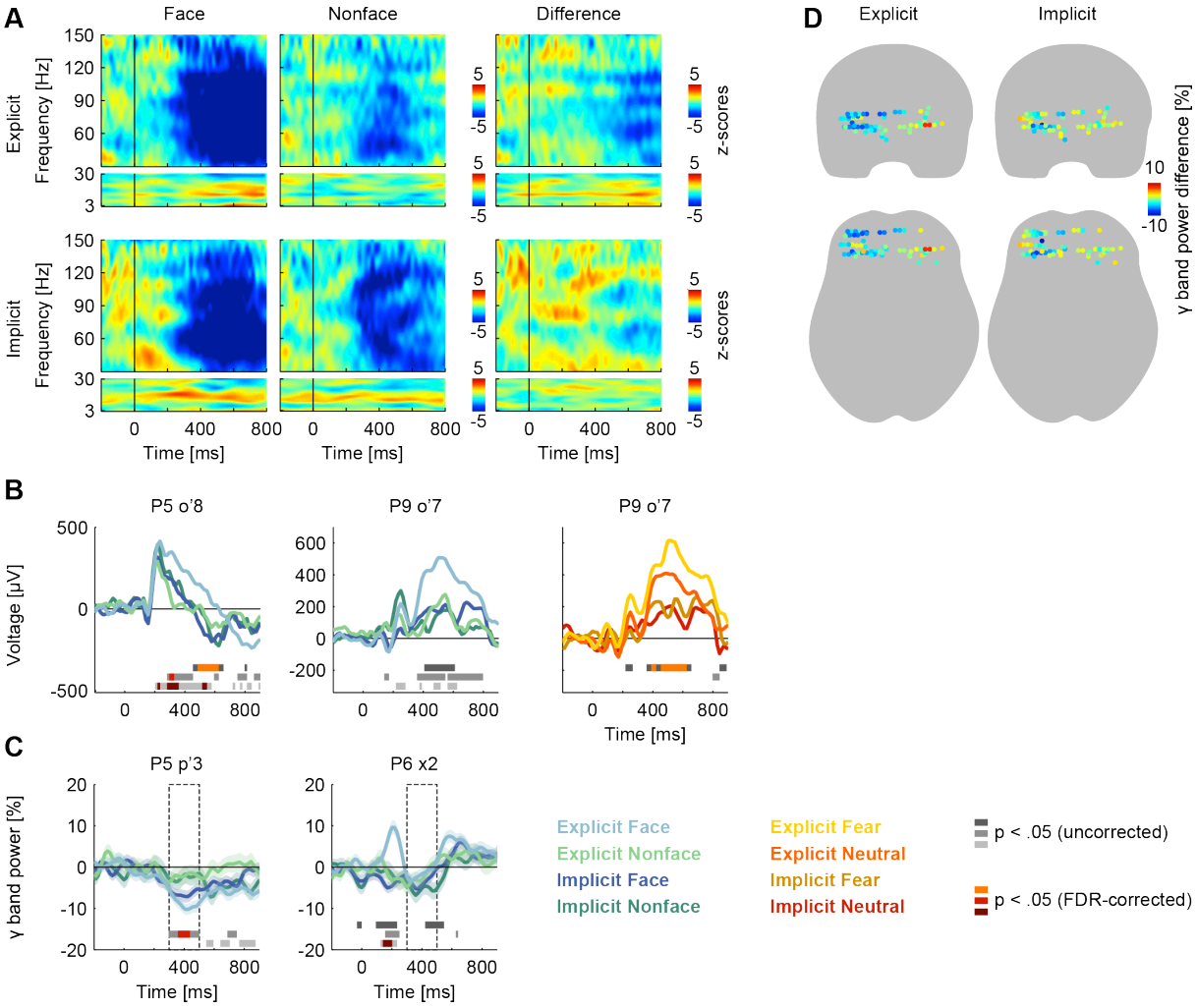

Figure 4.5. Results for the OFC. (A) TFR example for P6, site s3, for the conditions face, nonface, and their difference for explicit (upper panel) and implicit tasks (lower panel). (B) Power profiles for GBA are shown for four sites of three patients. The shading reflects the SEM. The bars illustrate the uncorrected and FDR-corrected results of the running ANOVA, color-coded for the main effect of task (top), condition (middle), and their interaction (bottom). Face vs. nonface condition effects are indicated. (C) The ERPs are shown for three patients (legend and statistics as described above). (F) Mean GBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 300-500 ms after stimulus onset (cf. dashed rectangles in B). Shown are all visually responsive sites in the grey matter of the OFC from all patients.

4.3.6 Amygdala

Careful inspection of individual MRIs identified 23 sites in the amygdala of nine patients (P1, P3, P4, P5, P6, P7, P8, P11, P12). All sites were considered irrespective of whether they were visually responsive (cf. selection of sites).

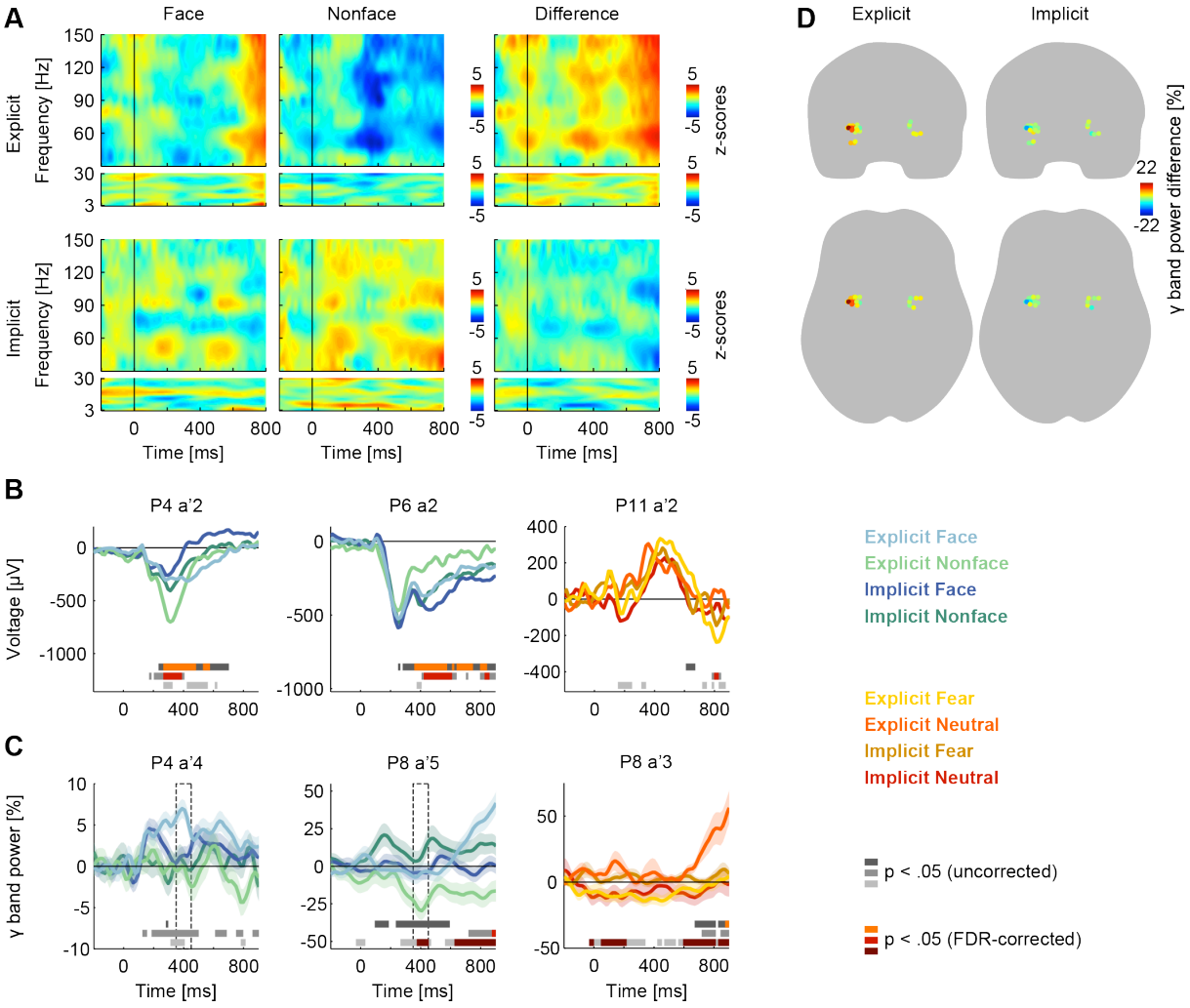

Figure 4.6. Results for the amygdala. (A) TFR example for P8, site a'5, for the conditions face, nonface, and their difference for explicit (upper panel) and implicit tasks (lower panel). (B) The ERPs are shown for three sites of two patients. The bars illustrate the uncorrected and FDR-corrected results of the running ANOVA, color-coded for the main effect of task (top), condition (middle), and their interaction (bottom). Face vs. nonface condition effects are indicated in the two leftmost plots and fearful vs. neutral condition effects in the rightmost one. (C) Power profiles for GBA are shown for three sites of two patients (legend and statistics as described above). The shading reflects the SEM. Face vs. nonface condition effects are indicated in the two leftmost plots and fearful vs. neutral condition effects in the rightmost one. (D) Mean GBA power difference (faces minus nonfaces) separately for explicit and implicit tasks between 350-450 ms after stimulus onset (cf. dashed rectangles in B). Depicted are all sites in the grey matter of the amygdala from all patients.

Six recording sites in the amygdala displayed a larger absolute difference of GBA in response to faces compared to nonfaces in explicit but not implicit tasks (Figure 4.6A and D).

The interaction between condition and task (350-450 ms and 600-900 ms) only survived the FDR correction in one site (P8 a'5, Figure 4.6C). Figure 4.6C further illustrates that the absolute difference between faces and nonfaces in explicit and implicit tasks resulted from different underlying response patterns. Only one patient exhibited stronger GBA (50-220 ms, 600-900 ms) for neutral compared to fearful faces in the explicit task, whereas no difference was found in the implicit task (P8 a'3, Figure 4.6C). There were no systematic effects in the ABBA in the amygdala.

The ERPs in the amygdala consisted of a biphasic deflection 170 ms after stimulus onset followed by a sustained negativity, which independently differed between tasks and conditions (Figure 4.6B). The direction of effects was heterogeneous (compare P4 a'2 with P6 a2, Figure 4.6B). As in the GBA, a late ERP difference starting at 800 ms was found between fearful and neutral faces (a'2 of P11, Figure 4.6B).

4.4 Discussion

We observed strong attentional modulation of neuronal activity during explicit face processing in all regions of the face-processing network. Endogenous, selective attention toward facial expressions modulated high frequency neuronal activity in the VOTC, VTC, insula, OFC, and amygdala. Recording sites within the VOTC and VTC exhibited early stimulus-specific responses to faces and nonfaces, that were only modulated by task demands beyond 200 ms. Responses in the anterior insula showed initially stimulus-unspecific responses to faces and nonfaces, that, comparably to responses in OFC and amygdala, differentiated by task demands beyond 200 ms. Except for the VOTC and VTC, in which also ABBA was suppressed, these effects were confined to the gamma band in the remaining ROIs. The ERPs were also modulated by endogenous attention although these effects were more heterogeneous than the GBA changes. Contrary to our hypothesis that fearful expression would bias exogenous attention and enhance face processing throughout the network, only a few recording sites showed reliable differences between fearful and neutral expressions beyond 200 ms.

Our results clearly demonstrate that the core system of the face-processing network (VOTC, VTC) shows early (< 200 ms) stimulus-specific responses to faces and is subsequently upregulated by endogenous, task-related attention. The extended system of the face-processing network (OFC, anterior insula, amygdala) is modulated by task demands. Effects

of exogenous attention to facial expressions emerge beyond 200 ms in the VOTC, insula, and amygdala but were small in size. GBA appears to be the most reliable neuronal marker for all of these effects.

In line with previous reports (Engell & McCarthy, 2011; Kawasaki et al., 2012; Lachaux et al., 2005; Tsuchiya et al., 2008; Vidal et al., 2010), responses in the VOTC were characterized by a rapid (< 100 ms) increase of GBA (40 out of 43), selective for faces in lateral recording sites (11 out of 43). High-frequency responses were accompanied by a suppression of ABBA in the majority of recording sites (Lachaux et al., 2005). This spectral signature has been associated with sensory processing in the visual cortex (Engel et al., 2001; Hipp et al., 2011; Hoogenboom et al., 2006; Singer, 1999).

The latencies we observed for the face-selective N170 shared important electrophysiological properties with previous reports such as negative polarity and categorical selectivity to faces (Allison et al., 1994; Engell & McCarthy, 2011; McCarthy et al., 1999; Pourtois et al., 2010a). Models of hierarchical and differential encoding of face information have postulated that early perceptual effects in the N170 time range of 140 to 160 ms would convey configurational analysis of faces, whereas effects between 180 and 200 ms would reflect processing of facial identity. Changeable or behaviorally relevant aspects of faces, such as emotion and gaze, would be processed between 310 and 1000 ms (Eimer, 2000; Pourtois et al., 2010a). In line with those models and previous reports (Allison et al., 1999; Halgren et al., 1994; McCarthy et al., 1999; Parvizi et al., 2012; Pourtois et al., 2010a; Puce et al., 1999; Tsuchiya et al., 2008), the earliest responses in the ERP we observed were restricted to category-selective responses to faces or nonfaces, suggesting configurational analysis of the stimuli. In a similar vein, face-selective information in the human VOTC could be decoded as early as 100 ms, and this decoding was invariant to viewpoint or scale (Liu, Agam, Madsen, & Kreiman, 2009).

All effects of facial expression, task-related attentional modulation, and their interaction were obtained considerably later than 160 ms in the present study, and were characterized by sustained GBA modulations. Consistent with our data, previous studies showed that effects of endogenous attention in the VOTC evolved only after 250 ms in both ERPs and GBA, whereas category-selective responses to faces and houses emerged earlier (Engell & McCarthy, 2010; Vidal et al., 2010). However, only a fraction of our recording sites exhibited modulations by facial expression as reported previously (Kawasaki et al., 2012). In conclusion, early responses in the VOTC around 100 ms were related to the stimulus category

and insensitive to facial expression or task demands. Effects of facial expression or attentional modulation appeared after 200 ms.

In accordance with previous iEEG and ECoG studies, the response properties between adjacent recording sites in the VOTC were different (Kawasaki et al., 2012; Lachaux et al., 2005), suggesting narrowly circumscribed sources for preferential selectivity to faces and nonfaces. The fusiform face area is not exclusively selective to faces if scrutinized with high-resolution functional imaging (Grill-Spector, Sayres, & Ress, 2006; Weiner & Grill-Spector, 2012, 2013). Face responsive patches in the fusiform face area, although anatomically arranged in a highly consistent manner (Weiner & Grill-Spector, 2013), are intermingled with subregions that exhibited preferential selectivity to a variety of nonface objects (Grill-Spector et al., 2006). Therefore, the existence of face-selective amid nonface-selective recording sites may corroborate the claim of a patchy organization in the VOTC.

Responses in the majority of sites in the VTC were modulated by attention. GBA differentiated faces and nonfaces exclusively during explicit tasks between 500 to 700 ms. When faces were task-irrelevant, GBA responses were lower in amplitude and less sustained. Consistent with our results, similar latency and frequency ranges have been observed for detected versus undetected faces at recording sites in the inferior temporal gyrus (Lachaux et al., 2005). Our data suggest that face processing in the VTC is not automatic but that the VTC is primarily recruited whenever additional care must be given to faces.

Stronger GBA for faces in a subset of recording sites (6 out of 50) in the VTC, comparable to responses in the VOTC and irrespective of the task, is in agreement with the finding of face-selective regions toward the anterior pole in healthy populations (Weiner & Grill-Spector, 2013). This result also confirms the role of the VTC in the core system of the face-processing network.

Consistent with our ERP results in the VTC, long-latency, face-specific potentials that were heterogeneous with respect to latency, waveform, and polarity were recorded previously (Allison et al., 1994; Allison et al., 1999; Puce et al., 1999). Such long-latency responses have partly been attributed to a phase reset of ongoing neuronal activity (Fell et al., 2004). Face-specific ERPs appear to be more heterogeneous and considerably later than responses in the GBA.

GBA responses in the anterior insula initially increased to faces and nonfaces and were subsequently modulated by task demands beyond 200 ms, i.e., we found GBA increases for faces only in the explicit task. A similar effect was observed in the ERPs of another iEEG study,

in which the potentials in the ventral anterior insula to the facial expression of disgust were more frequently observed and of longer duration during explicit than implicit emotion judgment (Krolak-Salmon et al., 2003). It has been proposed that the anterior insula detects salient stimuli and initiates appropriate control signals including the disengagement of the default mode network (Menon & Uddin, 2010), which is in good agreement that the latencies of insular responses are shorter than those in the OFC. The stimulus-unspecific onset responses of the anterior insula suggest that the anterior insula, comparable to the core system, is initially always active and subsequently upregulated by task demands.

High-frequency responses in the OFC were characterized by stronger GBA suppression to faces compared to nonfaces in most sites, especially when faces were task-relevant. This effect is reminiscent of GBA suppression observed during a visual search task (Ossandón et al., 2011) and consistent with the idea that the OFC, as part of the default mode network, deactivates, when attention is oriented toward external stimuli (Raichle, 2010; Shulman et al., 1997). Our findings corroborate the role of task-specific GBA suppression in mediating goal-directed behavior in the face-processing network.

