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Attentional threat biases and their role in anxiety: A neurophysiological perspective

Matthias J. Wieser^{a,b,*}, Andreas Keil^c^a Department of Psychology, Educational and Child Studies, Erasmus School of Social and Behavioral Sciences, Erasmus University Rotterdam, Rotterdam, the Netherlands^b Department of Psychology, University of Würzburg, Germany^c Center for the Study of Emotion and Attention, University of Florida, Gainesville, FL, USA

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ABSTRACT

One of the most important function of selective attention is the efficient and accurate detection and identification of cues associated with threat. However, in pathological anxiety, this attentional mechanism seems to be dysfunctional, which leads to an exaggeration of threat processing and significant functional impairment. This attentional threat bias (ATB) has been proposed as a key mechanism in the etiology and maintenance of anxiety disorders. Recently, evidence has accumulated that the behavioral assessment of ATB by means of reaction times is compromised by conceptual and methodological problems. In this review paper we argue that a brain-based assessment of ATB, which includes different mechanistic aspects of biased attention, may provide neuro-mechanistic knowledge regarding the etiology and maintenance of anxiety, and potentially start identifying different targets for effective treatment. We summarize examples for such an approach, highlighting the strengths of electrophysiological measurements, which include the sensitivity to time dynamics, specificity to specific neurocomputational mechanisms, and the continuous/dimensional nature of the resulting variables. These desirable properties are a prerequisite for developing *trans*-diagnostic biomarkers of attentional bias, and hence may inform individually tailored treatment approaches.

1. Threat biases in attention and perception: a mechanistic approach

The human nervous system is the product of millions of years of natural selection, driven by ever-changing environmental pressures. As such, it has evolved superbly refined mechanisms in the service of survival, optimizing how humans anticipate, perceive, memorize, and act upon threats and opportunities. One subset of these mechanisms has evolved to address the fact that sensory and cognitive systems have limited capacity but are exposed to an enormous wealth of data that exceed their bandwidth by several orders of magnitude (Posner, 1980). The concept of selective attention has been used to describe these mechanisms, which prioritize and select specific representations for in-depth processing, at the cost of other, competing information (Reynolds and Heeger, 2009). Research has identified many different types of selective attention mechanisms which are often defined by the task-relevant stimulus dimension, such as stimulus location, feature content, object category, or position in time, among other dimensions (Anllo-Vento and Hillyard, 1996; Müller et al., 1998). Each of these types of

attention may involve several neurocomputations that ultimately result in the attentive selection of a given sensory representation, memory, cognitive process, or motor program (Briggs et al., 2013; Reynolds and Heeger, 2009). How some of the best understood mechanisms involved in attention selection may inform research on attention bias to threat will be at the focus of the present review.

One of the most obvious functions of attention mechanisms is the efficient and accurate detection and identification of cues associated with threat and danger. Work in healthy observers has shown that threatening stimuli are detected more rapidly and accurately (Anderson, 2005; Öhman et al., 2001), are perceived more vividly (Markovic et al., 2014), are remembered better (Bradley et al., 1992), and interfere more strongly with competing tasks than neutral stimuli (Müller et al., 2008; Pessoa and Ungerleider, 2004). Together, these findings suggest that threat cues are prioritized at several levels of sensory and cognitive processing, resulting in a powerful adaptation that maximizes the likelihood of survival of the individual and the species. Consistent with the adaptive role of biases towards threat, there is mounting evidence that the disruption or dysregulation of these

* Corresponding author at: Erasmus University Rotterdam, Erasmus School of Social and Behavioral Sciences, Department of Psychology, Education, and Child Studies, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands.

E-mail address: wieser@essb.eur.nl (M.J. Wieser).

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biases is at the core of many psychiatric problems, including fear, anxiety, post-traumatic disorders, and mood disorders. As a consequence, there has been growing interest in the systematic and quantitative assessment of threat biases, and even in their use as a treatment target, with many intervention studies—including randomized clinical trials—conducted to date. In stark contrast to these developments, there is little consensus in the field regarding how to conceptualize and measure dysfunctional (excessive or deficient) attentional biases in individuals with mental health problems. As detailed below, current approaches towards this goal are inconsistent with the current science of selective attention at the conceptual and neurobiological level, while also lacking validity and reliability at the psychometric level. Moreover, viewing attention as a unitary phenomenon is also at odds with recent behavioral (Herrmann et al., 2010; Ling and Carrasco, 2006) and neurophysiological studies (Andersen et al., 2011; Hopf et al., 2004), which have demonstrated that mechanisms of attentive selection (i) vary with the to-be-attended stimulus dimension, (ii) are highly dependent on the experimental task and task context, and (iii) possess intricate and variable time dynamics. This complexity is expected from an evolutionary perspective, because most adaptive systems—such as the mammalian immune system (Howell and Shepherd, 2018)—possess more than one trick, and thus cannot be fully understood, nor adequately described, by any individual output parameter (Lang, 1993; Keil and Miskovic, 2015).

The present review addresses this problem by introducing neurophysiological metrics of attention bias dysfunction which possess favorable psychometric properties, and which reflect specific, operationally defined mechanisms. Table 1 presents a subset of these mechanistic concepts, established by experimental and computational research into selective attention in human and animal models. Many of the concepts listed are overlapping, may co-exist, and several are defined at different levels of observation, such as the molecular level (cholinergically mediated increase in neural response gain) versus the systems level (frontocortical bias signals entering visual cortex).

The goal of the present review is to address the potential of applying

experimentally and computationally defined neurophysiological mechanisms involved in selective attention to the assessment of attentional biases to threat in individuals with mental health problems. To this end, we first review the extant conceptual models that have guided research on attention biases. It will be evident that these models are grounded in perspectives from cognitive psychology and information processing, discussed next.

