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Brain dynamics of visual attention during anticipation and encoding of threat- and safe-cues in spider-phobic individuals

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This study systematically investigated the sensitivity of the phobic attention system by measuring event-related potentials (ERPs) in spider-phobic and non-phobic volunteers in a context where spider and neutral pictures were presented (phobic threat condition) and in contexts where no phobic but unpleasant and neutral or only neutral pictures were displayed (phobia-irrelevant conditions). In a between-group study, participants were assigned to phobia-irrelevant conditions either before or after the exposure to spider pictures (pre-exposure *vs* post-exposure participants). Additionally, each picture was preceded by a fixation cross presented in one of three different colors that were informative about the category of an upcoming picture. In the phobic threat condition, spider-phobic participants showed a larger P1 than controls for all pictures and signal cues. Moreover, individuals with spider phobia who were sensitized by the exposure to phobic stimuli (i.e. post-exposure participants) responded with an increased P1 also in phobia-irrelevant conditions. In contrast, no group differences between spider-phobic and non-phobic individuals were observed in the P1-amplitudes during viewing of phobia-irrelevant stimuli in the pre-exposure group. In addition, cues signaling neutral pictures elicited decreased stimulus-preceding negativity (SPN) compared with cues signaling emotional pictures. Moreover, emotional pictures and cues signaling emotional pictures evoked larger early posterior negativity (EPN) and late positive potential (LPP) than neutral stimuli. Spider phobics showed greater selective attention effects than controls for phobia-relevant pictures (increased EPN and LPP) and cues (increased LPP and SPN). Increased sensitization of the attention system observed in spider-phobic individuals might facilitate fear conditioning and promote generalization of fear playing an important role in the maintenance of anxiety disorders.

Keywords: fear; emotion; attention; phobia; event-related potentials (ERPs)

INTRODUCTION

Animal data suggest that defensive behavior is dynamically organized in several stages depending upon the proximity of the threat as outlined in the threat imminence model (Fanselow, 1994; Lang *et al.*, 1997). At the first stage, when the organism enters a context where a threat has been encountered previously but has not been detected yet (pre-encounter defense) preemptive behavior including threat-nonspecific vigilance is engaged. As soon as the threat-cue is identified (post-encounter defense), the organism freezes and increased selective attention is allocated to the threat. If the threat-cue does not disappear or even approaches, defensive response mobilization is engaged. When rats enter an area that was previously associated with danger, they show cautious exploratory behavior (pre-encounter defense). When they detect a threat-cue, the typical response pattern is characterized by freezing and an increased attention toward the source of danger (post-encounter defense). When the predator reaches a certain location, so that contact is inevitable, rats escape (if possible) or fight. When these options are not available, they completely immobilize (Fanselow *et al.*, 1988; Blanchard and Blanchard, 1989).

In humans, defensive behavior seems to be organized in a similar way. For example, specific-phobic individuals show increased visual scanning in a context in which phobic stimuli are likely to occur (Tolin *et al.*, 1999; Pflugshaupt *et al.*, 2007). When the phobic object is detected, potentiation of the startle response is observed (Hamm *et al.*, 1997) that parallels freezing in animal research. A recent functional magnetic resonance imaging (fMRI) study performed by Mobbs *et al.* (2010) demonstrated that increasing proximity of a live tarantula results in an enhanced subjective fear and increased fear circuit activity. The fear circuit was also demonstrated to monitor the threat movement with respect to its direction showing greater activation when the tarantula was on approaching *vs* descending trajectory, independent of its absolute proximity.

Recent studies that have begun to explore the brain dynamics of attentional modulation of stimulus processing using event-related potentials (ERPs) also support this dynamic view of defensive behavior. Several previous ERP studies showed that spider-phobic participants exposed to a context in which phobia-relevant stimuli are likely to occur respond with greater P1/N1 amplitudes not only to fear-relevant but also to fear-irrelevant pictures than non-anxious controls (Kolassa *et al.*, 2006; Michalowski *et al.*, 2009; Weymar *et al.*, 2013). This observation is in line with the hypothesis that phobic individuals show a hypervigilance to all visual stimuli when they are in a context in which visual phobic stimuli might occur (pre-encounter defense). In the same vein, if non-anxious individuals are instructed that an aversive shock might occur in one context but not in another context, the P1-amplitudes are also elevated to all pictures presented in the threat context (irrespective of their emotional content) relative to the safe condition (Bublatzky and Schupp, 2012).