In addition, drawing on findings from object recognition, the remarkably early increase in GBA exclusively during explicit face processing in a single patient may reflect construction of meaning (Adolphs, 2002) and some form of top-down facilitation of perception. Bar et al. (2006) investigated the recognition of briefly presented, masked objects with fMRI and MEG and observed that the OFC activation at 130 ms preceded that of the fusiform gyrus at 180-215 ms. Although the responses in the VOTC emerged earlier in our iEEG recordings, the latencies in the OFC are in good agreement with these data. Hence, early GBA increases in the OFC suggest that the OFC is involved in construction of meaning (Adolphs, 2002) and the allocation of resources (Sakai, 2008).

The amygdala displayed stronger GBA for faces compared to nonfaces especially when processing of faces was task-relevant. This effect started between 250 and 300 ms and peaked between 350 and 450 ms after stimulus onset. The observed latencies are in line with the report of face-selective neurons in the monkey amygdala with a firing-rate increase between 100 and 300 ms (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007; Leonard, Rolls, Wilson, & Baylis, 1985). Importantly, latencies exceeding those in the VOTC and strong attenuation in the implicit task argue against an automatic activation of the amygdala when confronted with fearful faces (Palermo & Rhodes, 2007; Vuilleumier, 2002).

The amygdala is also consistently activated when neutral faces are contrasted to baseline (Fusar-Poli et al., 2009). To date, only few studies have investigated GBA in the amygdala with intracranial EEG in humans. Increased GBA in the amygdala has been observed in response to unpleasant pictures, faces, fearful facial expressions, and solely the eyes of a face around 135-255 ms (Oya et al., 2002; Sato et al., 2011a, 2011b, 2012). However, none of those studies examined whether the amygdala response could be modulated by task demands or endogenous attention. We suggest that the increased GBA in the amygdala reflects higher stimulus salience of faces, when they were task-relevant. This interpretation is in line with proposals that the functional importance of the amygdala is not limited specifically to emotion but also comprises other abstract dimensions of information processing, such as salience (Adolphs, 2010b; Pessoa & Adolphs, 2010).

Neither the GBA nor the ERPs in the amygdala differentiated between fearful or neutral faces. This result conflicts with previous iEEG studies reporting higher ERP and GBA amplitudes for fearful compared to neutral faces (Krolak-Salmon et al., 2004; Pourtois et al., 2010b; Sato et al., 2011b) and a large body of functional neuroimaging literature (Fusar-Poli et al., 2009; Morris et al., 1996; Zald, 2003). Pourtois et al. (2010b) found higher ERP amplitudes for fearful versus neutral faces 140 ms after stimulus onset irrespective of task-relevance in a single patient implanted in the lateral amygdala. Likewise, augmented potentials have been observed exclusively for fearful relative to other expressions (Krolak-Salmon et al., 2004). However, those findings were only evident when attention had to be directed to facial expression. This discrepancy to our findings may be explained by the electrode location. Since electrode coverage was far from exhaustive, especially in the amygdala, we cannot draw strong conclusions about the null finding between fearful and neutral faces. Moreover, although fMRI and intracranial EEG provide good spatial resolution (Lachaux et al., 2003), intracranial EEG, in contrast to fMRI, does not cover the whole brain and provides only a limited anatomical field-of-view. Conversely, Rutishauser et al. (2011) elegantly showed that the amygdala responds selectively to whole faces rather than facial features between 250 and 500 ms. Our findings along with theirs corroborate the assumption that the amygdala is involved in "a more general […] aspect of face processing than an exclusive focus on expressions of fear" (Rutishauser et al., 2011, p. 1658).

A limitation of our experimental design is that not only facial expression but also faces as stimulus category became task-relevant at the same time during explicit tasks. The implicit task required color discrimination to detect target stimuli. In contrast, previous research

compared conditions of attention to gender with attention to facial expression (Krolak-Salmon et al., 2004; Monroe et al., 2013; Wronka & Walentowska, 2011). In both cases participants had to allocate attention to the face, though the facial features most relevant for the response differed between conditions. Participants either had to press a button to each stimulus (Monroe et al., 2013; Wronka & Walentowska, 2011) or silently count the number of targets (Krolak-Salmon et al., 2004), which required motor preparation or continuous update of working memory. Importantly, we designed the experiment such that targets could easily be discarded and confounding button presses were avoided. Even though this may be a reason why differences between fearful and neutral faces were only marginal if not absent, any automatic engagement of attention by fearful faces would have also been observable within the present experimental design. In addition, conclusions regarding the differential deployment of attention by explicit and implicit processing of facial expression can still be drawn even if the stimulus processing during implicit tasks was independent of any facial features because facial expression was nonetheless task-irrelevant.

In conclusion, our study demonstrated that all investigated regions of the face-processing network were clearly modulated by task demands and exhibited stronger changes in GBA when faces were task-relevant. The latencies we observed suggest an orchestrated activation in the face-processing network. The core system, including the VOTC and VTC, and the insula exhibited early responses around 100 ms that were stimulus-specific in case of the core system. Sustained GBA around 200 ms reflected effects of endogenous attention in the core system and the anterior insula, substantiating the role of the core system of face processing and indicating the allocation of attentional resources for further processing. In contrast, strong effects of endogenous attention in the OFC and amygdala beyond 300 ms supports the notion that the extended system of the face-processing network is only recruited if the task necessitates active processing of facial expression. Our results show that endogenous attention operates in the whole face-processing network and that these effects are best captured by frequency-specific changes in the gamma band.

5 STUDY III: FREQUENCY-SPECIFIC SYNCHRONIZATION OF NEURONAL ACTIVITY UNDERLYING THE ATTENTIONAL BIAS TO THREAT

5.1 Introduction

Significant events in our environment attract attention independently of the current focus of attention. That is why rubbernecking an accident on the opposite lane causes traffic jam and may produce even further accidents because people do not pay sufficient attention to driving. The idea that attention can, on the one hand, be captured by salient events but, on the other hand, can also be focused on the task or stimuli of the ongoing activity has been formalized in the biased competition model of visual attention (Desimone & Duncan, 1995). Incoming visual stimuli compete for representation in memory or motor systems. The winner of this competition will guide further action. The competition can be biased by bottom-up driven sensory mechanisms, such as salience or visual pop-out, or top-down control mechanisms, such as attention. Top-down feedback mechanisms have later been associated with fronto-parietal regions (Corbetta & Shulman, 2002; Duncan, 2006; Miller & Cohen, 2001), whereas bottom-up mechanisms appear to involve the temporo-parietal and inferior frontal cortex (Corbetta et al., 2000; Corbetta & Shulman, 2002).

One important dimension of stimulus salience seems to be threat-relatedness. The detection of threat-related information in the environment provides a crucial evolutionary advantage (Mogg & Bradley, 1998). In addition, the attentional bias to threatening stimuli seems to be relevant in the development of anxiety disorders. This bias is increased in individuals with high or clinical levels of anxiety (Mathews & Mackintosh, 1998), but has also been observed in healthy individuals (Koster et al., 2004). The attentional bias to threat has often been investigated with the so-called dot probe paradigm (MacLeod et al., 1986; Mogg & Bradley, 1998). Typically a neutral and a threat stimulus (e.g. words or facial expressions) are presented concurrently and immediately followed by a small dot at the location of one of the two stimuli. Participants are required to respond as quickly as possible to the dot. Attentional deployment is then tested by comparing the response times of trials in which the threat stimulus has been presented at the same (congruent) or opposite spatial position (incongruent) as the dot probe. It is assumed that response times to probes are faster if they occur at congruent compared to incongruent positions. This threat bias seems to originate from difficulty to disengage attention from threat rather than from stronger orienting to it (Koster et al., 2004).

Based on findings from neuroimaging studies, brain regions underlying this attentional orienting to threat can be incorporated into the biased competition model (Bishop, 2007, 2008). According to this model, the outcome of competition between emotionally neutral, task-relevant and threat-related, task-irrelevant stimuli is determined by the relative strength of modulating signals from the PFC and the amygdala. The amygdala supports detection of threat-related stimuli (Bishop, Duncan, & Lawrence, 2004; Luo et al., 2010), while the PFC exerts control to ensure task-relevant processing (Bishop, Duncan, Brett, et al., 2004). Anxiety may alter both of these functions leading to hyperfunction of the amygdala and/or hypofunction of the prefrontal control signal resulting in increased attentional bias to threat.

Although fMRI or PET studies advanced our understanding of the attentional bias to threat by identifying involved brain regions, they cannot uncover its underlying neuronal mechanism, since they only provide an indirect measure of neuronal activity (Logothetis, 2008). Lindquist and Barrett (2012) have proposed that emotional processing such as the threat bias emerges from basic psychological operations accomplished by distributed networks in the human brain. These networks are not uniquely dedicated to emotional processing. They argue that the specific mechanism of "how proposed basic psychological operations emerge from the interplay of these neurons" (p. 538) is yet unknown. Both holds true for the attentional bias to threat: amygdala and PFC are not exclusively involved in the attentional bias to threat (Adolphs, 2010b; Miller & Cohen, 2001) and the underlying neuronal mechanism of this bias remains largely unknown (Bar-Haim et al., 2007). It has been suggested that dynamic interactions of cell assemblies, reflected in synchronized frequency-specific oscillations, provide indices of network interactions (Engel et al., 2001; Siegel et al., 2012). Thus investigating temporal synchronization of neuronal activity with MEG can provide a promising tool to bridge the gap between the cell and the systems level of neuroscience. Methodological advances allow the estimation of neuronal sources underlying electrophysiological data (Gross et al., 2001; Van Veen et al., 1997). Some authors applied these methods to detect changes in neuronal activity in subcortical structures such as the amygdala (Cornwell et al., 2008; Luo et al., 2007). Thus, the neuronal mechanism underlying the attentional bias to threat may be reflected in temporal synchronization of neuronal activity in the network of identified brain regions, such as amygdala and PFC, and the MEG method is well suited to uncover it.

Visual attention has been characterized by a specific pattern of temporal synchronization of neuronal activity. Attention concurrently enhances power in gamma-band

frequencies (> 30 Hz) and decreases power in alpha-band frequencies (8-12 Hz; e.g., Fries et al., 2001). Interestingly, a MEG study using source reconstruction techniques could show that this pattern of synchronized oscillations operates along the whole dorsal visual pathway (Siegel et al., 2008), including the key regions of the dorsal fronto-parietal attention network such as the intraparietal cortex (Corbetta & Shulman, 2002). We hypothesize that the threat bias is reflected in a similar frequency-specific pattern of power changes in the alpha and gamma bands. Since the attentional bias is mediated by bottom-up driven mechanisms, we expect that these power modulations arise in ventral but not dorsal regions of the attention network, such as the temporo-parietal junction and inferior frontal cortex (Corbetta & Shulman, 2002) or the medial temporal lobe including the amygdala (Bishop, 2007, 2008). In addition, it remains elusive whether cognitive control over threat-related stimuli is also reflected in frequency-specific oscillations, presumably exerted by the PFC and/or dorsal fronto-parietal attention network (Pourtois et al., 2006).

So far, only one EEG study investigated frequency-specific modulations of the threat-related attentional bias in a dot probe paradigm. Unpleasant, threat-related cues elicited stronger theta synchronization than pleasant ones over posterior sensors, which was interpreted as the evaluation of emotional significance (Sun et al., 2012). Results however remain vague because the authors restricted the analysis only to the frequency range of 4-8 Hz (Sun et al., 2012). The remainder of electrophysiological studies investigated ERPs to both cue and probe (Eldar, Yankelevitch, Lamy, & Bar-Haim, 2010; Holmes et al., 2009; Pourtois et al., 2004). Pourtois et al. (2004) reported differences in occipital P1 component, a marker of visual attention, on the probe only when fearful but not happy faces preceded the probe. This effect originated in occipito-temporal cortices.

Increased bias to threat has also been associated with specific genetic variations underlying anxiety disorders. Specifically, carriers of the short allele (S group) of 5-HTTLPR exhibited higher anxiety-related traits compared to individuals homozygous for the long allele (L group; Lesch et al., 1996). Reduced serotonergic transmission as in the short variant of 5-HTTLPR has been associated with a stronger attentional bias toward threat-related stimuli (Beevers, Gibb, McGeary, & Miller, 2007; Carlson, Mujica-Parodi, Harmon-Jones, & Hajcak, 2012; Fox, Ridgewell, & Ashwin, 2009; Kwang, Wells, McGeary, Swann, & Beevers, 2010; Osinsky et al., 2008; Perez-Edgar et al., 2010), which received tentative support in a recent meta-analysis (Pergamin-Hight et al., 2012). Importantly, carriers of the short allele exhibited alterations in the corticolimbic circuitry (reviewed by Hariri & Holmes, 2006), including

increased amygdala responses to threat-related faces, decreased coupling with the ACC, and increased coupling with a more ventral region of the PFC. These lines of evidence are in agreement with the neurobiological biased competition model (Bishop, 2007) suggesting that genetic variations mediating vulnerability to anxiety may alter the balance between amygdalar threat detection and prefrontal control. Therefore, it seems reasonable that 5-HTTLPR modulates frequency-specific oscillations underlying the functional circuitry of the attentional bias to threat. To assess the impact of 5-HTTLPR, we selected our participants according to their genotype.

To investigate the underlying neuronal mechanism of the threat bias, we adapted the dot probe paradigm for MEG. Since attentional modulations operate on a rapid time scale (Siegel et al., 2008), stimuli were only briefly presented (Pourtois et al., 2004). Previous studies successfully measured the attentional bias to threat when cues were presented for 100 instead of 500 ms, also minimizing the impact of overt eye movements (Cooper & Langton, 2006). Importantly, all stimuli were presented bilaterally to ensure that no asymmetrical visual on- and offset responses across hemispheres were recorded with MEG. Instead of presenting a unilateral probe that served as a target, we dissociated target and probe. Fearful and neutral faces served as cues, Gabor patches as targets and distractors, and a small arrow as pointer. The pointer indicating the target position followed a bilateral display containing the target and a distractor. This required participants to span their attention covertly across both hemifields in order to succeed in this task.

We expected that target detection was influenced by the fearful face cue and that this attentional bias was particularly pronounced in the S group. We also predicted that attentional processing was associated with a contralateral increase of gamma-band and a concurrent decrease in alpha-band activity over occipito-parietal cortices. Furthermore, we hypothesized that the threat bias would be reflected in the same frequency-specific pattern in the ventral fronto-parietal attentional network, such as the temporo-parietal junction, inferior frontal cortex and the medial temporal lobe including the amygdala. This effect should be particularly prominent in the interaction contrast between the direction of attention and the position of the fearful face. In addition, the 5-HTTLPR genotype was considered as a group factor in all contrasts of interest. As previous studies have not examined frequency-specific effects of the 5-HTTLPR genotype and the attentional bias to threat, these analyses were exploratory.

5.2 Methods

5.2.1 Participants

Forty-eight healthy volunteers were recruited according to their 5-HTTLPR genotype and participated in this study. Since the short variant appeared to have a dominant effect in previous research (Hariri et al., 2005), participants were assigned to the group of S-carriers (S group; including the variants SS and SL) or to the L homozygous group (L group; LL variant). The whole experiment was double blind so that the group assignment was only revealed after data recording was accomplished. The genotyping procedure is described elsewhere (Raczka et al., 2010). All participants had normal or corrected to normal vision and none reported history of psychiatric or neurological illness. Four of them had to be excluded from further analysis due to excessive head movement in the MEG (> 20 mm) leaving a final sample of 44 participants (23 male, mean age 27.1 ± 4.5 years). Using the Hardy-Weinberg equilibrium calculator (www.oege.org/software/hwe-mr-calc.shtml; Rodriguez, Gaunt, & Day, 2009), the genotype distribution of 21 LL, 18 SL, and 5 SS variants did not deviate from the expected distribution ($\chi^2(1)= 0.14$, $p = 0.708$). Groups did not differ with respect to age, education, or the State-Trait Anxiety Inventory (STAI; Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, Gorsuch, & Lushene, 1970). Each participant provided written, informed consent. The ethics committee of the Hamburg Medical Association approved all procedures.

5.2.2 Stimuli

Fifteen male and fifteen female face stimuli depicting fearful and neutral expressions were taken from the FACES database (Ebner, Riediger, & Lindenberger, 2010). Faces were converted to gray-scale, matched for luminance and masked by an oval shape to remove hair, neck and background information. Gabor patches (sinusoidal gratings in a Gaussian envelope, 2 cycles per degree, 80% contrast) and images of random visual noise (normally distributed noise, 100 *SD*) were created in MATLAB (The MathWorks, Natick, MA, USA.) serving as targets and visual masks, respectively. Gabor patches were tilted clockwise and counterclockwise between 0° and 5° in steps of 0.5°, resulting in 21 distinct patches. Target Gabor patches were tilted either 3° clockwise or counterclockwise from the vertical meridian, while all 21 Gabor patches served as distractors. Face stimuli and their masks subtended 9° × 12°, whereas Gabor patches and their masks subtended 9° × 9°. All stimuli were presented in

the upper visual field at an eccentricity of 3° to the left and right of the vertical meridian and centered 6° above the horizontal meridian at a viewing distance of 52 cm. Stimuli were projected from a LCD projector outside of the magnetically shielded room on a gray background at a refresh rate of 60 Hz. Stimulus presentation was controlled using the Psychophysics Toolbox 3 (Brainard, 1997; Pelli, 1997) and MATLAB 7.5.0.