2. Cognitive theories of attentional threat bias (ATB) in anxiety

Vigilance to emotionally engaging and especially highly threatening stimuli is a natural and adaptive response (Keil and Miskovic, 2015; Lang, 1993; Öhman, 1993; Öhman et al., 2001; Whalen, 1998). Anxiety however, leads to an exaggeration of threat processing, which is maladaptive and comes with significant functional impairment (Barlow, 2002; Lang et al., 2000). Several cognitive biases in anxiety have been described over the last decades, covering the domains of attention, memory, interpretation, emotional association, and inhibitory control (see for example Armstrong and Olatunji, 2012; Cisler and Koster, 2010; Staugaard, 2010; Sussman et al., 2016; Van Bockstaele et al., 2014; Williams et al., 1996). For the purpose of this paper, we focus on research on the attentional bias to threat. Authors in this field have tested the overarching hypothesis that trait hypervigilance to threat cues may be a pathogenic factor. This hypothesis is based on cognitive theories that highlight the prioritized processing of threat cues as a central mechanism in the etiology and maintenance of anxiety (for a recent review see Van Bockstaele et al., 2014). One prediction of this mode is that individuals with high levels of self-reported trait anxiety, and patients with disorders in the fear and anxiety spectrum should show evidence of this so-called attentional bias, i.e., they are expected to display preferential allocation of attention to threatening cues, compared to other stimuli.

The most prominent cognitive theories of ATB in anxiety have proposed a bottom-up threat detection mechanism, responsible for automatically facilitating attention towards threatening stimuli (Bar-

Table 1

Neurophysiological mechanisms linked to selective attention. The table shows selected example mechanisms that map onto concepts that have been used in threat bias research. The specific role of these processes for enhancing threat cue perception is described along with example neurophysiological processes and how they can be measured.

Mechanism (Concept)	Role of attention	Example neurophysiological processes and indices
Response gain (general hypervigilance)	Broadly heightens neuronal firing rates by multiplicatively increasing neuronal output signaling	Acetylcholine release in sensory area (e.g. visual cortex) or control area (e.g. FEF) (Disney et al., 2007), unselective enhancement of C1 and P1 component in human ERP (e.g., Michalowski et al., 2015; Peschard et al., 2013; Rossignol et al., 2012; Walentowska and Wronka, 2012; Wieser and Moscovitch, 2015).
Contrast gain and biased competition (threat cue selection)	Selectively heightens sensitivity of specific neuronal populations to lower inputs, prompting heightened firing rates to less sensory stimulation by facilitating specific input signals.	Inter-area interactions (bias signals) selectively change the gain in specific populations of sensory neurons that are sensitive to the threat cue. Selective amplitude changes in ERP components such as N1, N2pc (e.g., Holmes et al., 2014; Kappenman et al., 2014; Reutter et al., 2019, 2017), ssVEP (e.g., McTeague et al., 2011; Wieser et al., 2011, 2012); divisive normalization, thalamo-cortical interactions targeting pyramidal and/or inhibitory interneurons.
Short-term plasticity (detection biases)	Repeated exposure to behaviorally relevant stimulus of feature prompts heightened primary sensory response.	Facilitation of synaptic efficiency; formation of new synapses; sharpening and sparsification of neural representations. Selective changes in C1 ERP component (Thigpen et al., 2017a), ssVEP (e.g., Ahrens et al., 2015; Wieser et al., 2014a, 2014b), psychophysics, fMRI (MVPA)
Lateral inhibition/distractor suppression/ (sharpening versus generalization of threat representation)	Suppression of neural responses that do not match the behaviorally relevant stimulus. May occur subsequent to and as a result of facilitated cue perception, or may result from inhibitory interactions	Inhibitory interactions between similar feature representations along the visual hierarchy; Divisive normalization (Reynolds and Heeger, 2009); push-pull mechanisms; distractor positivity (Pd); ssVEP (Antov et al., 2020; McTeague et al., 2015; Stegmann, et al., 2020); fMRI (MVPA)
Oscillatory sampling (expectancy/ interpretation biases)	Oscillatory activity in sensory or extra-sensory areas is temporally aligned to facilitate the processing of (and motor responding to) an attended/expected stimulus, compared to unattended/unexpected stimuli.	Alignment of ongoing oscillations with predictive context cues; inter-area interactions; alpha-band and theta band changes in power and inter-site phase clustering (e.g., Friedl and Keil, 2020; Panitz et al., 2019); cross-frequency coupling.

Haim et al., 2007; Cisler and Koster, 2010; Eysenck et al., 2007; Mathews and Mackintosh, 1998; Mogg and Bradley, 2018, 2016; Öhman, 1993; Okon-Singer, 2018; Williams et al., 1988; Yiend, 2010). Some models also incorporate the vigilance-avoidance hypothesis (Mogg et al., 1997), i.e., the initial attentional bias towards threat may be opposed by avoidance in controlled attention strategies, which may reflect an attempt to reduce subjective discomfort or danger. Other models have also posited that attention biases occur at the strategic level of information processing, in which an individual's top-down goals can either serve to maintain or shift attention towards threat, and thus attentional bias is a result of issues with the regulation of attention allocation (Bishop, 2007; Eysenck et al., 2007).

Overall, many cognitive models of anxiety overlap conceptually in that they contain two basic systems: a threat evaluation system that is largely unconscious and automatic, and a goal-oriented system that is largely conscious and voluntary, with some models postulating an intermediate stage between these two systems. Based on the aforementioned models and providing a prominent example for (neuro-)cognitive models of attention to threat, Li (2018) has recently proposed a synthesis of extant models which resulted in an integrative information processing account of anxiety. This account broadly defines three cognitive processes, organized into serial processing stages. The first stage (orienting mode) of this framework is characterized by basic, sensory processing of stimuli, tagging the stimuli with “threat labels” and triggering elaborate threat analysis in the later stages. The second stage (primal mode) is the main stage of information processing with preconscious multidimensional threat processing. Mechanisms in this stage include selective attention, intermediate-level perception, progressively elaborate threat evaluation, and autonomic arousal. In the third stage (metacognitive mode) conscious threat responses dominate and high-level, voluntary and goal-oriented (e.g. avoidance) responses are executed.