Supporting the dynamic view of defensive reactivity in our previous study, we found (Michalowski *et al.*, 2009) that the brain response shifts after the fear-unspecific hypervigilance (increased P1) into a fear-specific enhancement already at the very early processing stage starting with greater early posterior negativity (EPN, ~200–300 ms) toward feared than neutral pictures. The EPN effect suggests an early involuntary tagging of fear-relevant stimuli that might assist in selecting them for preferential processing at later processing stages. In fact, several previous ERP studies showed that specific-phobic individuals allocate more attentional resources for evaluative processing of phobia-

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relevant pictures than non-anxious controls, an effect that was indexed by an increased late positive potential (LPP, ~400–600 ms; Kolassa *et al.*, 2005; Kopp and Altmann, 2005; Miltner *et al.*, 2005; Michalowski *et al.*, 2009). In general, these data confirm that once the threat is detected (post-encounter defense mode), attention is selectively captured by the threat-cue.

Although we found evidence of general hypervigilance in specific phobia individuals in a context when phobic threat was expected, we did not manipulate these expectations experimentally in our previous study (Michalowski *et al.*, 2009). Therefore, it was not possible to discriminate whether spider-phobic participants responded with increased vigilance due to their expectations of their feared objects or whether they showed a general hypervigilance to all stimuli irrespective of the context. Thus, in this study, we systematically investigated the sensitivity of the phobic vigilance system by exploring vigilance and selective attention effects in spider-phobic and non-phobic volunteers during contexts where phobic objects were expected or not. We created a context in which spider stimuli could occur (phobic threat condition), a context in which other unpleasant stimuli but no spider pictures could occur (non-phobic threat condition) and a context in which neither unpleasant nor any phobic stimuli were presented (safe condition). To ensure that the spider-phobic individuals did not expect any occurrence of a phobic object in the non-phobic threat and in the safe condition, we carefully designed a cover story, in which our participants were led to believe that the study investigates the relationship between the attention style and the visual stimulus processing.

Using the P1 as an index of hypervigilance, we analyzed spider-phobic and non-fearful control subjects during the three conditions described above (phobic threat *vs* non-phobic threat *vs* safe). Animal data show that exposure to threat might sensitize the fear circuit for a longer period of time (Rau *et al.*, 2005; Rau and Fanselow, 2009). Rats exposed to repetitive footshocks exhibited increased anxiety and fear conditioning in contexts that were not paired with shocks even several days after shock exposure. To investigate such sensitization effects, we compared the P1 for subjects who were exposed to non-phobic stimuli either prior to or after the exposure to phobic pictures. In other words, in a between-subject design, one group saw non-phobic threatening and/or safe cues in blocks presented before they were exposed to phobia-relevant spider pictures (pre-exposure group). The other group viewed the same non-phobic threatening and/or safe cues presented in blocks after being exposed to phobia-relevant spider pictures (post-exposure group).

A further goal of this study was to replicate previous research showing that the initial hypervigilance to all stimuli, i.e. pre-encounter defense indexed by the unspecific group differences in the P1, is followed by a shift into post-encounter defense, prompted by the detection of the threat stimulus. If so, spider-phobic participants would show enlarged EPN and LPP during the encoding of phobia-relevant pictures compared with non-fearful controls. No group differences were expected for non-phobic neutral and non-phobic threatening materials.

Building upon previous findings demonstrating increased attention to threat-instructed pictures obtained by Bublatzky and Schupp (2012), we also investigated whether such context effects also affect visual signals that predict a certain outcome. Learning about threat-contingencies through various forms of observation or communication is of high relevance to prevent future harm and danger. We, therefore, also measured the dynamics of the brain responses to signal cues in threatening and non-threatening conditions to investigate whether context variables would not only modulate the processing of the target cues in the predicted way but would also affect the processing of signal cues providing information about the upcoming event. Each picture presented to our participants was preceded by a fixation cross presented in one of three different colors (blue or green or dark yellow) that signaled the category of the upcoming picture (see Methods section for details). We planned to analyze differences in the P1-amplitude between the spider phobia and the control group to examine whether the P1-effects observed during picture processing would already be present during these perceptually simple signal cues.

Assuming that the increased P1 reflects hypervigilance to all external cues, we did not expect that presenting cues signaling the category of upcoming pictures would diminish the effects of increased P1 during picture processing. We may rather expect spider phobics to respond with even larger P1 amplitudes to these signal cues during and also after the exposure to spider stimuli. Moreover, we expected to observe preferential processing of threat-associated signal cues as reflected by elevated EPN- and LPP-amplitudes when compared with cues signaling neutral events. We also expected that threat signaling when compared with safety cues would elicit increased stimulus-preceding negativity (SPN) as another ERP component reflecting anticipatory attention during cues signaling task-relevant stimuli within a predictable time interval [see Brunia and van Boxtel (2001) for a review]. Several studies found an increased SPN during anticipation of emotionally arousing stimuli, such as an electric shock (Rockstroh *et al.*, 1989; Baas *et al.*, 2002), noise (Regan and Howard, 1995) or emotional pictures (Simons *et al.*, 1979; Lumsden *et al.*, 1986).