5.2.3 Procedure

Each trial (Figure 5.1) started with an initial fixation period jittered between 1000 and 1500 ms. A face cue consisting of one actor portraying a fearful and a neutral expression, respectively, a pair of Gabor patches serving as target and a distractor, and a spatial probe were presented for 100 ms each in every trial. A 33 ms mask covering the same size as the masked stimuli directly followed faces and Gabor patches to avoid afterimages. The stimulus onset asynchrony (SOA) between presentation of face cues and Gabor patches was set to 133 ms (short SOA) or 633 ms (long SOA) in order to probe allocation of attention at two different time points. The pointer consisted of a small arrow pointing to the left or right of the fixation dot and indicated the target Gabor patch requiring the response. After 700 ms, the white fixation dot turned blue, serving as a go cue for the participants' response. Participants had to indicate the tilt direction of the target Gabor patch by button press with the right index or middle finger for 'left' and 'right', respectively. Responses were delayed to eliminate the impact of button presses on the electrophysiological data during the time interval of interest. Therefore, accuracy scores instead of reaction time were required, which also seems to be a reasonable approach (Van Damme, Crombez, & Notebaert, 2008). Response mapping to button presses was kept constant across participants. Participants had to span their covert attention across both hemifields in order to succeed in the task because the spatial probe followed the target Gabor patch. Furthermore, participants were instructed to avoid head or eye movements and to maintain fixation throughout a trial.

We are aware that the slightly lateral presentation of the pointer is suboptimal because the visual stimulation is dissimilar between attentional conditions. In behavioral pilot experiments, a centrally presented, isoluminant color-coded dot was used as spatial pointer (i.e. red for left and blue for right or vice versa). However, mapping of colors to hemifield was too difficult for the participants so that we decided to use this easier, lateralized pointer instead.

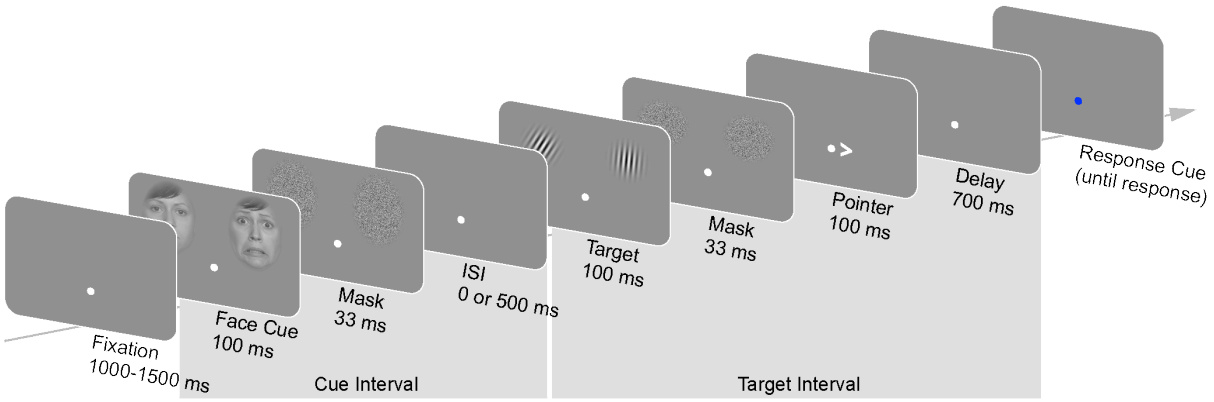

Figure 5.1. Schematic of experimental design. The fixation dot was presented at the center of the screen. Participants had to report the tilt direction (left/right) of the Gabor patch denoted by the subsequent pointer. In ten percent of the trials, a cue identification trial displaying "What was the gender of the face pair in the preceding trial?" was presented so that face cues were not completely ignored. Abbreviations: ISI, interstimulus interval.

Ten blocks of 96 trials each were presented in random order. Participants were allowed to have short breaks between blocks and to continue at their own pace. The first and the second five blocks were recorded in separate MEG sessions allowing for a larger break in between. Facial identities, visual hemifield of the fearful face, delay between face cue and Gabor patches, tilt direction of the target Gabor patch, and direction of the pointer were counterbalanced across trials. The tilt of the distractor Gabor patch was pseudo-randomized across trials. Additionally, in ten percent of the trials a cue identification trial followed the participants' response asking for the gender of the faces presented in the preceding trial. Only the question "What was the gender of the face pair in the preceding trial?" was displayed until response. These cue identification trials were introduced to ensure that face stimuli were attended. Importantly, the emotional expression of the faces was irrelevant to the cue identification trials. Prior to data acquisition, all participants performed at least 40 practice trials with a different set of five faces to become familiar with the task.

5.2.4 Data Acquisition

Participants were seated in a magnetically shielded and sound-attenuated room. MEG data were acquired with a whole-head 275-channel axial-gradiometer system (Omega 2000, CTF Systems Inc., Canada). To exclude metal artifacts, participants were screened in advance by means of a questionnaire and asked to dress in scrubs. Four defective MEG sensors were removed from further analysis. Head position relative to the MEG sensors was measured

continuously during each recording session. Head displacements were below 20 mm for all analyzed datasets. MEG data were low-pass filtered online (cutoff 300 Hz) and sampled at 1200 Hz. The EEG, electrooculogram and electrocardiogram were acquired simultaneously for offline artifact rejection within the CTF system. For the electrooculogram, two electrodes were placed below each eye and referenced against one above the nasion. The electrocardiogram was recorded bipolarly with one electrode below the right clavicle and one below the lowest costal arch on the left. Additionally, an EEG electrode was placed 5 cm above the inion and referenced against nose tip for offline control of miniature eye movements. The ground electrode was attached to the left forearm. Impedances were kept below 8 kOhm. In addition, skin conductance responses were recorded from two electrodes at the thenar of the left hand with a BrainAmp ExG amplifier (BrainProducts, Germany). Structural T1-weighted MRIs were obtained with a 3 tesla MR Scanner (Trio, Siemens, Germany) for all participants in order to create individual head models.

5.2.5 Data Analysis

Behavioral data. Behavioral data were only considered of participants, who were included in the MEG data analysis. Notably, results did not change when all participants were included. Trials with premature button presses, i.e. before the onset of the response cue, were excluded from further analysis. In total, the number of premature button presses per participant did not exceed 20 out 960 trials in total. Since the primary interest of the experiment was the impact of the face cue on attentional processing, behavioral responses were pooled according to ipsi- or contralateral presentation of the fearful face relative to the target (emotion ipsi vs. contra). Since habituation to the emotional impact of the face cue was expected, the behavioral performance of the first and second MEG session was analyzed separately. The percentage of correct responses was subjected to a mixed-model ANOVA with emotion (ipsi, contra) and SOA (short, long) as within-subject factors and 5-HTTLPR groups (S group, L group) as between-subject factor. Simple main effects were calculated separately for each 5-HTTLPR group to follow up on interaction effects. If needed, post-hoc paired *t* tests, Bonferroni-corrected, were conducted to test for simple effects at a significance-level of $p < 0.05$ two-tailed. The percentage of correct responses in the cue identification trials were compared in a mixed model ANOVA with face cue gender (male, female) as within-subject factor and 5-HTT group (S, L) and participant's gender (male, female) as between-subject

factors. Estimates were Greenhouse-Geisser-corrected whenever appropriate. Original degrees of freedom are reported. Effect sizes were reported as eta-squared, representing the proportion of accounted variance ($\eta^2 < 0.1$ = small effect size; $0.1 < \eta^2 < 0.25$ = medium effect size; $\eta^2 > 0.25$ = large effect size).

Preprocessing of MEG data. Analysis of MEG data was performed using MATLAB 7.10.0 and FieldTrip 20120418 (Oostenveld et al., 2011). Off-line responses were high-pass filtered at 0.5 Hz and low-pass filtered at 170 Hz (Butterworth filter of order 3 and 4, respectively). Due to non-stationarity of the line noise artifact, a discrete Fourier transform for frequency ranges of 49-51 Hz, 99-101 Hz, and 149-151 Hz was applied on 10 s data segments from the continuous signal including the epochs of interest in the center. Trials containing muscle artifacts or signal jumps were automatically rejected from further analysis based on FieldTrip's default filter settings (threshold criteria: z-value of 15 and 30, respectively). Moreover, data were baseline-corrected and trials with amplitudes exceeding 0.75e-11 T were rejected (assumingly artifacts produced by environmental noise, e.g. cars). For data reduction, data were resampled to 400 Hz. The recorded signal was segmented into epochs of –1100 to 1500 ms for short and of –1600 to 1500 ms for long SOA trials around the onset of the target. To account for a delay of the visual onset between trigger and MEG signal, MEG trigger were shifted by 20 ms. Eye movements, eye blinks, and electrocardiographic activity were corrected by applying extended infomax independent component analysis on the segmented, filtered, and resampled data. In a first step, data were reduced to 64 components by principal component analysis. In a second step, the independent component analysis was applied using a weight change $< 10^{-7}$ or a maximum number of 600 iterations as stop criteria. Independent components representing artifacts were determined by visual inspection of the components' scalp topographies and time courses. These artifacts were then removed by back-projecting all but these components. Across all participants, between 2 to 9 components were rejected. The number of trials per condition varied between 82 and 119 across all participants.

Sensor-level analysis. TFRs were computed using a sliding-time-window Fourier transformation with Hanning windows and multitapers as sliding windows for low and high frequencies, respectively. For the multitaper approach (Mitra & Pesaran, 1999), the data in each sliding time window were multiplied by a set of orthogonal tapers. Then the Fourier transformation was calculated for each of the tapers and the spectra for each individual taper were magnitude squared. Finally, the power for each tapered data segment was averaged. Each trial was zero padded up to 4 s of length. The length of the sliding time window ΔT and the

amount of spectral smoothing Δf determines the number of tapers k = ((ΔT * Δf)-1). For the analysis of low (2.5-30 Hz in steps of 2.5 Hz) and high frequencies (30-150 Hz in steps of 10 Hz), sliding time windows of fixed length (ΔT = 400 ms and ΔT = 200 ms, respectively) with a step size of 20 ms and fixed frequency smoothing (Δf = 2.5 Hz and Δf = 20 Hz, respectively) were used. These settings led to one taper for low and three tapers for high frequency ranges. Therefore, frequencies below and above 30 Hz were analyzed separately. For frequencies above 30 Hz, orthogonal Slepian tapers were used. These tapers optimally concentrate the spectral energy over the frequency range of interest (Mitra & Pesaran, 1999). For frequencies below 30 Hz, a single Hanning taper was used instead. For the calculation of total power, frequency decomposition was performed on single-trial data and power values of single trials were then averaged. These power estimates include signal components that are phase-locked and non phase-locked to the stimulus onset (Tallon-Baudry & Bertrand, 1999). Furthermore, responses were characterized as the percentage of signal change according to the formula:

$$\text{total power} = 100*(\text{poststimulus}_{\text{total}} - \text{prestimulus}_{\text{total}})/\text{prestimulus}_{\text{total}}$$

In order to avoid an overlap of the baseline window with the poststimulus window, the baseline period spanned from the (beginning of the epoch +½ ΔT) to (face cue onset –½ΔT), with ΔT = 400 ms for low and ΔT = 200 ms for high frequencies, respectively. Thus, the baseline period differed for high and low frequencies and the two SOAs.

A cluster-based randomization test was applied for statistical analysis (Maris & Oostenveld, 2007). This nonparametric test controls for multiple comparisons with multidimensional data by clustering adjacent points in the sensor-time-frequency plane exhibiting the same effect. The sensor space was divided into six ROIs excluding the central midline (left/right fronto-central, left/right parieto-occipital, left/right temporal; Figure 5.2). Effects in the cue interval were tested in two time bins before target onset (–633 to –300 ms and –300 to 0 ms). Based on the contrast attend left compared to attend right, effects in the target interval were tested in two time bins after target onset (0 to 400 ms and 400 to 1000 ms) for low frequencies and one for high frequencies (100 to 700 ms).

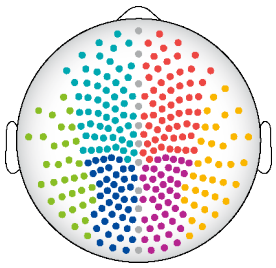

Figure 5.2. Regions of interest (ROIs) for the analysis of time-frequency data. Sensors belonging to the same ROI are indicated by the same color and are named based on their locations (left/right fronto-central, left/right parieto-occipital, left/right temporal).

For the cluster-based randomization test, first a dependent sample *t* test was calculated between conditions for each sensor-time-frequency point within a given ROI and time bin. The results of the *t* test were thresholded at an α level of $p = 0.1$. Adjacent sensor-time-frequency points exceeding the threshold were selected for the second test, the cluster-level test. Here, cluster-level statistics were calculated by taking the sum of the *t* values within every cluster. The maximum of the cluster-level statistics represented the test statistic. This test statistic was compared against a Monte Carlo estimated significance probability distribution. Assuming no difference between experimental conditions, this distribution was obtained by 1000 times randomly swapping the conditions in a given subject and calculating the maximum cluster-level statistic. The Monte Carlo *p* value for the observed test statistic is computed as the proportion of random partitions resulting in a larger test statistic than the observed one. Using 1000 draws, the Monte Carlo *p* value is an accurate estimate of the true *p* value. The null hypothesis of no differences between conditions was rejected when $p < 0.025$ (two-sided).

For evoked power, frequency decomposition was performed on the average of all trials. Evoked power estimates solely contain signal components that are phase-locked to stimulus onset. Since the evoked power of the prestimulus baseline is expected to be very low, i.e. close to zero, the normalization with these power values would yield very high numbers. Therefore, evoked responses were normalized with the total power of the prestimulus interval instead according to the following formula:

$$\text{evoked power} = 100*(\text{poststimulus}_{\text{evoked}} - \text{prestimulus}_{\text{evoked}})/\text{prestimulus}_{\text{total}}$$

Source-level analysis. To reconstruct the sources of the different spectral components, we used a linear beamforming approach (Gross et al., 2001). Briefly, this technique computes an adaptive spatial filter that passes activity from the location of interest with unit gain while

maximally suppressing activity from all other locations. The spatial filter is calculated based on a forward model at the location of interest (the leadfield matrix) and the cross-spectral density, i.e. the covariance matrix in frequency space, between all MEG sensor pairs at the frequency of interest. This approach is particularly suitable for the analysis of total power, because linear beamforming is based on the calculation of the covariance matrix between single sensors in every trial. Recent studies have successfully applied beamforming to reconstruct sources from MEG (Siegel et al., 2008) and EEG data (Schneider, Debener, Oostenveld, & Engel, 2008), also in subcortical areas (Cornwell et al., 2008).

In detail, the adaptive spatial filter was calculated as follows. TFRs for the time-frequency point of interest were computed using the multitaper approach (see above). The data for the time window of interest were multiplied by a set of orthogonal tapers. Then the cross-spectral density matrix between all sensor pairs was estimated and the auto spectrum of each sensor was multiplied with the complex conjugate spectra of all other sensors for each individual taper before averaging across tapers. A single Hanning window was used on a single 400 ms time bin for low frequencies and three Slepian tapers were used on a single 200 ms time bin for high frequencies. Since we were interested in the percent change of the power spectra, cross-spectral density matrices were calculated both for pre- and poststimulus epochs (depending on the latency of the effect at sensor-level) and the experimental conditions of interest.

Each participant's brain volume was divided into a regular 7 mm grid, excluding central voxels on the x-axis for reasons of symmetry. For each grid point, individual leadfields (Nolte, 2003) were computed for each participant and recording session using single shell head models constructed from the individual structural MRIs, which were aligned to the measured head positions relative to the MEG sensors. The TFRs of the two contrasted experimental conditions and their corresponding prestimulus intervals were appended, so that a common spatial filter could be constructed for each grid location. The regularization parameter was set to 5% of the average of the eigenvalues of the cross-spectral density matrix. Then TFR data of each condition and corresponding prestimulus interval, for the short SOA and long SOA conditions centered around –540 ms and –1040 ms, respectively, were projected through this filter. This resulted in an estimate of the source power for the time-frequency point of interest and the respective experimental conditions and their baseline period. Importantly, the source estimate for the experimental conditions of interest and their baseline periods was based on the cross-spectral density averaged across all epochs (pre- and

poststimulus interval of all conditions). All source reconstructions were baseline corrected according to the formula:

$$\text{source power} = (\text{poststimulus}_{\text{source}} - \text{prestimulus}_{\text{source}})/\text{prestimulus}_{\text{source}}$$

Source power data were averaged across participants and MEG sessions after spatial normalization of all individual data to the International Consortium for Brain Mapping template (MNI, Montreal, Canada) based on the individual structural MRIs. Paired *t* tests were performed to examine differences between the conditions of interest. Unpaired *t* tests were applied to examine group differences. These *t* values were transformed to z-scores and are reported uncorrected but thresholded at $p < 0.05$, corresponding to a $z = 1.96$. Subsequently, functional z-scores were linearly interpolated on a 1 mm grid and projected to the same MNI template brain for visualization. Results of the source reconstruction analysis are given in coordinates (x, y, z in mm) in MNI space (Evans et al., 1993). Anatomical regions were identified with the AAL atlas (Tzourio-Mazoyer et al., 2002) in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Cluster statistics on source level data were performed to obtain a measure for the reliability of results. The same parameters as described for the analysis of sensor-level data were used. Clusters were considered meaningful when $p < 0.2$ and the voxel size exceeded 300 voxels. Please note that effects at source level can be considered significant at the level of the whole brain (9878 voxels), if $p < 0.025$ (two-sided), although we applied a more lenient threshold for reporting clusters. However, all effects that were followed up at source level were significant at sensor level.