Overall, the cognitive accounts discussed above are deeply rooted in the early tradition of cognitive psychology, where researchers attempted to map aspects of behavior to broad concepts that lent themselves to illustration in box-and-arrow flowcharts. Limitations of this approach have been widely noted and include for example a lack of neurophysiological plausibility, and a lack of evidence for neural processes that may correspond to cognitive concepts or distinct processing stages. Furthermore, models of ATB have been built almost exclusively on clinical observations and behavioral evidence, largely before the advent of advanced neurophysiological methods for assessing attentive processing. The question arises if these models hold up to more recent evidence, including evidence from neuroscience-based work. As we will see in the following sections, a substantial body of research has used the methods of cognitive neuroscience to identify neural correlates of cognitive processing stages postulated by cognitive attention bias models. This work in turn has strongly relied on experimental designs developed for the behavioral assessment of biased information processing, discussed next.

3. Cognitive task performance indices of ATB and their psychometric properties

The behavioral measurement of ATB has preferentially involved behavioral (i.e. response time) tasks. The by far most often used task with the goal of quantifying—and recently also of modifying—attention biases (Amir et al., 2009) is the dot-probe task (e.g., MacLeod et al., 1986). The standard dot-probe paradigm presents two lateralized cues, one of which is subsequently replaced by a probe (dot), oriented vertically or horizontally. Observers are instructed to respond to the orientation of the dot-probe as quickly as possible. Fast responses to the probes are taken to index selective attention to the preceding congruent (i.e., same-location) cue. Accordingly, relatively faster responses to probes replacing threat cues are interpreted as an attention bias towards threat (see Yiend et al., 2013 for a review). Recently, several

studies have criticized the task's lack of reliability, poor external validity, and lack of correlation with pathology (Chapman et al., 2019; Puls and Rothermund, 2018; Reutter et al., 2019, 2017; Rodebaugh et al., 2016; Schmukle, 2005; Staugaard, 2009; Van Bockstaele et al., 2014; Waechter et al., 2014; Waechter and Stolz, 2015), likely rendering RT bias unsuitable for research on individual differences. Particularly concerning for the application of attentional bias modification (ABM) measures is that due to this unreliability, symptom changes hardly correlate with alterations in RT bias (Jones and Sharpe, 2017). It may come as no surprise that studies on the effectiveness of ABM on anxiety have reported broadly disappointing outcomes (see Mogg and Bradley, 2018 for an extensive review). Often, ABM threat-avoidance training is not more effective in reducing ATB and hence anxiety than control attention training, which includes the same amount of threat-cue exposure but does not encourage threat-avoidant orienting (e.g., Reutter et al., 2019). The poor external validity of the dot-probe task, in terms of quantifying intrinsic, nondirected attentive selection irrespective of probe/cue location, was recently confirmed in a study by Thigpen et al. (2018) who used an electrophysiological measure of selective attention, the steady-state visual evoked potential (ssVEP) together with a reverse correlation approach in a modified dot-probe task. Here, each member of a pair of lateralized face cues, flickered at one of two frequencies, before one cue was then replaced by a response probe. Analysis of the ssVEPs evoked by these face cues revealed that ssVEP amplitude changes prior to the probe demonstrated heightened facilitation in fast probe trials for cues presented in the left visual field. By contrast, fast responses to right visual field probes were associated with relatively diminished ssVEP amplitude evoked by right visual field cues, suggesting less selection, or relative suppression, of the right visual field cue in fast probe-response trials, compared to slow-response trials.

Two meta-analyses on ATB by Bar-Haim et al. (2007) and Dudeney et al. (2015) showed that anxious adults and children indeed attend more to threatening information than non-anxious individuals. This effect however seems to be heavily modulated by age and other factors, as a recent large-scale study showed (Abend et al., 2019). Thus, the presence and role of an ATB in children and adolescents is under debate (Roy et al., 2015). Another meta-analysis on the content specificity of ATB (Pergamin-Hight et al., 2015) found no support for a disorder-specific threat bias in six dot-probe studies with a total sample of 115 clinically anxious individuals. In addition, the most recent meta-analysis (Kruijt et al., 2019) including ATB assessment of 1005 clinically anxious individuals reports a lack of any ATB.

Based on the aforementioned findings, MacLeod et al. (2019), Dennis-Tiway et al. (2019) and Rosen et al. (2019) concluded that based on RT-based indices, the evidence for the existence of an ATB in anxious adults or children is none, or very weak at best. Considering these challenges, they suggest that current forms of attentional bias assessment may reveal characteristics of groups rather than individuals, which seems especially problematic if attentional bias indices are used in the context of individual ABM treatment procedures. Accordingly, main priorities of further research on ATB should therefore be to 1) increase the reliability of single-session assessment measures, 2) to have multiple assessments individuals' attentional bias, and 3) apply assessments which are able to catch the dynamic nature of an ATB within a single-session. As mentioned above, cognitive neuroscience approaches have aimed at finding correlates of attention bias and furthermore, partly guided by the goal to provide better (i.e. more reliable) measures of biased threat processing. We will review the extant research in this field of research next.

4. Cognitive neuroscience studies of ATB in anxiety

The standard paradigm of cognitive neuroscience ultimately relies on using brain data to constrain and test theoretical concepts based on cognitive psychology. This paradigm has been fruitful in investigating

predictions of the cognitive theories discussed above in terms of suitable neural variables derived from EEG/ERP or fMRI/BOLD data. A plethora of studies have aimed to map the cognitive stages of information processing as described above onto empirical, brain-based indices of what are considered corresponding processes and stages of threat processing. The ERP method provides appealing measures towards this goal, given its exquisite temporal resolution (Luck, 2005). Accordingly, ERPs have been widely used to characterize the stages of attentive threat processing, and to test predictions derived from cognitive models of attention biases. Many of these studies have focused on visual ERP components such as the C1, P1 (indexing early visual processing; modulated by response gain and plasticity-related changes), N1, N2pc (indexing attentive selection of specific features, modulated by divisive normalization and inter-area interactions) and the late positive potential (LPP; broad motivational engagement with emotionally engaging stimuli, reflective of widespread interaction between perceptual, motivational, and motor signals). For recent detailed summaries of this work, the reader is referred to these extensive reviews (Gupta et al., 2019; MacNamara et al., 2013; Torrence and Troup, 2018). Across studies, the available evidence may be taken to suggest that for initial ERP components, a broad threat - non-threat discrimination seems to take place, affecting the C1, P1, and the N170 amplitudes in the case of face stimuli, whose sources seem to be in the occipital cortex including the extrastriate and occipital fusiform cortices (Carlson and Reinke, 2010; Eimer and Holmes, 2007; Holmes et al., 2008; Krusemark and Li, 2011; Miskovic and Keil, 2012; Pizzagalli et al., 1999; Pourtois et al., 2005, 2004; Wieser and Brosch, 2012). These studies point at the notion that threat processing takes place as early as the initial sweep of sensory processing (Vuilleumier and Pourtois, 2007). Anxiety seems to exaggerate these early sensory responses, as indicated by augmented P1 and C1 amplitudes in response to threat in anxious individuals (e.g., Holmes et al., 2008; Krusemark and Li, 2011; Mueller et al., 2009; Rossignol et al., 2013). These results have been corroborated by fMRI data showing enhanced visual cortical activity in response to threat in anxious patients and individuals (e.g., Etkin and Wager, 2007; Lipka et al., 2011; Straube et al., 2005). Other studies support the notion that anxious individuals exhibit a broad, *nonspecific* enhancement of early visual processing as shown in elevated P1 and C1 responses in general (Helfinstein et al., 2008; Kolassa et al., 2009, 2007; Kolassa and Miltner, 2006; Michalowski et al., 2015; Mühlberger et al., 2009; Peschard et al., 2013; Rossignol et al., 2012; Walentowska and Wronka, 2012; Wieser and Moscovitch, 2015). Studies using visual search paradigms or the dot-probe task, which both present threatening stimuli together with at least one distractor and thus create competition, have investigated the N2pc component of the target and distractor evoked brain potential attention allocation (Luck and Hillyard, 1994). Its function has been associated with selective visual processing but not attentional shifts (Kiss et al., 2008). Several studies found enhanced N2pc amplitudes in response to threatening target stimuli such as angry faces or spiders (Eimer and Kiss, 2007; Feldmann-Wustefeld et al., 2011; Holmes et al., 2014; Kappenman et al., 2014; Reutter et al., 2019, 2017; Weymar et al., 2011). This index of attentional capture has also been used to evaluate the success of attentional bias modification training (Osinsky et al., 2014; Reutter et al., 2019).

Sustained engagement with threatening stimuli is often investigated by means of the late positive potential (LPP). A modulation of the LPP by emotional stimuli begins at about 300 ms after stimulus onset, and is sustained for the entirety of stimulus presentation (Cuthbert et al., 2000; Schupp et al., 2000). It has been reported that patients with anxiety disorders or high anxious individuals show enhanced LPP amplitudes to feared compared to non-feared stimuli (e.g., Flykt and Caldara, 2006; MacNamara and Hajcak, 2009). Imaging studies revealed that this early threat detection is linked to heightened neural activity in visual brain areas including primary (V1) and associative (e.g., fusiform, lateral occipital) visual cortices (Lang et al., 1998;

Lindquist et al., 2012; Phan et al., 2002; Sabatinelli et al., 2013; Vuilleumier and Pourtois, 2007), which has been found that it can operate independently of attention and awareness (Morris et al., 1998; Pessoa, 2005; Vuilleumier et al., 2001). Due to the sluggishness of the BOLD signal, fMRI studies however are not able to disentangle the putative stages of information processing at the same fine-grained temporal resolution as can be achieved by means of ERP studies.

A large body of work has adopted hypotheses regarding the selective processing of threat cues that were proposed in the context of rodent-model work (LeDoux, 1996). Most notably, this includes the hypothesis that amygdala activation reflects defensive mobilization, regulated and kept in check via inhibitory input originating in prefrontal cortical areas. Despite the fact that in human and non-human primates the role of the amygdala is not limited to defensive processing (Paton et al., 2006), converging neuroimaging studies suggest that anxiety disorders are associated with hypoactivity in the prefrontal cortices and hyperactivity in the amygdala in response to threat (Bishop et al., 2004). Therefore, many cognitive neuroscience models of anxiety have included the inhibitory prefrontal-amygdala circuit, and its putative dysfunction, as an index of pathology in response to threat, (Etkin and Wager, 2007; Rauch et al., 2003; Shin and Liberzon, 2010). However, mounting evidence from intracranial recordings in epilepsy patients with depth electrodes in the amygdala has shown that threat-induced responses in the amygdala seem to have latencies well above 100 ms, (Kreiman et al., 2000; Kuraoka and Nakamura, 2007; Oya et al., 2002; Wang et al., 2014), which renders the amygdala's re-entrant influence on early threat discrimination in visual cortex not swift enough to contribute to early threat perception (Adolphs, 2008). Together with lesion studies which demonstrated almost intact threat recognition in patients with amygdala lesions (e.g., Bach et al., 2011; Edmiston et al., 2013; Tsuchiya et al., 2009), this suggests that early processing of threat could recruit multiple parallel pathways, some of which are located outside the amygdala (Chikazoe et al., 2014; Pessoa and Adolphs, 2010). Indeed, fear-conditioning studies have shown that visual and other sensory systems may discriminate threat from non-threat via short-term plasticity in the primary and associative sensory cortex (Dunsmoor and Paz, 2015; McGann, 2015; Miskovic and Keil, 2012; Ohl and Scheich, 2005). One assumption here is that threat learning may initially rely on amygdala activation, but over time is taken over by long-term plasticity in sensory cortices. Thus, threat representations in sensory cortices may contribute to the early threat discrimination without trial-by-trial involvement of the amygdala (Miskovic and Keil, 2012; Thigpen et al., 2017a). This led to a re-formulated tripartite model of threat processing consisting of a sensory-prefrontal-cortex-amygdala circuit that has gone dysbalanced and dysfunctional in anxiety (Li, 2018). Overall, the studies reviewed above support fundamental assumptions from cognitive models of anxiety, which assume early threat detection and somewhat later elaborated valence-tagging and voluntary attention allocation processes. Nevertheless, these studies are limited by the breadth (“early”, “late”) and debatable definition (“automatic”; “voluntary”) of the concepts used. In addition, some of the behavioral paradigms used have uncertain reliability and validity. In the next section, we discuss examples for using measures that are primarily defined at the level of neurophysiology, rather than cognitive psychology, for quantifying biased perception.