5.3 Results

5.3.1 Behavioral Data

Behavioral performance is depicted in Figure 5.3 and results of the ANOVAs are listed in Table 5.1. Since the mixed model ANOVA of the first MEG session revealed an interaction between all three factors, genotype groups were tested separately. Within the S group, two independent main effects were revealed. The S group performed worse when the fearful face was presented ipsilaterally to the attended hemifield and in short SOA trials. Performance in the L group was decreased, when the fearful face was presented contralaterally to the attended hemifield but only in the short SOA condition. In the second MEG session, only an effect of SOA remained. All participants were more accurate in long SOA trials.

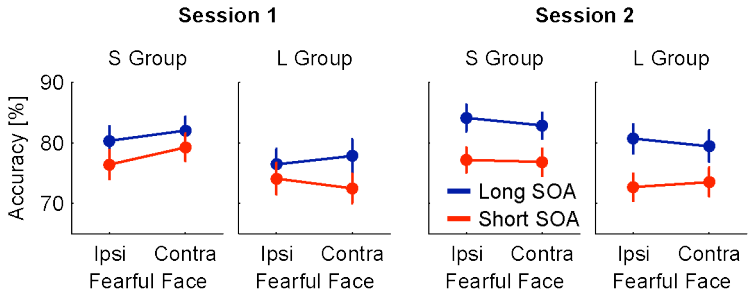

Figure 5.3. Behavioral performance split according to MEG session and genotype. Results were pooled over attention conditions so that trials with fearful faces presented ipsilaterally to attended hemifield could be compared to those with fearful faces presented contralaterally.

These results suggest that (1) the task difficulty in long SOA trials seems to be decreased as reflected in higher accuracy scores, (2) S-carriers are prone to interference of the fearful face when presented ipsilaterally to attended hemifield, and (3) the L group exhibits less disengagement when the fearful face is presented contralaterally and the cognitive load is high. Although the numerical difference between accuracy scores suggested that the S group seemed to outperform the L group (Homberg & Lesch, 2011), this group difference did not approach significance.

Table 5.1. Results of the ANOVAs for the attentional probe task.

	Session 1				Session 2			
	df	*F*	*p*	η^2	*df*	*F*	*p*	η^2
All (N = 44)								
Emotion (ipsi vs. contra)	**1, 42**	**4.21**	**0.047**	**0.09**	1, 42	0.58	0.449	0.01
SOA (short vs. long)	**1, 42**	**27.04**	**< 0.001**	**0.39**	**1, 42**	**65.92**	**< 0.001**	**0.61**
Group (S group vs. L group)	1, 42	1.57	0.217	0.04	1, 42	1.43	0.238	0.03
Emotion x SOA	1, 42	0.86	0.360	0.02	1, 42	2.15	0.150	0.05
Emotion x group	**1, 42**	**5.09**	**0.029**	**0.11**	1, 42	0.20	0.660	0.01
SOA x group	1, 42	0.14	0.715	0.00	1, 42	0.08	0.776	0.00
Emotion x SOA x group	**1, 42**	**4.20**	**0.047**	**0.09**	1, 42	0.32	0.576	0.01
S group (N = 23)								
Emotion	**1,22**	**12.65**	**0.002**	**0.37**	NC			
SOA	**1,22**	**12.82**	**0.002**	**0.37**	NC			
Emotion x SOA	1, 22	0.60	0.447	0.03	NC			
L group (N = 21)								
Emotion	1,20	0.02	0.900	0.00	NC			
SOA	**1,20**	**14.11**	**0.001**	**0.41**	NC			
Emotion x SOA	**1,20**	**4.78**	**0.041**	**0.19**	NC			

Abbreviations: *df*, degrees of freedom; *F*, *F*-value; *p*, *p*-value; *η2*, effect size; N, sample size; NC, not computed because no interaction.

Average performance on the cue identification trials was good ($M \pm SE = 75.64 \pm 1.51$) confirming that the participants paid sufficient attention to the face cues. Cue identification

was better for short compared to long SOA trials ($F(1,40) = 17.07$, $p < 0.001$, $\eta 2 = 0.30$), when the memory trace was not yet decayed. Performance for female actors was worse than for males ($F(1,40) = 8.31$, $p = 0.006$, $\eta 2 = 0.17$), due to the fact that male actors were less ambiguous and thus less often identified as female actors than vice versa.

5.3.2 Temporal Synchronization at Sensor- and Source-Level

Comparison of fearful face left vs. fearful face right trials (cue interval). The impact of fearful facial expressions could not be differentiated from neutral ones, since both expressions were presented simultaneously. By comparing trials in which the fearful face was presented at the left vs. right hemifield we could assess laterality differences of facial expression processing. Only long SOA trials were analyzed in the cue interval.

In the cue interval, the cluster-based randomization procedure identified three significant clusters (Figure 5.4A). Stronger beta suppression with a left temporal topography were identified in two time windows (Figure 5.4B), when fearful faces were presented in the right hemifield: an early effect between –580 to –500 ms peaking at 17.5 Hz ($p = 0.011$) and a late effect between –100 to –20 ms peaking at 22.5 Hz ($p = 0.015$). The source reconstruction did not reveal any meaningful clusters for the early and late beta suppression effects (cf. 5.2.5). In addition, an increase in the gamma band with a right occipital topography between –620 to –540 ms peaking at 80 Hz ($p = 0.017$) was found (Figure 5.4B), when fearful faces were presented in the left visual hemifield. The underlying sources for this effect ($p = 0.104$) were estimated over the right angular gyrus (58, –62, 34) extending into the middle temporal and middle occipital gyrus and between the right superior frontal (26, 34, 54) and mid frontal gyrus (Figure 5.4C).

Comparison of S vs. L group for fearful face left vs. fearful face right trials (cue interval). We also assessed whether the genotype groups exhibited laterality differences of facial processing by comparing S and L groups for the contrast fearful face left vs. fearful face right trials.

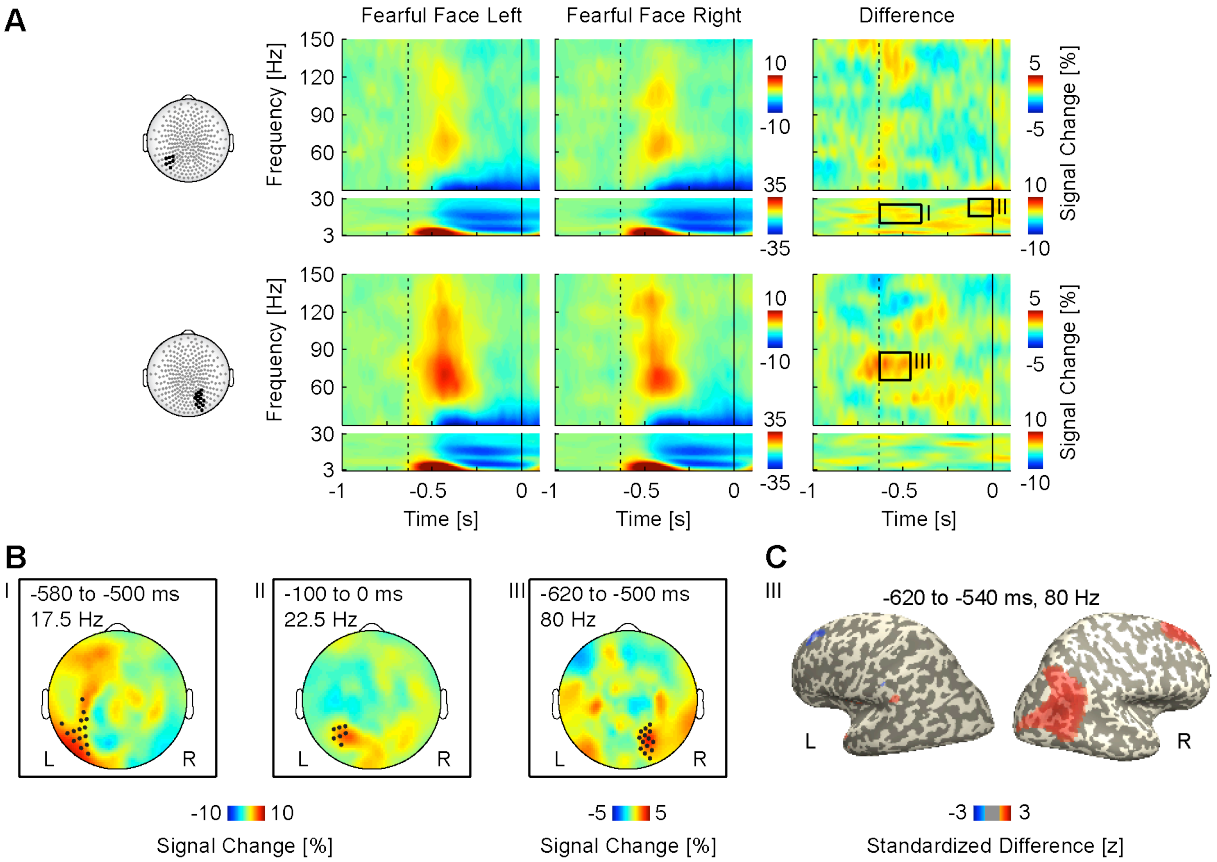

Figure 5.4. Fearful face left vs. fearful face right trials during the cue interval. (A) Time-frequency representation (TFR) is depicted for the conditions fearful face left vs. fearful face right and their difference for a cluster of left temporal (upper panel) and right occipital sensors (lower panel). The dashed and solid lines mark face cue and target onsets, respectively. (B) Topographic maps illustrate condition differences in the beta and gamma band (cf. black rectangles in TFR). (C) The results of the source reconstruction are shown for the gamma band effect.

In the cue interval, stronger theta synchronization with a left temporal topography was found in S-carriers compared to the L group when the fearful face was presented at the left hemifield during the whole first time bin (peaking at 5 Hz, –560 ms, $p = 0.010$; Figure 5.5A-D). Although the underlying sources for this effect did not survive the criterion of meaningfulness ($p < 0.2$, size > 300 voxels), they will be reported because they parallel the sources of the same contrast at the later time window. Two clusters in the medial temporal lobe were estimated as sources (Figure 5.5E). The first one ($p = 0.277$) extended from the left inferior temporal gyrus (–48, –50, –6) into the middle and fusiform gyrus. The second one ($p = 0.758$) extended from the right hippocampus (26, –26, –4) into the thalamus and fusiform gyrus. An inspection within each of the genotype group revealed that this effect was due to relative stronger increase in theta in the S group to fearful face left vs. fearful face right, whereas the L group did not consistently differ between these two conditions (Figure B1).

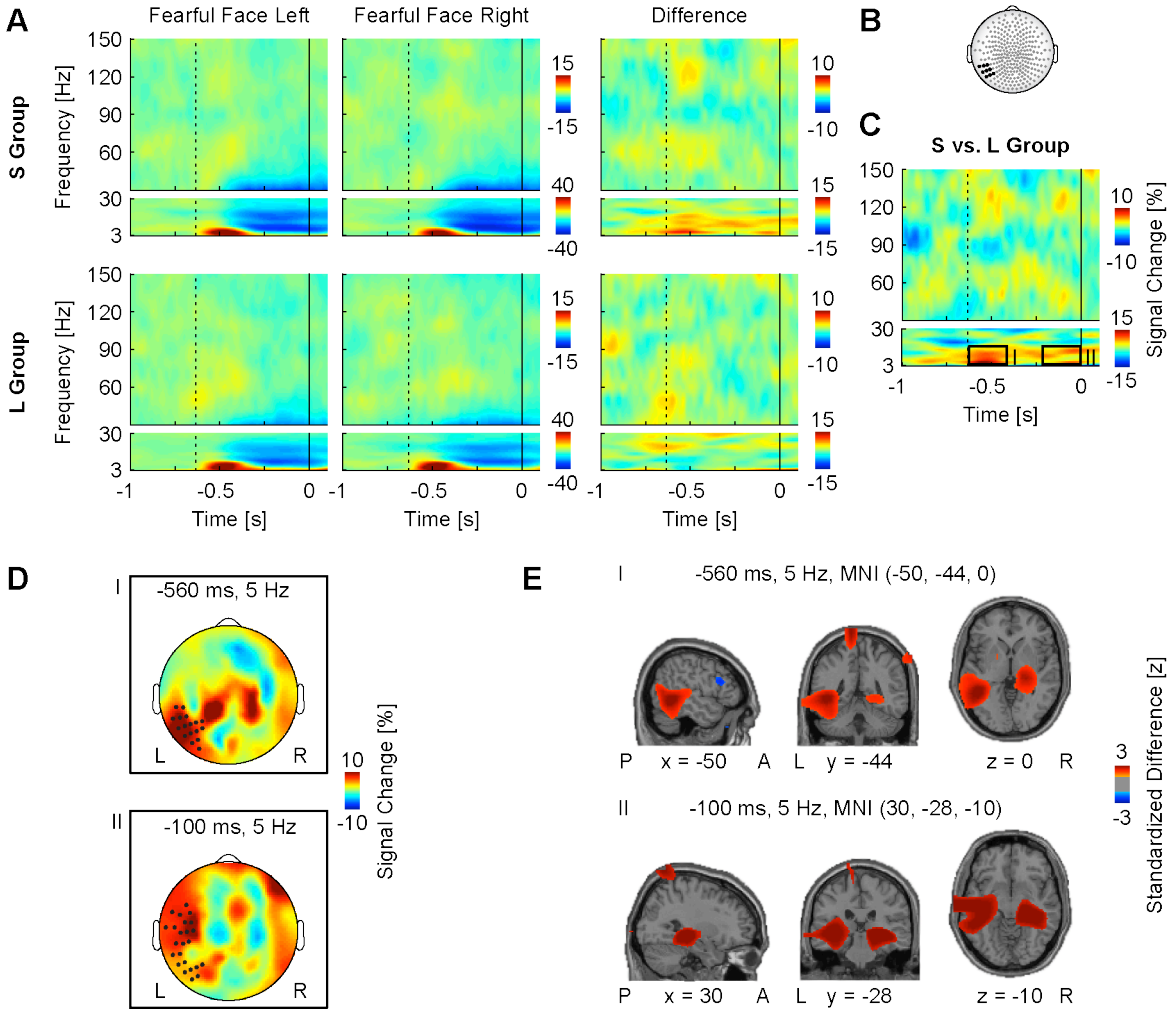

Figure 5.5. Fearful face left vs. fearful face right trials by genotype during the cue interval. (A) TFRs depict the conditions fearful face left vs. fearful face right and their difference separately for the S and L group (upper and lower panel, respectively). The dashed and solid lines mark face cue and target onsets, respectively. (B) Cluster of left temporal sensors for which all TFRs are shown. (C) TFR depicts the group difference. (D) Topographic maps illustrate group differences in the theta band for two different time windows (cf. black rectangles in TFR). Please note that the early effect (I) did not survive the criterion for reporting but is shown for comparison with the later effect II. (E) The results of the source reconstruction are shown for each of the effects.

In the second time bin, an increase in theta activity between the S and L group was found with a left temporal topography (peaking at 5 Hz, –100 ms, p = 0.018; Figure 5.5A-D). Underlying sources were estimated bilaterally in the medial temporal lobes. The first cluster (p = 0.019) extended from the left inferior temporal gyrus (–62, –10, –28) into the middle temporal and fusiform gyrus, the amygdala, the hippocampus, the thalamus, the putamen, and the insula, whereas the second cluster (p = 0.180) expanded from the right hippocampus (36, –30, –8) into the middle temporal, fusiform and parahippocampal gyrus, the thalamus, and the putamen. To specify the contribution of each genotype group to this effect, the topographic maps and source reconstructions were plotted for the corresponding time-frequency point separately for each group (Figure B2). The suppression over temporo-

occipital regions was stronger in the S group, when fearful faces were presented in the right hemifield, resulting in a relative increase over temporal regions. This increase could be attributed to increased activity preferentially within the left medial temporal lobe. The L group instead showed less suppression over temporo-occipital but increased activity over frontal regions. This topography was accompanied by underlying sources preferentially within the right medial temporal lobe.

Comparison of fearful face left vs. fearful face right trials (target interval). In the target interval, no differential responses to fearful face left vs. fearful face right trials were identified at sensor-level.

Comparison of S vs. L group for fearful face left vs. fearful face right trials (target interval). In the target interval, only one cluster comparing the genotype groups for the fearful face left vs. fearful face right contrast in the short SOA survived the randomization procedure at sensor-level. This effect with a left temporal topography (peaking at 20 Hz, 620 ms, $p = 0.024$) was due to stronger beta suppression in the L group, when the fearful face was presented at the right hemifield, whereas the S group did not show differential suppression.

Comparison of attend left vs. attend right trials (target interval). To assess the attention effect, we compared trials in which the participants were asked to respond to targets in the left vs. the right hemifield. The resulting pattern at sensor and source level was clearly lateralized and very similar for both SOAs.

For the long SOA condition, effects in the theta, alpha, and gamma band were observed (Figure 5.6). Since the effects in the gamma and alpha band correspond to the previously reported oscillatory signature of attention (Fries et al., 2001; Siegel et al., 2008), these effects are summarized first. Gamma-band power (Figure 5.6A-B) concurrently decreased over ipsi- (peaking at 80 Hz, 400 ms, $p < 0.001$) and increased over contralateral parietal sensors (peaking at 110 Hz, 400 ms, $p = 0.002$). This parietal topography (Figure 5.6B) could be attributed to sources in the middle occipital (left hemisphere: –24, –86, 22, $p = 0.025$) and angular gyri (right hemisphere: 46, –70, 42, $p = 0.019$) extending into parietal and temporal areas (Figure 5.6C). Contrary, alpha-band power increased over ipsi- (peaking at 7.5 Hz, 600 ms, $p = 0.006$) and decreased over contralateral parietal sensors (peaking at 10 Hz, 600 ms, $p = 0.004$). Hence, the lateralization and latency of alpha power changes were reversed and later, respectively, than those in the gamma band (Figure 5.6A-B). The changes in alpha power originated from the occipital cortex (left hemisphere: –40, –70, –8, $p = 0.004$; right hemisphere: 32, –98, 6, $p = 0.023$) and extended into parietal and temporal regions, especially

in the left hemisphere (Figure 5.6C). In addition, power in the high alpha and low beta band increased in right temporal sensors (peaking at 22.5 Hz, 880 ms, $p = 0.006$). The attentional signature in the alpha and gamma band was preceded by an early, lateralized modulation in the theta band (Figure 5.6A). Theta-band power decreased over ipsi- (peaking at 2.5 Hz, 250 ms, $p = 0.022$; Figure 5.6B) and increased over contralateral occipital sensors, although this increase did not reach significance. At source level, this effect (left hemisphere: –22, –89, 28, $p = 0.048$; right hemisphere: 34, –90, –2 $p = 0.031$) was restricted to occipital regions including the middle occipital, fusiform, lingual, and angular gyrus (Figure 5.6C).