5. Using in-vivo visual neurophysiology to develop biomarkers of biased attention in anxiety

As briefly reviewed in Section 2, the past decades have seen rapid progress in defining specific neurophysiological mechanisms of selective attention, using rodent models as well as human and non-human primate data. Based on these developments, studies can be designed that target specific neurophysiological processes that are not defined by cognitive constructs, but instead link neurophysiological indices to operationally defined behaviors, with hypotheses not constrained by

cognitive psychology, but informed by knowledge from neuroanatomy, physiology, histology, etc.

As an example for this approach, we summarize recent studies employing steady-state visual evoked potentials (ssVEPs) technology to investigate aforementioned neurophysiological processes. An elaborated review of this technology is beyond the scope of this paper. The interested reader therefore is directed to the extensive reviews introducing the concept of ssVEPs, current research paradigms, and recommendations for analysis (Norcia et al., 2015; Vialatte et al., 2010; Wieser et al., 2016). The ssVEP is evoked when a visual stimulus is periodically modulated in terms of luminance or contrast (Norcia et al., 2015; Wieser et al., 2016). The resulting oscillatory signal can then be extracted from scalp EEG signals as a robust periodic response at the exact frequency of the driving stimulus (often including higher harmonics), primarily originating in pericalcarine regions of the visual cortex (Di Russo et al., 2007). Of interest for paradigms with competing stimuli, the ssVEP signal and frequency-tagging technique enable researchers to separately measure the visuocortical neural population response associated with concurrently presented stimuli (Ding et al., 2006; Wang et al., 2007; Wieser et al., 2011). Due to their excellent signal-to-noise ratio (SNR), ssVEPs also offer the opportunity to track the dynamics of visuocortical changes at the level of single trials (Keil et al., 2008; Wieser et al., 2014b). This is particularly interesting in research on the short-term plasticity in visual cortex due to (aversive) learning, and may also be an appropriate measure to tackle the dynamics of attentional bias in anxiety.

5.1. Studies of neural gain at the level of visuocortical population activity

Single stimulus paradigms are ideally suited to measure neural gain at the level of neural population activity (hundreds of thousands of neurons), e.g., by presenting one flickering or pattern-reversing stimulus at a time and recording the ssVEP. Amplitude changes in this measure reflect changes in the excitability of the stimulated neurons, mediated for example by neuromodulator release (e.g., acetylcholin) in the tissue, by changes in synaptic efficiency mediated locally (adaptation, Hebbian learning), or through top-down influences. Using ssVEPs as a measure of population-level neural gain, two studies have investigated the influence of social anxiety on the visuocortical processing of facial expressions (McTeague et al., 2017, 2011). In a first study with high socially anxious individuals, ssVEP amplitude enhancement for emotional (angry, fearful, happy) relative to neutral expressions was found only in high socially anxious individuals, and this was maintained throughout the entire 3500-ms viewing epoch. These data suggest that a temporally sustained, heightened visuocortical gain in response to affective facial cues is associated with social anxiety. Interestingly, no affective modulation of face-evoked ssVEPs was evident in non-anxious individuals, suggesting that luminance-sensitive neurons predominantly in primary visual cortex are insensitive to emotional expression, unless expression has high motivational relevance for the observer. In a follow-up study with the same paradigm, treatment-seeking patients were investigated (McTeague et al., 2017). In this study, it was found that only circumscribed social anxiety patients showed facilitated gain to aversive facial expressions. Healthy control participants as well as patients with panic disorder with agoraphobia showed no bias. Interestingly, patients with generalized social anxiety also showed no bias. More finely stratifying the sample according to clinical judgment of social anxiety severity revealed a linear increase in visuocortical bias to aversive expressions for all but the most severely impaired patients. This group showed an opposing sustained attentional disengagement.

Taken together, these studies indicate enhanced neural gain in response to affective expressions in social anxiety, which however seems not specific to angry faces. However, the most impaired patients show the opposite pattern, which may indicate perceptual avoidance. Results further demonstrate that a temporally dynamic vigilance-avoidance

pattern within the first second of stimulus processing as sometimes reported in behavioral studies, seems to not exist at the level of visuocortical population activity. In conclusion, linking characteristics of the stimulus and the observer with specific neurophysiological indices allows testing hypotheses at a more specific level, including hypotheses regarding the time course and neuroanatomical locus of biased attention.

5.2. Studies of divisive normalization/biased competition

Neurophysiological mechanisms related to selectively attending one stimulus, location, or feature out of several have traditionally been described by processes of competition for limited capacity (Desimone and Duncan, 1995; James, 1890). One widely used neurocomputational principle has been divisive normalization, the idea that attending to a stimulus or feature involves a multiplicative gain boost for that stimulus or feature, which then is normalized by the sum of all suppressive influences present in the field of view (Reynolds and Heeger, 2009). These influences include the competitive cost of non-attended stimuli, with salient (bright, high-contrast, or threatening) distractors causing stronger competition (Müller et al., 2008). Thus, divisive normalization is a useful principle that captures key properties of popular neurophysiological models of attention such as the biased competition model, or the feature-similarity gain model. Applied to studies of threat biases, divisive normalization predicts strong competitive influences of threatening stimuli on a primary non-threatening stimulus (Bradley et al., 2012). Importantly, this suppressive/competitive drive of threatening distractors is predicted to be heightened in observers with attention biases to threat.