As the same lateralized pattern was observed for the short SOA condition (Figure B3), the statistical parameters are briefly summarized. Theta-band power decreased significantly around 250 ms in the left hemisphere (peaking at 2.5 Hz, 250 ms, $p = 0.006$). Sources were localized to left (–20, –98, 0, $p < 0.001$) and right middle occipital gyrus (40, –90, 8, $p = 0.024$), extending ventrally into left the fusiform gyrus. Gamma-band power decreased over ipsi- (peaking at 40 Hz, 400 ms, $p < 0.001$) and increased over contralateral parietal sensors (peaking at 140 Hz, 400 ms, $p = 0.005$). Sources of this gamma-band modulation extended into the left (–34, –88, 12, $p = 0.012$) and right (42, –86, 14, $p = 0.119$) middle occipital gyrus. Synchronization in the alpha band increased over ipsi- (peaking at 10 Hz, 600 ms, $p = 0.015$) and decreased over contralateral parietal sensors (peaking at 10 Hz, 600 ms, $p < 0.001$). Underlying sources were located in left (–32, –94, –8, $p = 0.043$) and right (20, –60, 10, $p < 0.001$) occipital areas. The sources in the right hemisphere extended ventrally more into temporal and frontal and dorsally into parietal areas than in the left hemisphere.

An inspection of the evoked power (Figure B4) revealed that responses in the theta band were phase-locked to the target onset, whereas alpha- and gamma-band responses were less phase locked.

Comparison of fearful face ipsi- vs. fearful face contralateral to target trials (target interval). To assess the influence of emotional face cues on target processing, we compared trials in which the fearful faces were presented ipsilaterally to the target with those in which it was presented contralaterally. In both SOAs, effects in the high gamma band in the same time range were observed, although these effects differed in their topography.

In the long SOA condition, gamma power increased (local maximum at 110 Hz, 360 to 400 ms; Figure 5.7A) over central sensors ($p = 0.005$; Figure 5.7B), when fearful faces were presented ipsilaterally to targets. At source level, this effect ($p < 0.001$) had its maximum in

the middle frontal gyrus (32, 6, 48) and extended into frontal, central and parietal regions particularly in the right hemisphere.

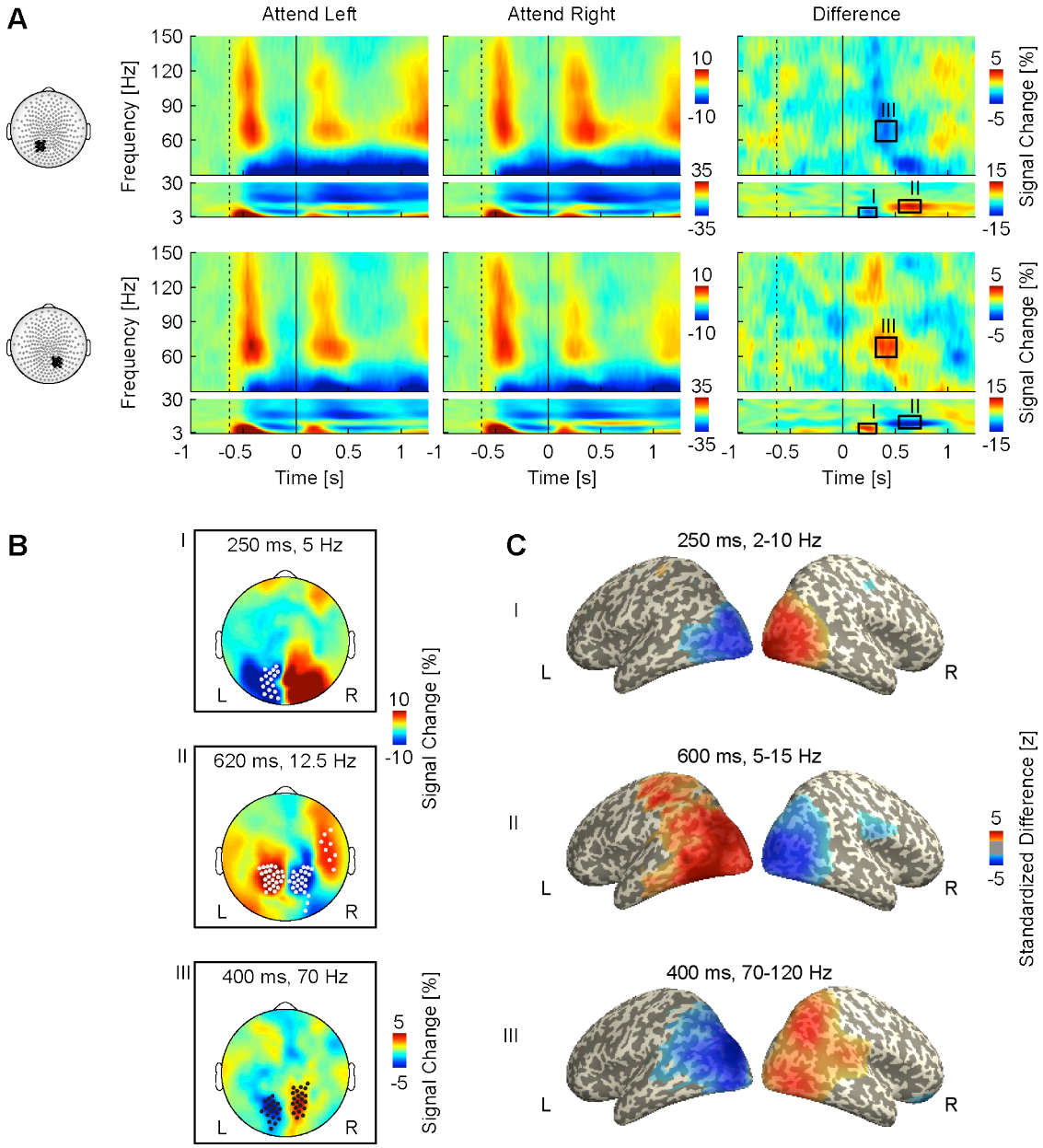

Figure 5.6. Attend left vs. attend right trials during the target interval. (A) TFRs depict the conditions attend left vs. attend right and their difference for clusters of left and right parietal sensors (upper and lower panel, respectively). The dashed and solid lines mark face cue and target onsets, respectively. (B) Topographic maps illustrate differences in the theta, alpha and gamma band for different time windows each (cf. black rectangles in TFR). (C) The results of the source reconstruction are shown for each of the effects. Frequency bands instead of the peak frequencies have been chosen for illustration purposes.

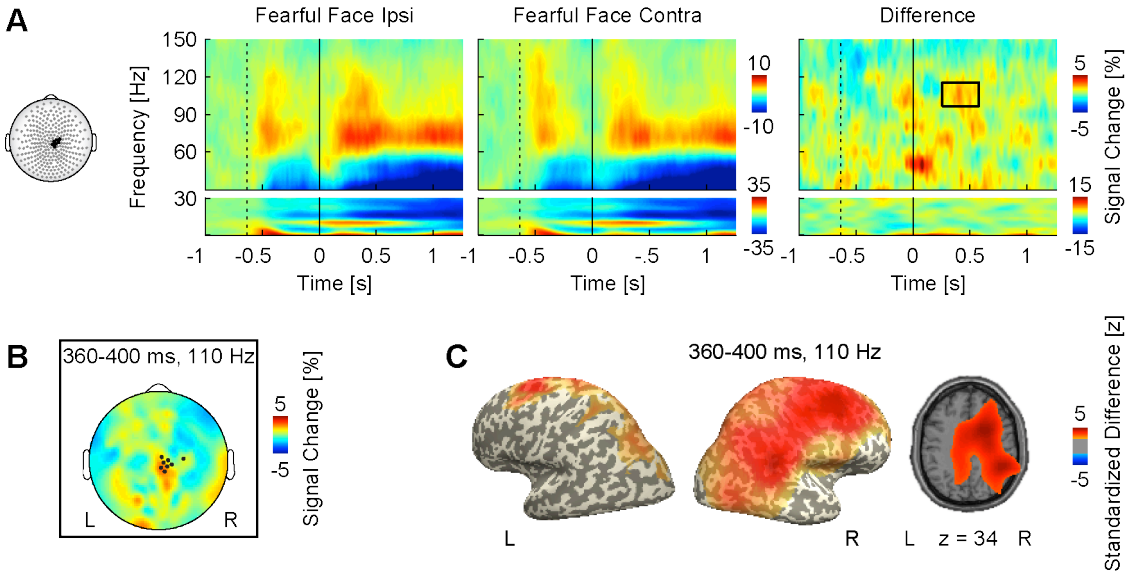

Figure 5.7. Fearful face ipsi- vs. contralateral to target in long SOA trials during the target interval. (A) TFRs depict the conditions fearful face ipsilateral vs. fearful face contralateral and their difference for a cluster of central sensors. The dashed and solid lines mark face cue and target onsets, respectively. (B) Topographic map illustrates the difference in the gamma band between 360-400 ms (cf. black rectangle in TFR). (C) The results of the source reconstruction are shown for the same effect.

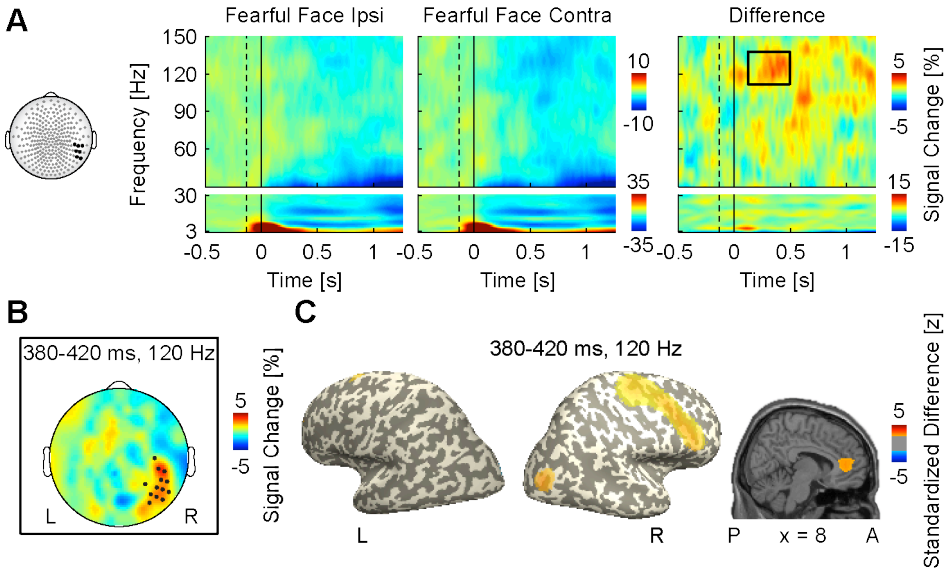

Figure 5.8. Fearful face ipsi- vs. contralateral to target in short SOA trials during the target interval. (A) TFRs depict the conditions fearful face ipsilateral vs. fearful face contralateral and their difference for a cluster of right temporal sensors. The dashed and solid lines mark face cue and target onsets, respectively. (B) Topographic map illustrates the difference in the gamma band between 380-420 ms (cf. black rectangle in TFR). (C) The results of the source reconstruction are shown for the same effect. The sagittal slice shows activity in the anterior cingulum.

In the short SOA condition, gamma power increased (peaking at 80 Hz, 380 to 420 ms; Figure 5.8A) over right temporal sensors (p = 0.022; Figure 5.8B), when fearful faces were presented ipsilaterally to targets. At source level, this effect (p = 0.133) included clusters in the

right inferior parietal cortex (58, –36, 56), along the right middle frontal gyrus (44, 10, 56), and in the bilateral ACC (6, 42, 14).

Comparison of S vs. L group for fearful face ipsi- vs. fearful face contralateral to target trials (target interval). To assess whether the interaction of the emotional face cue and target processing was modulated by genotype, we calculated the difference between trials, in which fearful faces were presented ipsilaterally and contralaterally to targets, and compared the genotype groups.

In long SOA trials (Figure 5.9, Figure B5), theta-band activity increased at 7.5 Hz around 560 ms over left temporal sensors (p = 0.005). The inspection of the topographies within each group revealed that S-carriers exhibited stronger suppression over left temporal sensors when the fearful face was presented contralaterally to targets, whereas the L group had the tendency of stronger suppression over left sensors when fearful faces were presented ipsilaterally, resulting in a positive net effect. The source reconstruction did not reveal any meaningful cluster for this time-frequency window (all ps > 0.381).

In short SOA trials (Figure 5.10, Figure B6), an increase in the beta band at 17.5 Hz between 400-800 ms with a right temporal topography was observed (p = 0.023). The inspection of the topographies within each group revealed that S-carriers exhibited stronger suppression over right temporal sensors when the fearful face was presented contralaterally to targets, whereas the L group did not show a differential effect. At source level, this effect originated from a cluster (p = 0.092) in the right rolandic operculum (50, –6, 10) including the insula, inferior frontal operculum and the superior temporal gyrus and the ACC (Figure 5.10E).

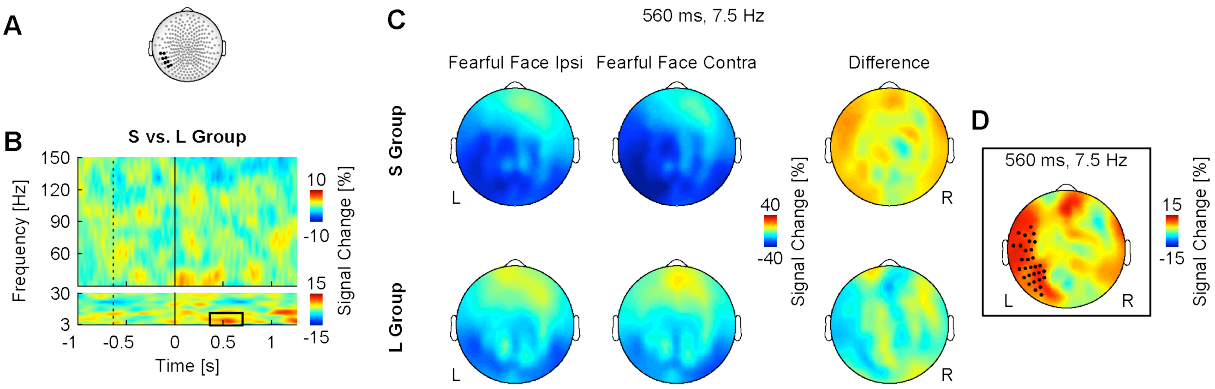

Figure 5.9. Fearful face ipsi- vs. contralateral to target by genotype in long SOA trials during the target interval for the difference between S and L groups. (A) Cluster of left temporal sensors for which the TFR is shown. (B) TFR depicts the group difference in the theta band. The dashed and solid lines mark face cue and target onsets, respectively. (C) Topographic maps illustrate the responses in the S (upper panel) and L group (lower panel) in

the single conditions and (D) their difference for the corresponding time-frequency point (cf. black rectangle in TFR).

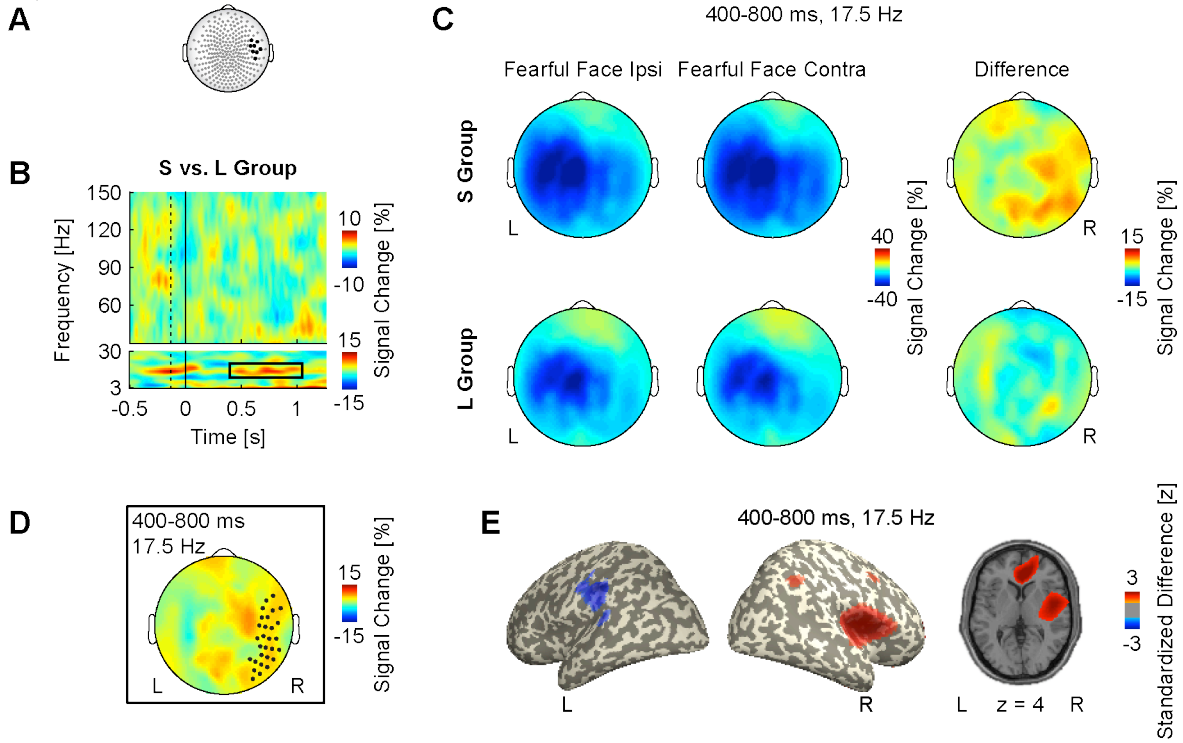

Figure 5.10. Fearful face ipsi- vs. contralateral to target by genotype in short SOA trials during the target interval for the difference between S and L groups. (A) Cluster of right temporal sensors for which the TFR is shown. (B) TFR depicts the group difference. The dashed and solid lines mark face cue and target onsets, respectively. (C) Topographic maps illustrate the responses in the S (upper panel) and L group (lower panel) in the single conditions and (D) their difference for the corresponding time-frequency point (cf. black rectangle in TFR). (E) The results of the source reconstruction are shown for the same effect. The axial slice shows activity in the anterior cingulum.

5.4 Discussion

Our results revealed an impact of the bottom-up driven threat bias on attentional processing at two different processing stages, as reflected in both SOAs. This effect was confined to the gamma band and included ventral and dorsal fronto-parietal regions particularly of the right hemisphere. Contrary to our hypothesis, the contrast of fearful face left vs. right did not elicit a lateralized frequency-specific pattern in the temporo-parietal and inferior frontal regions of the ventral attention network (Corbetta & Shulman, 2002).

In line with previous work (Bauer et al., 2012; Fries et al., 2001; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Siegel et al., 2008), our paradigm elicited lateralized attentional responses over parieto-occipital sensors in the alpha and gamma band, although the latencies differed between experiments. According to previous reports, alpha power is already suppressed several hundred milliseconds after cue and before stimulus onset. A contralateral increase in the gamma band emerges only after stimulus onset (Bauer et al.,

2012; Fries et al., 2008; Siegel et al., 2008; Worden, Foxe, Wang, & Simpson, 2000). In the present study, enhancement in the gamma band preceded the suppression in the alpha band, reflecting our presentation order (the target was presented before the probe). This raises the possibility that contralateral gamma in- and alpha decrease reflect working memory instead of spatial attention processes. However, this argumentation also applies to many previous studies of spatial attention. In several cueing studies, the cue information also has to be held in working memory to impact the subsequent response on the target, because target presentation is often delayed (Posner, 1980; Siegel et al., 2008; Worden et al., 2000). Moreover, it has been suggested that spatial attention and working memory share common mechanisms, resulting in similar responses at the behavioral and neuronal level (Awh & Jonides, 2001).

It needs to be discussed whether the lateralized attention effects were purely stimulus driven. As the probe was slightly lateralized and unmasked, we cannot rule out that the early response around 250 ms was dominated by sensory processing rather than attentional modulation (Awh, Belopolsky, & Theeuwes, 2012). The latency of total power theta modulation was very short and paralleled by a modulation of evoked power in the same frequency range 250 ms after target onset, which was only 117 ms after probe onset. Accordingly, Mishra, Martinez, Schroeder, and Hillyard (2012) reported recently that the attentional modulation of very early, visual ERPs was conversely reflected by stimulus-induced neuronal enhancements in the theta frequency range. Regarding effects in the alpha- and gamma-band range, the results in evoked power and experimental design contradict sensory-driven effects. First, alpha- and gamma-band responses were not fully phase-locked to the stimulus and hence cannot fully account for the corresponding effects in total power. Second, participants would build up an expectation about the pointer information even though it succeeded the target because it validly indicated the target. In contrast, traditional Posner experiments include invalid trials, in which the cue indicates the position opposite of the target. Since we presented Gabor patches always bilaterally, this case did not occur in the current experiment. Instead, the participants expected the probe information, or they wouldn't have been able to perform the task. This expectation can be considered a form of top-down processing. Therefore, it seems likely that the alpha- and gamma-band effect reflect top-down processing (Fries et al., 2001; Siegel et al., 2008), whereas the lateralized response in the theta band rather reflects sensory event-related activity.

The interpretation of the isolated main effect of attention is fundamental for understanding the interaction of threat cue and target processing. This interaction was

reflected by stronger net gamma-band power around 400 ms after target onset irrespective of SOA, when the threat cue was presented ipsi- vs. contralaterally to targets. This effect did not depend on the physical location of the fearful face because fearful faces were pooled to be ipsi- or contralateral to the attended hemifield (i.e., irrespective of whether they were presented in the left or right hemifield). However, the net increase resulted from suppression in the short and enhancement in the long SOA condition. At source level, its clearly right-lateralized anatomical distribution was different from the pure attention effect, although it included regions from the ventral and dorsal fronto-parietal attention network (Corbetta & Shulman, 2002). The observed differences between the two SOAs can be attributed to different stages of threat-related processing.

In the short SOA condition, gamma-band power was more suppressed, when the fearful face was presented contralaterally to the targets. In these trials, the fearful face automatically drew attention, which again had to be rapidly disengaged and quickly allocated to the target in the opposite hemifield to succeed in the task. Thus, the emotional conflict imposed by the task-irrelevant fearful face is largest in these trials. The sources of the net gamma-band increase in the bilateral ACC and middle frontal gyrus in the short SOA condition likely reflect conflict detection and emotion regulation. Consistent with our finding, gamma-band suppression in extrastriate visual cortex previously reflected active suppression of task-irrelevant information during processing of threat-related stimuli (Maratos et al., 2012). The ACC has been associated with attention and emotion-related processing (Bishop, Duncan, Brett, et al., 2004; Bush, Luu, & Posner, 2000). A recent review of neuroimaging data put forward that the rostral part of the ACC, which is exactly the region observed here, is critically involved in emotion regulation and inhibition in response to emotional conflict (Etkin, Egner, & Kalisch, 2011). Moreover, ACC and medial prefrontal areas exhibited increased GBA under emotion regulation (Popov, Steffen, Weisz, Miller, & Rockstroh, 2012). Gray matter volume of the ACC has also been found to correlate with increased attentional bias to threat (Carlson, Beacher, et al., 2012). The middle frontal gyrus also seems to be consistently activated in functional imaging studies for emotional vs. neutral facial expressions (Sabatinelli et al., 2011). Lateral parts of the PFC, such as the middle frontal gyrus, have close anatomical connections to the cingulate cortex and seem to be involved in attention and executive control (Barbas, 2000; Rothé, Quilodran, Sallet, & Procyk, 2011). Taken together, the ACC and middle frontal gyrus reflect the activation of a network of

emotion regulation and attentional control. This network was also identified in our modified dot probe task.

Consistent with previous reports (Balconi & Lucchiari, 2008; Luo et al., 2007), processing threat-related, negative facial expressions was associated with increased responses in the gamma band in long SOA trials. This effect was observed in a widespread network in frontal, central and parietal regions with predominance over the right hemisphere, including parts of both ventral and dorsal fronto-parietal attention network. Inferior parietal and middle frontal regions also showed up in the short SOA condition, but sources were stronger in long SOA trials with a delay between face cue and target. Drawing on the extended model of emotion regulation (Todd, Cunningham, Anderson, & Thompson, 2012), the observed pattern of activation may reflect a later stage of threat processing (i.e., compared to the activation seen in the short SOA condition), which is exerted by the executive control network to (re-)focus on the ongoing task. The extended model of emotion regulation proposes that affective salience is not only processed in a bottom-up fashion but can also been seen as one form of habitual top-down control with a bias toward affective stimuli acquired during development (Todd et al., 2012; Vuilleumier, 2005). Although an amygdala-centered network has been suggested to execute such executive control (Todd et al., 2012; Vuilleumier, 2005), our results advocate the idea that refocusing on the ongoing task once the threat-related fearful face has biased attention is exerted by the dorsal and ventral fronto-parietal attention network (Corbetta & Shulman, 2002). This argumentation would imply that a strict differentiation between top-down and bottom-up driven processing is mitigated in case of affective salience. Furthermore, the present study provides evidence that this bias is conveyed by frequency-specific neuronal activity in the gamma range. The dominance of the right hemisphere accords well with right-hemispheric lateralization for emotion (Keil et al., 2001; Müller et al., 1999), attention (Mesulam, 1999; Petersen & Posner, 2012; Posner & Petersen, 1990; Siman-Tov et al., 2007), and face processing (Gao et al., 2013; Herrington, Taylor, Grupe, Curby, & Schultz, 2011; Noesselt et al., 2005) and has also been observed for the ventral fronto-parietal attention network (Corbetta et al., 2000; Corbetta & Shulman, 2002). In summary, the right hemispheric activation in long SOA trials reflects increased bottom-up strength in response to the detection of the fearful face cue and top-down control to re-allocate biased attention on the ongoing task.

The interaction of attention and emotion was further modulated by genotype in the theta- and beta-frequency range in the long and short SOAs, respectively. In both SOAs, this

modulation was due to stronger suppression of neuronal activity in the S group, when fearful faces were presented contralaterally to targets. However, the lateralization at sensor-level differed between the two SOAs. The short duration of theta power changes in the long SOA condition at sensor level may have prohibited robust source estimation. The underlying sources for the beta-band effect in the short SOA were located in the right insula and bilateral ACC. The beta rhythm has been traditionally related to motor function, although a recent review suggested that beta activity rather signals the "status quo" not only in the motor system but also in cognition generally (Engel & Fries, 2010; W. J. Ray & Cole, 1985). This means that the beta rhythm reflects the maintenance of the current motor, cognitive or perceptual set. Consequently, a suppression of beta power, as observed here, would reflect a disruption of the current setting by a novel or unexpected event. In line with that, the stronger beta suppression points to greater bottom-up interference in S-carriers, particularly when they have to switch attention to the hemifield contralateral to the fearful face. Related to that, beta-band power was diminished in anticipation or during delivery of painful stimuli, presumably functioning as an alerting signal (Pomper et al., 2012; Senkowski, Kautz, Hauck, Zimmermann, & Engel, 2011; Worthen, Hobson, Hall, Aziz, & Furlong, 2011). Furthermore, decreased beta activity over temporal areas has also been associated with tasks that require sustained monitoring of externally emotionally laden stimuli (W. J. Ray & Cole, 1985). This would match with the interpretation that the S group needs to regulate more than the L group as reflected in augmented beta suppression.

Similar to the ACC, the insula has also been involved in attentional and emotional processing mediated by arousal (Critchley, 2009). It has been proposed that the insula forms part of a salience network with strong connections to limbic structures including the anterior cingulate (Menon & Uddin, 2010; Mesulam & Mufson, 1982a, 1982b; Mufson & Mesulam, 1982) and with two subsystems differently contributing to regulation of goal-driven attention and affective salience processing (Eckert et al., 2009; Seeley et al., 2007; Taylor, Seminowicz, & Davis, 2009; Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012). Furthermore, the insula has also been associated with anxious anticipation of aversive events (Paulus & Stein, 2006). In line with that, aberrant insula activation during fear acquisition in a conditioning experiment has recently been reported in S-carriers (Hermann et al., 2012). Conversely, the gray matter volume of the ACC and functional coupling between amygdala and ACC was reduced in S-carriers (Pezawas et al., 2005). Altogether, the increased beta suppression in the S group that was mapped to the insula and ACC seems to reveal increased

conflict and emotion regulation elicited by the threat bias. This notion also fits well with the extended model of emotion regulation (Todd et al., 2012) arguing that the threat bias has been shaped across development and therefore reflects a habitual bias, since the S allele is associated with chronic decrease in serotonergic neurotransmission (Hariri & Holmes, 2006; Wiggins et al., 2012).

Behaviorally, we observed a small emotional bias in target detection performance. The face cue biased target processing differently in the S and L group. This bias vanished over the course of the whole experiment. In line with existing research (Carlson, Mujica-Parodi, et al., 2012; Pergamin-Hight et al., 2012), the S group exhibited stronger interference by threat-related stimuli, when presented ipsilaterally to targets. Interpretation of results from the L group is not straightforward because performance was only impaired when the face cue was presented contralaterally to targets and load was high.

Finally, 5-HTTLPR elicited differential effects in the theta band when participants were processing the face cues. Although theta-band power was increased for fearful faces presented in the left hemifield in the S compared to the L group during the long SOA, this net effect was due to a differential increase in the early and suppression in the late time window of the cue interval. The underlying sources encompassed regions within the bilateral medial temporal lobes including the fusiform gyrus, the hippocampus, the thalamus and also, in the late time window of the cue interval, the amygdala. Interestingly, lesion and imaging studies have revealed that face processing is particularly lateralized to the right hemisphere (Gao et al., 2013; Herrington et al., 2011). Lesion studies also indicated greater impairment in face recognition after right- than left-hemispheric lesions (Adolphs, Tranel, & Damasio, 2001; Anderson, Spencer, Fulbright, & Phelps, 2000). This right-hemispheric lateralization is notably prominent when faces are presented in the left visual field (Ferneyhough, Stanley, Phelps, & Carrasco, 2010; Noesselt et al., 2005; Rhodes, 1985; Yovel, Levy, Grabowecky, & Paller, 2003; Yovel, Tambini, & Brandman, 2008). It has also been proposed that processing of facial expressions in particular does not only depend on face selective regions in the fusiform gyrus but also on modulating input from the amygdala (Herrington et al., 2011; Vuilleumier & Driver, 2007). Consistent with the finding that the amygdala in carriers of the short allele is hyperactive (Klucken et al., 2013; Munafò et al., 2008), it may be speculated that the S group was more susceptible to the influence of the fearful face, which resulted, in combination with the right-hemispheric advantage, in enhanced theta power directly after presentation of the fearful face in the left visual field (around –560 ms before target presentation). This

interpretation is substantiated by the underlying sources in the medial temporal lobe that form part of the face processing network (Vuilleumier & Pourtois, 2007). The theta rhythm has previously been associated with processing emotionally salient stimuli (Knyazev, 2007; Maratos et al., 2009). In line with our source reconstruction, the correlation structure of theta oscillations has a prominent hub in the medial temporal lobe at rest (Hipp, Hawellek, Corbetta, Siegel, & Engel, 2012). Furthermore, previous electrophysiological work on animals attributed an important role to theta activity in fear-related arousal (Pape & Driesang, 1998), which has also been found to be disturbed in 5-HTT deficient mice (Narayanan et al., 2011). However, the functional meaning of stronger desynchronization in S-carriers shortly before target onset is unknown. It could reflect a perturbation of the resting state in S-carriers (T. W. Lee et al., 2011).

Drawing strong conclusions regarding the genotype effects is hindered by the relatively small sample size and the inclusion of both sexes (Bigos & Weinberger, 2010). Second, the target pointer might have induced a sensory- instead of attention-driven effect because it was lateralized and not masked. Therefore, it is difficult to associate the observed attention effects with purely attention-related processes. However, it must be emphasized that, although the pointer may have influenced sensory processing, the pointer itself had not to be differentiated and could never predict the correct response to the target. Third, the sensory input of targets and distractors was unequal because targets could only have one of two and distractors one of 21 possible tilt directions. This may have introduced a response bias toward the target by the varying tilt direction of the distractor stimulus. Equal input in left and right visual fields, i.e. presenting targets and distractors with the same tilt, would have resulted in a ceiling effect because targets and distractors would have been equally informative and no allocation of attention to the target would have been necessary. However, pseudo-randomizing the tilt of the distractor patch across trials was applied to minimize a putative bias. Hence, we think that a strong sensory bias is rather unlikely. Finally, our experimental design cannot disentangle the specific contribution of engagement to or disengagement from threat. This would have necessitated the additional introduction of baseline trials (Koster et al., 2004; Van Damme et al., 2008), which was not possible given the long duration of the experiment.

In conclusion, the current study provides first insight that the attentional bias to threat is exerted through dynamic interactions between the ventral and dorsal fronto-parietal attention network particularly in the gamma-band range. Furthermore, carriers of the short

allele of 5-HTTLPR were characterized by stronger activation in low frequencies that was located to regions previously involved in emotion processing and regulation such as the insula and ACC. These findings extend earlier results on the modulation of attentional processing by 5-HTTLPR by showing that, at neuronal level, the anxiety propensity in S-carriers is associated with frequency-specific oscillations.

6 GENERAL DISCUSSION

All three studies of this thesis investigated how emotional facial expressions bias competition and capture attention. The paradigms of all studies independently manipulated emotional content and attention processing. The results concur in the contention that emotional stimuli are processed more efficiently than neutral stimuli and interfere with ongoing task processing (Studies I and III). The present work extended electrophysiological evidence for the attentional bias to threat by showing that task-irrelevant fearful face distractors modulated gamma-band responses to unemotional targets in the ventral and dorsal fronto-parietal attention networks and the ACC (Study III). Furthermore, the threat-related face cue differentially modulated beta-band activity based on the 5-HTTLPR variant in the insula and ACC, which has previously been implicated in the attentional control over threat-related stimuli (Bishop, Duncan, Brett, et al., 2004). Thus, the results of Studies I and III accord well with accounts of biased competition by threat-related stimuli (Bishop, 2007, 2008). Directing attention to facial expressions resulted in an increase of gamma power in all examined regions of the face-processing network (Study II). This effect was specific to faces compared to nonfaces but not specific to threat-related facial expressions, so that strong conclusions regarding the attentional bias to threat-related fearful expressions are impeded.