Using the ssVEP frequency tagging technique, several studies have examined this prediction in the context of both spatial and feature-based competition between task stimuli and task-irrelevant distractors. In a first study showing spatially competing faces in the left and right visual field, Wieser et al. (2011) found heightened electrocortical engagement in response to threat (angry faces) in socially anxious participants, which was present in the first second of stimulus viewing and was sustained for the entire presentation period. No evidence for competition were found, meaning that the enhanced processing of threat did not come at cost for the processing of the competing stimulus, i.e. the heightened gain was independent of the sum of the suppressive influences across the visual field. This suggests that the facilitatory and suppressive fields varied independently—evidence of variable pools of limited capacity, or of non-overlapping neural representations for threat and concurrent non-threatening cues. To test the latter notion, a subsequent study used a fully overlapping competition paradigm in which both targets and threat cues tapped into the same population of retinotopic neurons. It was found that competition effects of threatening faces were solely observed among individuals high in social anxiety. In these observers, ssVEP amplitudes were enhanced at the tagging frequency of angry distractor faces, whereas at the same time the ssVEP evoked by the task-relevant Gabor grating was reliably diminished compared with conditions displaying neutral or happy distractor faces (Wieser et al., 2012). These two findings point to the notion that biased competition to threat is related to anxiety, but is only evident in frequency-tagged ssVEPs when stimuli compete for the same populations or retinotopic neurons, which is not the case in spatial competition paradigms. In the same vein, Woody et al. (2017) investigated biased competition in depressed observers, using a similar paradigm involving fully overlapping faces and Gabor patches: Women with depression, relative to never-depressed women, displayed difficulty inhibiting attention to all emotional distractors before a negative mood induction, with the strongest effect for negative distractors (sad faces). Following the mood induction, depressed women's attention to emotional distractors remained largely unchanged. Among women with depression, lower WM capacity predicted greater difficulty inhibiting attention to negative and neutral distractors. Results demonstrated that

women with depression display impaired attentional inhibition of emotional distractors independent of state mood and that this bias is strongest among those with lower WM capacity.

Deweese et al. (2016) investigated competition of snake pictures for attentional resources in visual cortex by recording ssVEPs to continuously flickering random dot kinematogram (RDK) stimuli in women with high or low levels of snake fear. For high-fear women, snake pictures elicited a greater and longer attenuation of task-evoked SSVEP amplitudes than other unpleasant stimuli, while this was not the case for low-fear women suggesting a sustained hypervigilance pattern for snake pictures in high-fear women. Using the same RDK paradigm, Voges et al. (2019) investigated the effect of pictures of one's own body and other bodies as distractions in 24 women with low and 20 women with high body concerns. Both groups showed a sustained SSVEP amplitude reduction, which was more pronounced for average-weight or thin bodies than for overweight bodies. For women with high body concerns, SSVEP amplitudes decreased more in the case of pictures of their own body. The results indicate covert vigilance and maintenance patterns for body stimuli, especially for bodies representing the thin ideal. Moreover, women with high body concerns attend more to information about their own body, which might maintain body dissatisfaction. Taken together, studies using the RDK paradigm show that anxiety is related to greater competition between disorder-relevant affective and neutral scene elements. Recently, Boylan et al. (2019) demonstrated that visuocortical amplification of an individual threat feature (acquired through Pavlovian fear conditioning) in an RDK did not come at the cost of concurrent feature selection at the same location in healthy observers. Also using fear conditioning in healthy observers, Miskovic and Keil (2013) showed that cortical facilitation for the threatening stimulus was selective and did not decrease by simultaneously presenting safe and associatively novel cues.

Together, these findings support the notion that threat biases can be operationally defined as the competitive influences exerted by a threat cue on a concurrent stimulus. When implementing this operationalization in non-anxious individuals, threat processing did not increase biased competition effects on concurrent stimuli. ssVEP competition effects consistent with divisive normalization were also absent when concurrent stimuli occupied different locations in the visual field. However, growing evidence shows that anxious observers may evince competition, opening avenues towards investigations of the conditions under which such competitive costs arise, and how robust they can be measured. If biased competition as reflected in ssVEP suppression is an indicator of pathological information processing in anxiety, then it can be assessed quantitatively and objectively, with neurophysiological specificity, allowing systematic and programmatic hypothesis development and hypothesis testing.

5.3. Studies of changing representations as a function of experience

While the studies discussed above investigated the cortical gain elicited by inherent threat (angry, fearful faces, aversive pictures) in anxious individuals and patients, other studies have also considered changes in neural gain as observers acquire contingencies between novel threat cues and aversive outcomes. Several studies employing aversive learning paradigms have observed that aversive conditioning prompts selectively facilitated visuocortical processing of conditioned threat cues, compared to conditioned safety cues (Ahrens et al., 2015; Gruss et al., 2016; Gruss and Keil, 2019; Kastner et al., 2015; Miskovic and Keil, 2014; Stegmann et al., 2019; Talmi et al., 2019; Wieser et al., 2014b, 2014a). Systematically probing different mechanisms along the early visual processing stream, Thigpen et al. (2017a) found that several hundreds of trials, over a period of hours are needed for direct evidence of primary visual sensory plasticity to arise when learning takes place in one laboratory session: When viewing oriented line patterns in an extended conditioning regimen, the initial C1 component (70–90 ms post-stimulus) was electively heightened for line patterns

paired with a noxious noise, in a fashion that was eye-specific, location-specific, and orientation-specific. These findings suggest that extensive aversive experience prompts biased perception at increasingly lower levels of the traditional visual hierarchy. Notably, later visuo-cortical responses, which allow for re-entrant modulation through communication among different brain regions, display changes after substantially fewer conditioning trials. As mentioned above, single-trial analysis of the ssVEP allows for a more fine-grained representation of trial-by-trial changes in cortical facilitation that may occur within an experimental learning block (Wieser et al., 2014b). Although most of this work examined healthy observers unselected for anxiety status, one study in socially anxious individuals demonstrated that selectively facilitated neural gain to conditioned threat cues may represent an adaptive function of the non-anxious brain: Using a differential aversive learning paradigm in which faces were paired with either neutral, negative or positive sentences, Ahrens et al. (2015) observed that a differentiation of neural gain in response to threat-associated faces was missing in high socially anxious participants. Recently, this result has been conceptually replicated in a context and cue conditioning paradigm, in which trait anxious participants also showed less differentiation of threatening and safe contexts (Stegmann et al., 2019).

In summary, these studies suggest that the selected visuocortical facilitation of threatening information can be learned through Pavlovian associative learning, within a single laboratory session. This can be interpreted as an adaptive mechanism, enabling observers to selectively attend new stimulus configurations that are predictive of noxious outcomes. Thus, these findings show the malleability of visuocortical function, where processes such as short-term plastic changes enable biased perception at increasingly lower levels of the traditional hierarchy as learning progresses (Miskovic and Keil, 2012). Such observations may be used to inform cognitive theories (Li, 2018), but also lend themselves to quantitative computational modeling (McTeague et al., 2018). Interestingly, ongoing studies from our laboratories with high-anxious observers have suggested that this visual discrimination learning may be compromised in those high in self-reported anxiety.

5.4. Studies of lateral inhibition between visuocortical representations

A final example for how specific neurophysiological mechanisms can be translated into hypotheses regarding threat biases comes from a study by McTeague et al. (2015). These authors used animal and computational models of orientation selectivity in the visual cortex to derive the hypothesis that a grating orientation associated with a noxious sound would over time prompt heightened visuocortical population responses. At the same time, because of the lateral inhibitory interactions between orientation selective populations organized in cortical orientation columns, it can be predicted that this learned gain increase should be accompanied by decreased responses to similar (but not dissimilar) orientations that were never paired with the noxious events. To test the hypothesis that learned biases indeed involve sustained facilitation of the threat feature, prompting lateral inhibition of similar features, one oriented grating out of a gradient of similar orientations was paired with an aversive noise. After few pairings of the grating with aversive sound, visual cortical responses to the sound-paired grating showed selective amplification of ssVEP amplitudes. Furthermore, as learning progressed, responses to the orientations with greatest similarity to the sound-paired grating (i.e. generalization stimuli) were increasingly suppressed, suggesting that inhibitory interactions between orientation-selective neuronal populations arose as a consequence of selective and sustained facilitation of synaptic efficiency when processing the threat cue. Findings overall suggested that the short-term retuning of human visual cortical neurons involves distal top-down projections as well as local inhibitory interactions. These results, recently replicated with the same (Antov et al., 2020) and different face stimuli (Stegmann et al., 2020), illustrate the potential of testing mechanistic neurophysiological hypotheses in healthy and

patient samples. Specifically, they have promise for identifying novel treatment targets.

6. Neurophysiological indices as potential dimensional biomarkers in the RDoC framework

Anxiety disorders are severely disabling and remain difficult to treat (Pine et al., 1998). Furthermore, the comorbidity of anxiety and stress-related disorders with other psychiatric disorders is high (Kessler et al., 2012). As a consequence, there is an urgent need to improve diagnostic assessment in a fashion that is (i) oriented towards identifying novel treatment targets while also (ii) providing mechanistic information regarding the specific etiology and symptoms observed in a given patient. Basing diagnostic assessment on biobehavioral markers and cross-diagnostic mechanisms may well open avenues towards these goals, with the long-term aim of personalized psychiatry, in which tailored interventions are offered based on a patient's neurobehavioral profile (Bálan et al., 2020). Neurophysiological markers of attentional bias to threat are promising objects of study in this context. Because they exist as continuous variables, they also lend themselves well to dimensional analyses as implemented in the Research Domain Criteria (RDoC) framework pursued by the U.S. National Institutes of Health.

The RDoC is a multi-level research framework for characterizing mental illness by means of quantifiable, mechanistic variables determined by the methods of neuroscience, biology, and experimental psychopathology. Its overall aim is to describe the mental health challenges of a given patient in a space spanned by dimensional constructs rather than by one categorically defined diagnosis. The current RDoC design includes a matrix with six domains: (1) positive and (2) negative valence, (3) cognitive systems, (4) social processes, (5) arousal and regulatory systems, and, just added to the original five domains, (6) sensorimotor systems (National Institute of Mental Health, 2019). One of the key advantages of the RDoC matrix is that constructs can be defined within multiple units of analysis, including genes, molecules, cells, neural circuits, physiology, behavior, and self-report. Within the RDoC's Negative Valence Systems Domain, the construct of sustained threat has been related to attention to threat (Cuthbert, 2014). As mentioned above, attentional biases can be assessed at several of these units of analysis, including behavioral (e.g., reaction times or eye tracking), and neurophysiological units of analysis, as demonstrated above. Thus, ATB could be one mechanism linking personality traits and life experiences to cognitive and neural mechanisms of information processing, which in turn may be linked to key elements of anxiety, including a stronger initial anxiety response and anxiety perseveration. Interestingly, initial work suggests that different patterns of attentional bias to threat are differentially related to these components of anxiety (Rudaizky et al., 2014).