How was the influence of emotional stimuli on attention processing assessed? Attention was manipulated by the lag between T1 and T2 (Study I), two types of tasks (Study II), and the target position in the left and right hemifield (Study III). Hence, each of these tackled a different domain of attention: Study I investigated fluctuations of attention over time, Study III examined spatial attention, and Study II addressed feature-based attention in its broadest sense. The emotional content in all studies was operationalized by the comparison of different facial expressions. Since also happy faces were presented in Study I, more general conclusions regarding the impact of emotional stimuli on attention processing can be drawn than in Studies II-III, in which only the effects of threat-related and neutral facial expressions can be compared. Facial expressions were presented centrally in Studies I-II and lateralized in Study III. The effect of this procedural difference on the neurophysiological data is discussed in more detail below. In the following, similarities and differences of the results are examined in more detail.

At the behavioral level, biased competition for attentional resources towards threat-related stimuli was observed in Studies I and III. In line with previous reports, happy and

fearful faces attract attention even under periods of limited awareness in Study I (de Jong & Martens, 2007; De Martino et al., 2009; Fox et al., 2005; Milders et al., 2006). Yet, when target faces are too dissimilar from distractors, targets easily win the competition for attentional resources and outlive the AB (Landau & Bentin, 2008). In Study III, the face cue biased target processing differently in the 5-HTTLPR groups during the first session of the experiment. In line with previous results, stronger interference in the S group was observed when the fearful face cue was presented at the same side as the target (Carlson, Mujica-Parodi, et al., 2012; Pergamin-Hight et al., 2012). Furthermore, behavioral performance in Study III was qualified by state anxiety in the S and L groups. Consistent with existing research (Fox et al., 2009; J. M. G. Williams et al., 1988, 1997), state-anxious S-carriers exhibited stronger vigilance toward fearful face cues, whereas state-anxious individual homozygous for the long allele avoided those.

At the neuronal level, stronger gamma-band synchronization in response to task-irrelevant faces was observed in Study III, which might reflect the attentional bias to threat. In Study II, however, gamma-band synchronization differed for faces and nonfaces but was relatively unaffected by facial expression. This apparent conflict can be resolved by pointing to procedural differences between the studies elaborated in the following. Stimuli were presented centrally and longer in Study II than in Study III. In addition, the attentional modulation was blocked, whereas participants of Study III had to direct attention to the left and right hemifield on a trial-by-trial basis after target offset. Thus, the task in Study II was much easier than in Study III. These procedural differences resulted in the development of a very robust task set in Study II, i.e., by configuring the mental state according to the specific operations demanded by the task. Matching between the stimulus of a given trial and the task set might be reflected in gamma-band synchronization at the neuronal level. In case of Study II, gamma-band responses might have generally increased to faces in the explicit condition and may have overridden any exogenous bias of fearful faces, since fearful and neutral faces shared more visual features with happy target faces than nonfaces. This assumption receives support from the fact that gamma-band synchronization was generally stronger for faces compared to nonfaces but did not differentiate between fearful and neutral expressions. In contrast, nonfaces and faces were equally often targets in the implicit condition, in which the low-level feature "red tint" denoted targets, so that gamma-band synchronization to faces might have been weaker. In accordance to this claim, two EEG studies observed intermediate to strong GBA following stimuli partially and completely matching the target stimulus, respectively,

when participants had to identify predefined stimuli by button presses (Herrmann & Mecklinger, 2001; Lenz et al., 2008). Such target-matching effects could be interpreted as feedback from higher cortical areas, when the perceived stimulus matches with an existing memory representation of the target stimulus.

The present results further inform at which stages threat-related facial expressions bias competition. Competition for attentional resources is assumed to occur at two processing stages (Bishop, 2007, 2008; Lavie, 2005). Perceptual competition corresponds to the initial stage, at which processing of distractors terminates when perceptual load is high. Under conditions of low load, competition for further processing resources occurs. This later stage includes active recruitment of prefrontal control mechanisms to inhibit the processing of salient distractors. Competition for attentional resources by threat-related distractors may occur subsequent to the initial stage of perceptual competition and may be supported by the amygdala (Bishop, 2007, 2008). The present results concur with this claim for two reasons. First, perceptual representations of task-irrelevant, emotional faces must have been formed, since these stimuli influenced behavioral performance in Study I[2] and Study III. Support for this notion also comes from traditional AB models suggesting that the perceptual representation for T2 cannot be transferred into working memory during the AB interval (Chun & Potter, 1995; Potter et al., 2002; Shapiro et al., 1997; Shapiro et al., 1994) unless T2 is particularly salient (Bowman & Wyble, 2007; Wyble et al., 2009). Thus, the perceptual load in both studies was low enough to allow perceptual representation of emotional distractors, which subsequently biased competition.

Second, ventral and dorsal fronto-parietal sources characterized biased competition by threat-related cues in Study III. As the recruitment of those brain regions has been related to endogenous top-down control (Corbetta & Shulman, 2002; Miller & Cohen, 2001), it may reflect effort to maintain control over task-related processing after potential threat detection by the amygdala (Figure 1-2). Similar mechanisms might operate during the AB. A previous fMRI study identified greater responses in fronto-parietal regions and deactivations in the amygdala for detected, unemotional T2, suggesting reallocation of attention to T2 and

[2] Please note that emotional facial expression was task-relevant in the majority of experiments in Study I (Experiments 1-6), as participants had to report the detection of emotional facial expressions. Facial expression was only task-irrelevant in Experiment 7 of the AB series, in which participants had to detect a second face. Thus, biased competition by emotionally significant stimuli occurred irrespective of whether facial expressions were task-relevant or not.

inhibition of interference, respectively (Kranczioch, Debener, Schwarzbach, Goebel, & Engel, 2005). Another recent fMRI study confirmed that the advantage of emotional T2 during the AB interval involved activation of the amygdala (Schwabe et al., 2011). The results of this thesis suggest that endogenous, effortful control, reflected in synchronized GBA, is necessary to refocus on the current task. Adding to the notion that threat-related stimuli automatically bias exogenous attention (Cisler & Koster, 2010), these findings also highlight that our mind is capable of continuing the task at hand in the presence of emotional distractors.

The experimental work opens several promising avenues for further explorations. One open question related to Study I is whether the impact of emotional facial expressions on the AB is mediated by gamma-band synchronization in fronto-parietal regions similar to the effects observed in Study III. Since Study I examined whether emotional targets have a competitive advantage compared to neutral targets during the AB period, emotional T2 were neither task-irrelevant nor imposed a distracting but rather facilitating effect on performance. Thus it would be interesting to assess the opposing effect of emotionally significant T1 stimuli on the AB in a future EEG or MEG study. A promising experimental design for such a study would be that of Most et al. (2005) because their emotionally unpleasant stimulus was completely irrelevant to the task. In their study, participants had to search for a single target in a RSVP. An irrelevant unpleasant or neutral picture preceded the target by two or eight items (i.e., at comparable positions as T1 is typically presented). Task-irrelevant, unpleasant stimuli captured attention and induced a deficit in reporting the target (i.e., comparable to the AB). In addition, emotional distractors elicited responses in the amygdala and the rostral ACC, especially in participants scoring high in harm avoidance (Most et al., 2006). Drawing on findings from Study III and from the fMRI study by Kranzcioch et al. (2005), it is hypothesized that task-irrelevant emotional distractors increase gamma-band synchronization in fronto-parietal and theta-band synchronization in medial-temporal regions. Such a future study could also provide insight into the temporal dynamics of the functional connectivity between underlying brain areas by employing connectivity measures such as coherence or phase coupling measures. It would be intriguing if similar neurophysiological patterns for the interference of emotional distractors on the allocation of temporal and spatial attention could be observed.

In Study III, coherence and phase coupling measures, analyzing the connectivity between brain areas, could be employed to investigate network interactions between medial temporal and fronto-parietal regions and possible differences of such network indices

between S and L groups. In particular, it may be assumed that directed interactions exist between medial temporal and fronto-parietal regions, and that medial-temporal theta-band activity correlates with fronto-parietal GBA. Finally, nesting of gamma oscillations in the phase of alpha cycles has been suggested as a mechanism for prioritizing salient unattended stimuli (Jensen, Bonnefond, & VanRullen, 2012). It would be interesting to explore whether such a mechanism also holds true for threat-related distractors.

Future research should aim to establish a closer link to anxiety disorders. One important question that could not be answered in Study III is whether the increased attentional bias in the S group is indeed a vulnerability factor for prospective anxiety disorder. Prospective long-term studies with genetically predefined participants may shed light on this. Importantly, other risk factors for the development of anxiety disorders include environmental ones, such as aversive life events, that interact with the genetic configuration of an individual (Caspi & Moffitt, 2006). Although the investigation of genetic variations in healthy populations gained important insights in mechanisms of psychiatric disorders such as anxiety and depression, it should be noted that such interactions are extremely complex given the size of the human genome. By considering environmental factors, prospective long-term studies, at least partially, account for the complexity of gene-environment interactions.

In the last years, results on the attentional bias to threat advanced promising therapeutic avenues for the treatment of anxiety disorders and depression. Attentional training to reduce the attentional bias to threat, referred to as attentional bias modification, has proven capable of ameliorating clinical symptoms of anxiety (Bar-Haim, 2010; Beard, Sawyer, & Hofmann, 2012; MacLeod & Mathews, 2012). In particular, variants of the dot probe task are employed, in which the target location is systematically biased toward the location of the intended training bias. If the training protocol aims at reducing the attentional bias to threat toward neutral stimuli, the probe appears more frequently at the location of the neutral stimuli. A recent fMRI study demonstrated that attentional bias modification altered lateral PFC activation to threat-related stimuli (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). PFC activation increased especially when the rule induced by training was violated (i.e., stronger PFC activation for attention toward threat when participants were previously biased away from threat and vice versa). It would thus be intriguing to replicate Study III in patients with clinical levels of anxiety before and after attentional bias modification away from threat. It is expected that the alleviation of anxiety symptoms after successful bias modification would be accompanied by a reduction of fronto-parietal GBA to

the location of fearful faces or by a reversal in favor of the neutral stimulus. Future studies like these could underpin the role of neuronal communication in the attentional bias to threat.

The studies of this thesis investigated different domains of attention. Yet, they converged in showing that the attentional bias to threat equally operates for temporal and spatial attention and mobilizes attentional control mechanisms. This work demonstrated that flexible synchronization processes underlie the attentional bias to threat and thus established important guideposts for further work on the topic, especially for the domain of clinical anxiety.

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5-HTTLPR	serotonin-transporter-linked polymorphic region
AB	attentional blink
ABBA	alpha-beta-band activity
ACC	anterior cingulate cortex
ANOVA	analysis of variance
BA	Brodmann area
ECoG	electrocorticography
EPN	early posterior negativity
ERP	event-related potential
FDR	false discovery rate
(f)MRI	(functional) magnetic resonance imaging
(i)EEG	(intracranial) electroencephalography
GBA	gamma-band activity
L group	individuals homozygous for the long allele of 5-HTTLPR
M	mean
MEG	magnetoencephalography
MNI	Montreal Neurological Institute
OFC	orbitofrontal cortex
PET	positron emission tomography
PFC	prefrontal cortex
ROI	region of interest
RSVP	rapid serial visual presentation
SD	standard deviation
SEM	standard error of the mean
S group	carriers of the short allele of 5-HTTLPR
SOA	stimulus onset asynchrony
ssVEP	steady-state visual evoked potential
T1	first target in dual task paradigm
T2	second target in dual task paradigm
TFR	time frequency representation
VOTC	ventral occipito-temporal cortex
VTC	ventral temporal cortex

12 APPENDIX

12.1 Appendix A

Table A1. Studies investigating the AB for face stimuli (second targets only)

	Stimuli			Task								
Name	**T1**	**T2**	**Distractors/Masks**	**T1**	**T2**	**SOA (ms)**	**T2/trials (%)**	**Duration (ms)**	**ISI (ms)**	**RSVP length**	**Size (°)**	**Main findings**
Awh et al., 2004	3 numbers (experiment 2); 3 female faces (experiment 6)	3 male faces	Patterns (for numbers), mosaic-scrambled faces (for faces) presented for 59 ms	3AFC number identification	3AFC face identification	0, 59, 118, 176, 236, 294, 353, 412, 529, 706	100	71	-	4[1]	5.5x4	Numbers as T1: no AB; faces as T1: AB
Fox et al., 2005	Flowers, mushrooms	FE, HA faces	NE faces	2AFC flower discrimination	2AFC emotion detection	220, 330, 440, 550, 660, 770	63	110	-	15	n/a	AB for low anxious participants, attenuated for fearful faces in high anxious participants
Jackson & Raymond, 2006	10 square, 10 circle patterns	1 unfamiliar face	Unfamiliar faces	2AFC pattern discrimination	2AFC face detection	85, 170, 255, 340, 425, 510, 595, 680	50	85	-	15	2.9x3.4	AB for unfamiliar but not familiar faces irrespective of familiarity of distractors
Milders et al., 2006	12 green-tinted FE, 12 green-tinted NE faces	12 FE, 12 NE faces	24 mosaic-scrambled faces	2AFC gender discrimination	2AFC face detection	160, 240, 400, 560	50	80	-	22	15.6x19.7	AB for neutral faces, attenuated for fearful faces
Einhäuser et al., 2007	Faces[2], watches	Faces, watches	Face	2AFC face and/or watch identification	2AFC face and/or watch identification	Depending on RSVP frequency[3]	100	25, 33, 50, 67, 83, 67	-	5 sec	6x6	AB
de Jong & Martens, 2007	48 AG, 48 HA faces	48 AG, 48 HA faces	299 180° rotated NE faces	3AFC number of faces	2AFC emotion discrimination	240, 360, 960	100	120	-	16	531x720 px	AB, modulated by facial expression
Ryu & Chaudhuri, 2007	40 houses	6 highly distinct, 6 typical faces	Mosaic-scrambled houses and faces	3AFC house identification	3AFC face identification	100, 200, 300, 400, 500, 600, 700, 800	100	100	-	10	7x8.5	AB for distinct and typical faces
Landau & Bentin, 2008	60 tulips, 60 sunflowers	115 faces, 115 watches	240 furniture objects	2AFC flower discrimination	2AFC T2 detection	79, 237, 553	50	79	-	20	3x3.2	AB for watches but not faces (experiment 1); small AB for faces when T1 also faces (experiment 2); AB for faces when T1 load increased (experiment 4)
Maratos et al., 2008	1 AG, 1 HA, 2 NE schematic faces	1 AG, 1 HA, 2 NE schematic faces	Feature-scrambled schematic faces	2AFC number of faces	3AFC emotion discrimination of last face viewed	257, 386, 514, 643, 771, 1028, 1157	75	129	-	20	5.7x7.5	AB for neutral faces, attenuated for fearful and happy faces between 257 and 386 ms

Sy & Giesbrecht, 2008	NE, HA, FE faces, pink frame	NE, HA, FE faces, green frame	NE, HA, FE faces, grey frame	2AFC gender discrimination	2AFC gender discrimination	480, 1120	100	80	80	15	4.2x2.9	AB, modulated by target-target similarity
De Martino et al., 2009	Indoor, outdoor scenes	FE, NE faces	Mosaic-scrambled scenes and faces	2AFC scene discrimination	3AFC face identification	350	100	70	-	15	8.5x8.5	AB for neutral faces, attenuated for fearful faces
Ganis & Patnaik, 2009	1 male familiar face (Tom Cruise)	1 male unfamiliar face	15 male unfamiliar faces	None	2AFC face detection	200, 600, –200	50	100	-	16	10x14	AB
Raymond & O'Brian, 2009	10 square, 10 circle patterns	12 value-laden male faces, 24 novel male faces	20 mosaic-scrambled faces as masks	2AFC pattern discrimination	Old/new decision	200, 800	100	85	-	4[4]	2.9x3.6	AB for loss-associated but not win-associated faces of prior value learning task
Serences et al., 2009	3 numbers (experiment 2); 3 faces of opposite gender than T2 (experiment 3)	3 faces	Mosaic-scrambled faces presented for 59 ms	3AFC number or face identification[5]	3AFC face identification	0, 59, 118, 176, 236, 294, 354, 412, 472, 529	100	47 (T1), variable (T2)	-	3[1]	5.5x4	Numbers as T1: no AB; faces as T1: AB
Miyazawa & Iwasaki, 2010	5 flower symbols	3 face icons	Symbols	5AFC symbol identification	4AFC face discrimination	79, 140, 210, 350, 560	75	70	-	16	2x2	AB for neutral and fearful faces, attenuated for happy faces
Srivastava & Srinivasan, 2010	2 letters	4 HA, 4 SA faces	Random lines presented for 200 ms	2AFC letter identification	2AFC emotion discrimination	0, 100, 200, 400, 600, 900	100	~64 ms (variable)	-	4[1]	4.5x5.9	AB for sad faces, attenuated for happy faces
Stein et al., 2010	12 green-tinted NE faces flanked by 2 NE faces	12 FE, 12 HA faces	72 mosaic-scrambled NE faces	2AFC gender discrimination of central face	2AFC face detection	166, 581	50	83	-	22	3.9x5.5	AB for happy faces in both load conditions, attenuated for fearful faces in low-load condition
Darque et al., 2011	10 square, 10 circle patterns	1 upright NE, 1 inverted NE face	Lines (for patterns), patches (for faces) as masks	2AFC pattern discrimination	2AFC eye position discrimination	85, 510	100	85	-	4[4]	2.5x3	AB for inverted but not upright faces
Milders et al., 2011	8 green-tinted NE faces	8 FE, 8 HA, 8 AG faces with directed or averted eye gaze	24 mosaic-scrambled faces	2AFC gender discrimination	2AFC face detection	160, 560	86	80	-	22	11.6x15.7	AB, no modulation by gaze or emotion
Van Dam et al., 2012	10 NE, 10 HA, 10 FE male faces	10 NE, 10 HA, 10 FE male faces	54 180° rotated NE faces	3AFC emotion discrimination	3AFC emotion discrimination	321, 642	80	107	-	16	8x11.4	AB for neutral faces, attenuated for fearful and happy faces