As mentioned above, behavioral indices of attentional bias are often related to RT and errors in probe detection tasks. However, because behavioral response measures are several processing stages remote from the actual allocation of attention to target stimuli, a great deal of processes unrelated to attention (e.g., variability in action selection, action preparation, decision making, motor execution etc.) may interfere with the assessment of attentional bias towards threat. Particularly in interference tasks (e.g., the dot-probe task), responses are often made to targets that co-occur with or replace the actual stimuli of interest (threatening and non-threatening stimuli), and therefore provide an indirect measure of the actual allocation of attention to the previous threatening stimulus, which is also heavily depending of the duration of the preceding threatening stimulus (snapshot of attention). By contrast, electrophysiological activity can be measured in response to threatening stimuli themselves (rather than to targets that replace threatening stimuli)—and is a temporally more proximal measure of attention. In this vein, event related brain potentials (ERPs) have been suggested as an important tool to assess attention processes in response to threat stimuli in healthy and anxious individuals (MacNamara et al.,

2013), and can inform models of the development of, and risk for, psychopathology (Hajcak et al., 2019). Indeed, such studies examining different time course facets of defensive responses have shown that transdiagnostic groups of individuals with internalizing psychopathologies exhibit abnormalities at early stages of threat processing (Klumpp and Shankman, 2018). Importantly and in contrast to behavioral measures of ATB, ERPs show moderate-to-strong internal consistency and test-retest reliability especially for ERP amplitudes (Huffmeijer et al., 2014; Moran et al., 2013; Thigpen et al., 2017b). A recent review on ERPs of attentional bias towards faces in the dot-probe task (Torrence and Troup, 2018) concluded that while ERPs may be more reliable and consistent than solely relying on RT, there is still some inconsistent results probably due to reliance on dot-probe task. They propose that the time is ripe for the development of new tasks and methods (time-frequency analysis of EEG) that could assess differences in orientation, engagement, and disengagement and all facets of attention processes during confrontation with threat.

In this paper, we have summarized neuroscientific evidence of several attentional mechanisms and their investigation with regard to attentional bias in anxiety, and argue that steady-state visual evoked potentials (ssVEPs) with frequency-tagging may be ideally suited to overcome long-standing issues in this field of research, providing measures for assessing specific attentional mechanisms reliably, individually, and with high external validity. We argued that experimental psychopathology will benefit from including recent developments in attention neuroscience as part of its conceptual and methodological toolbox. Work in animal and human models suggest that a simplistic view of “attention” as a unitary phenomenon is highly unlikely, as is the notion that dysfunctional attention biases in a given observer can be adequately characterized by a single paradigm. Using brain-based measures with high signal-to-noise ratio and specificity to a defined neurophysiological process may enable researchers to assess specifically targeted facets of attentive processing however, and it may do so robustly at the level of single sessions and individual participants. Pursuing such a research program, grounded in animal model work, and addressing specific neurophysiological mechanisms provides a promising avenue towards establishing dimensional diagnostic assessment and personalized, tailored, treatment interventions.

7. Conclusions and future directions

In this paper we advocate a research program towards a multi-faceted neurocognitive assessment of attentional bias to threat, which includes different mechanistic aspects of biased attention. We discussed examples for such an approach, highlighting the strengths of electrophysiological measurements, which include the sensitivity to time dynamics, specificity to specific neurocomputational mechanisms, and the continuous/dimensional nature of the resulting variables. These desirable properties are a prerequisite for developing *trans*-diagnostic biomarkers of attentional bias, and hence may inform individually tailored treatment approaches.

A brain-based approach to quantifying biases would also enable a research line to test predictions from a recent model of the heterogeneity of ATB in anxiety (Dennis-Tiwary et al., 2019), which assumes that two potential processes may underlie the heterogeneity and temporal characteristics of ATB in anxiety, namely threat-safety discrimination and under- and overregulation of attention allocation. Thus, expanding a multi-faceted neuromechanistic account of attention to threat by including neurophysiological indices of cognitive control (e.g., the error-related negativity) may assist in more comprehensively capturing the causal and contributory factors involved in the etiology of anxiety.

While previous studies have recognized that both vigilance and avoidance are critical in maintaining anxiety (e.g., Bögels and Mansell, 2004; Evans et al., 2016; Mogg et al., 1997), there are currently no brain-based measures that objectively index these behavioral

dispositions, or define how these alternative strategies maintain anxiety. Perhaps for this reason, there has been little consideration of how different dominant behaviors might be most successfully addressed in assessment and treatment. Considering the range of existing therapies (e.g., cognitive restructuring, exposure, applied relaxation, safety behaviors, video feed-back, etc.; see e.g., Acarturk et al., 2009; Weisman and Rodebaugh, 2018), some components might well be uniquely effective if therapy could be targeted on a specific subtype (e.g., Aderka et al., 2013; Clark et al., 2006; McManus et al., 2009). We envision objectively distinct EEG measures of attentional bias (vigilance and avoidance), reflecting different neurophysiological mechanisms maintaining separate behaviors. These different diatheses could potentially be addressed by uniquely focused, tailored treatments.

Together, we propose that research along these lines will provide neuromechanistic knowledge regarding the etiology and maintenance of anxiety, and potentially start identifying different targets for effective treatment. If individual differences in attentional bias such as vigilance and avoidance differentially activate defensive and appetitive neural circuits, the mechanism of the reinforcing event is different, with implications for both successful treatment and prognosis. To the extent that anxiety is mediated by heightened defensive reactivity to threat cues, reducing hypervigilance and hyperarousal through prolonged exposure may be an appropriate treatment regime. On the other hand, to the extent that anxiety prompts avoidance behavior maintained instead by its rewarding consequences (e.g. no exposure to social threat stimuli), successful treatment may first involve significant cognitive restructuring prior to exposure, without the ability to escape, as well as a focus on eliminating safety behaviors. ssVEP indices of vigilance/avoidance could be used in assessment contexts to identify individual treatment targets and for monitoring intervention outcome in a personalized treatment context. Objective, validated measures of specific cognitive processes related to threat are also crucial for developing dimensional, objective tools for diagnostic assessment and for monitoring treatment efficacy.

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