Notes: [1] dwell time paradigm: targets presented horizontally and vertically; [2] faces wearing scarves and sunglasses; [3] different RSVP procedure; [4] only four stimuli used: 2 targets, 2 masks, no distractors; [5] in some blocks speeded responses needed; T1, first target; T2, second target; SOA, stimulus onset asynchrony; ISI, interstimulus interval; RSVP, rapid serial visual presentation; AB, Attentional Blink; FE, fearful; HA, happy; NE, neutral; 2AFC, 2 alternatives forced choice; SA, sad;

12.2 Appendix B

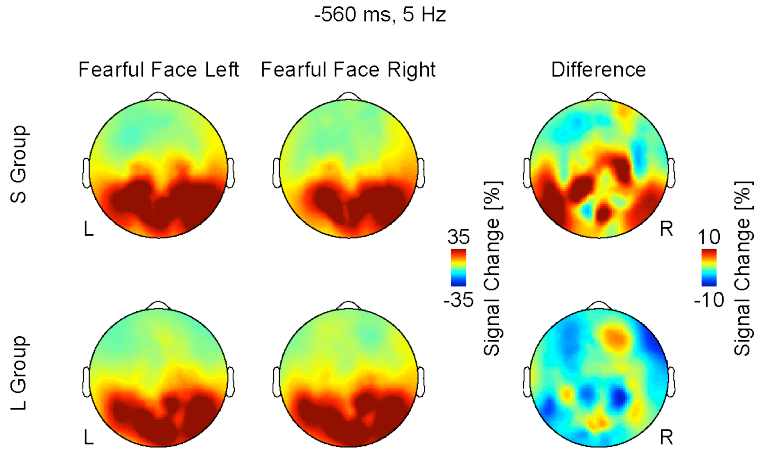

Figure B1. Topographic maps during the cue interval for the contrast fearful face left vs. fearful face right show differential activity over temporal and centro-parietal regions for the S group (upper panel) around –560 ms, which is absent in the L group (lower panel).

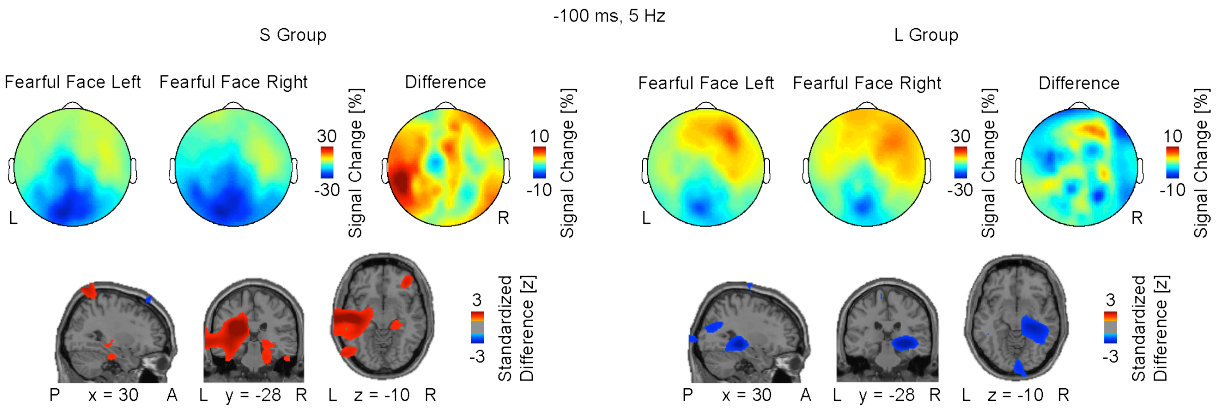

Figure B2. Topographic maps and results of the source reconstruction during the cue interval for the contrast fearful face left vs. fearful face right separately for the S group (left column) and the L group (right column) in the theta band around –100 ms.

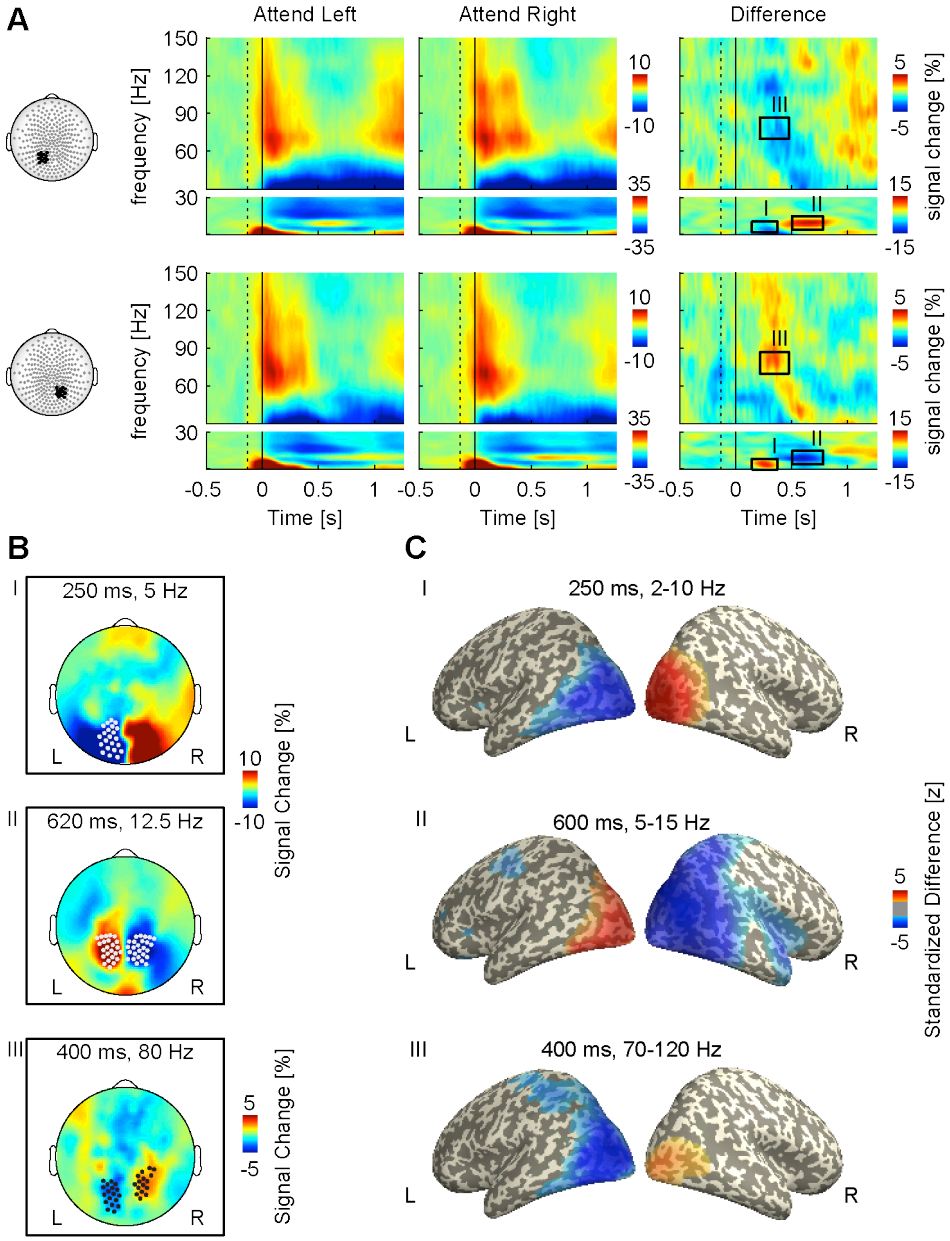

Figure B3. Results for the contrast of attend left vs. attend right trials during the target interval. (A) TFRs depict the conditions attend left vs. attend right and their difference for clusters of left and right parietal sensors (upper and lower panel, respectively). The dashed and solid lines mark face cue and target onsets, respectively. (B) Topographic maps illustrate differences in the theta, alpha and gamma band for different time windows each (cf. black rectangles in TFR). (C) The results of the source reconstruction are shown for each of the effects. Frequency bands instead of the peak frequencies have been chosen for illustration purposes.

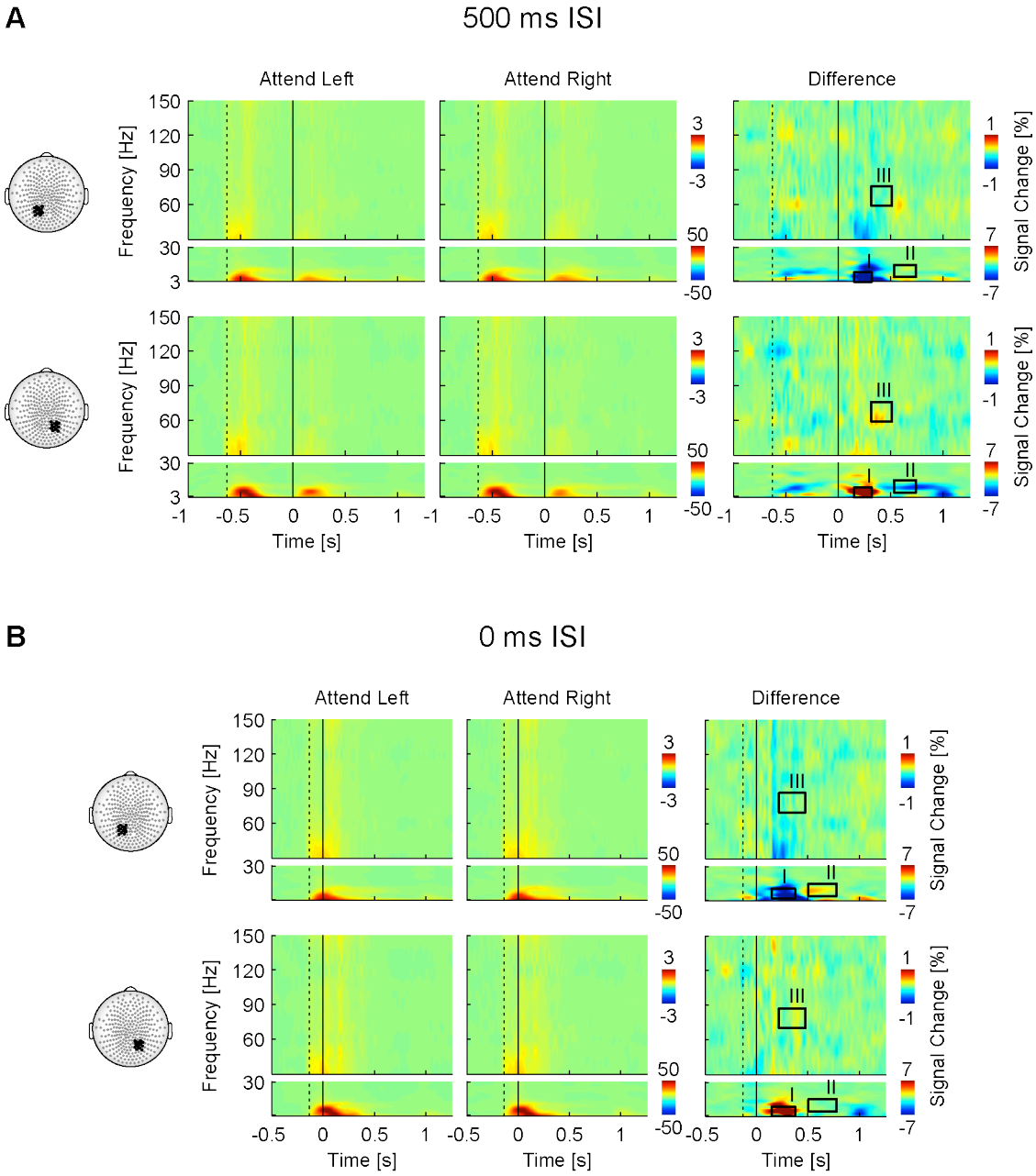

Figure B4. Evoked power for the attention contrast during the target interval. (A) TFRs depict the conditions attend left vs. attend right and their difference for (A) the long ISI and (B) short ISI conditions for clusters of left and right parietal sensors (upper and lower panel). The dashed and solid lines mark face cue and target onsets, respectively. The time frequency windows of the effects of the total power are overlaid for comparison (cf. black rectangles). Abbreviations: ISI, interstimulus interval.

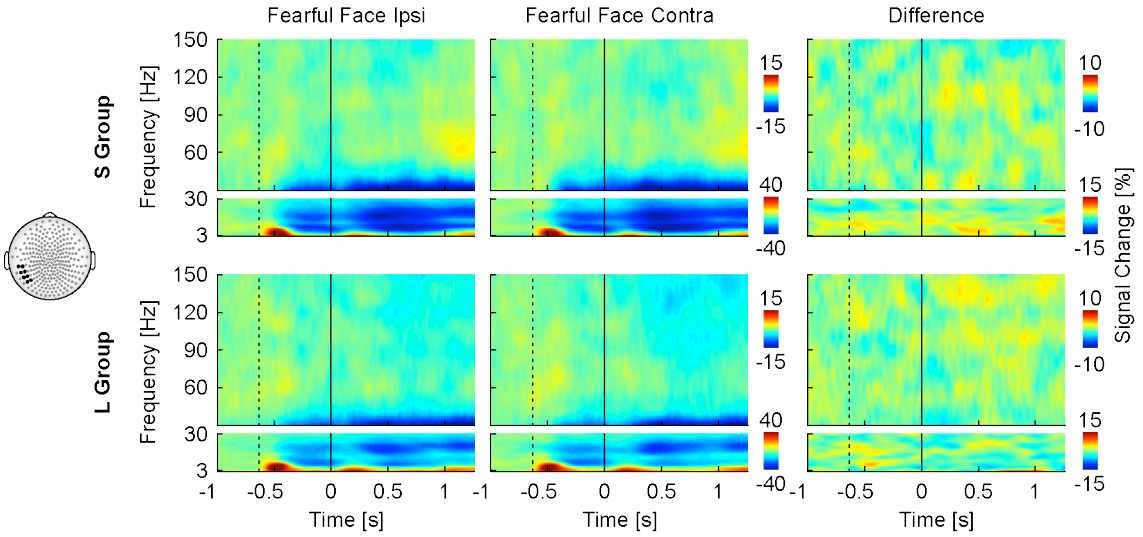

Figure B5. TFRs for the contrast of fearful face ipsi- vs. fearful face contralateral to target by genotype in long SOA trials during the target interval for the S (upper panel) and L group (lower panel), shown for a cluster of left temporal sensors. The dashed and solid lines mark face cue and target onsets, respectively.

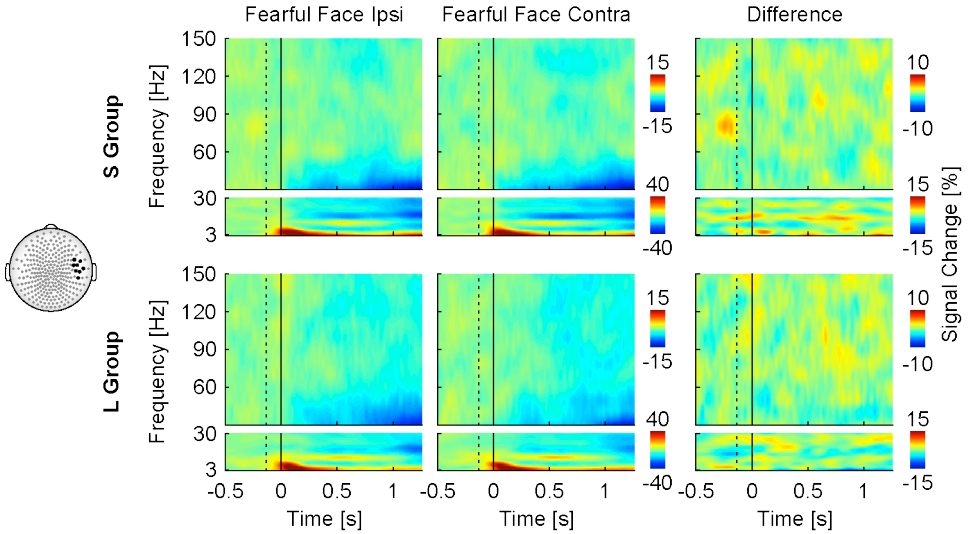

Figure B6. TFRs for the contrast of fearful face ipsi- vs. fearful face contralateral to target by genotype in short SOA trials during the target interval for the S (upper panel) and L group (lower panel), shown for a cluster of right temporal sensors. The dashed and solid lines mark face cue and target onsets, respectively.

Erklärung nach § 9 Abs. 1, Nr. c der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich, dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Hamburg, den 7.12.2013

Unterschrift

Eidesstattliche Erklärung nach § 9 Abs. 1, Nr. d der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe. Andere als die angegebenen Quellen und Hilfsmittel habe ich nicht benutzt und die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht.

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Unterschrift