METHODS

Participants

A total of 50 participants were selected from a questionnaire screening of 532 students performed during several courses at the University of Greifswald. Students were screened twice within a period of at least 4 weeks. During the first screening, students completed the German version of the 31-item spider phobia questionnaire (SPQ; German version, Hamm, 2006) administered by personnel from the University of Greifswald that was later not associated with recruitment and EEG assessment. During the second screening, students were given the Test of Attention Styles (van de Bosch *et al.*, 1993) by the first author of this article. A cover story was prepared (all participants were instructed that they have been selected because of their good selective attention performance) to ensure that animal fearful students did not establish any relation between their spider fear and the study. Informed consent about viewing of spider pictures was obtained later, just before running the presentation of the block that included spider pictures. Twenty-five participants (22 females) who reported elevated spider fear and scoring above the 85th percentile of the distribution on the SPQ ($M = 20.0$, s.d. $= 3.2$ for females and $M = 17.0$, s.d. $= 2.6$ for males) were allocated to the spider phobia group. The remaining 25 participants (22 females) of the control group reported low spider fear, i.e. scoring below the 33rd percentile of the distribution on the SPQ ($M = 3.9$, s.d. $= 1.6$ for females and $M = 3.3$, s.d. $= 1.2$ for males). The study protocol was approved by the institutional ethics committee.

Experimental stimuli and procedure

A total of 160 color pictures were selected, including 96 neutral (e.g. landscapes, buildings and people) and 32 unpleasant pictures (e.g. human threat) chosen from the International Affective Picture System (Lang *et al.*, 2005) as well as 32 phobia-relevant spider pictures taken from our own picture pool (see Hamm *et al*, 1997; Globisch *et al.*, 1999; Michalowski *et al.*, 2012). The selected pictures were allocated to the three separate experimental conditions that were run counterbalanced across participants. In the safe condition, 32 neutral pictures were presented in one block without any emotional pictures. In the non-phobic threat condition, 32 neutral and 32 unpleasant pictures were presented. In the phobic threat condition, 32 neutral and 32 spider pictures were presented. In each condition, pictures

Table 1 Numbers of safe- and non-phobic threat blocks presented to the spider-phobic and control participants before and after spider exposure

Group	Safe block ($N = 50$)		Non-phobic threat block ($N = 50$)	
	Pre-exposure participants	Post-exposure participants	Pre-exposure participants	Post-exposure participants
Spider phobia ($N = 25$)	13	12	15	10
Control ($N = 25$)	13	12	12	13

were presented twice in a pseudo-random order with the restriction that the same picture could not occur on two consecutive trials. The order of the three conditions varied across participants, so that there were six different presentation orders, and each condition was presented either at the beginning or in the middle or at the end of the experiment. The safe block (only neutral stimuli) was presented to 26 participants prior to the exposure to spider pictures (13 controls/13 spider phobics see Table 1) and to 24 participants after the exposure to spider pictures (12 controls/12 spider phobics) resulting in a 2×2 between-subjects factorial design including Group (25 spider phobics *vs* 25 controls) and Order (26 participants viewing safe block prior to the presentation of spider pictures *vs* 24 participants viewing safe block after the exposure of spider pictures). The non-phobic threat block (neutral and unpleasant but non-phobic stimuli) was presented to 27 participants prior to the exposure to spider pictures (12 controls/15 phobics) and to 23 participants after the exposure to spider pictures (13 controls/10 phobics) also resulting in a 2×2 between-subjects design including Group (25 spider phobics *vs* 25 controls) and Order (27 participants viewing non-phobic threat block prior to the exposure to spider pictures *vs* 23 participants viewing non-phobic threat block after they were exposed to spider pictures). Order distribution did not vary significantly between spider phobia and control participants; $\chi s2(1) < 1$, ns. Each picture was displayed for 1500 ms, preceded by a colored fixation cross (1000 ms) and followed by an inter-trial interval of 750, 1000 or 1250 ms (in random order). The color of the fixation cross (blue or green or dark yellow equated in brightness) was informative in terms of signaling the category of an upcoming picture. Assignment of colors to the specific stimulus category (neutral, unpleasant, spider) was explained just prior to each experimental condition. Of importance, participants were not informed about the color signaling a spider picture before the phobic threat condition was introduced.

Following the attachment of a Polar WearLink chest strap for a wireless recording of the heart rate and the 257-lead EEG HydroCel Geodesic Sensor Net (EGO: Electrical Geodesics, Inc., Eugene, OR), participants were seated in a recliner in a dimly lit and sound-attenuated room in front of a 20" computer monitor located approximately 1.5 m from their eyes. Heart rate was assessed during a 5-min resting period at the beginning of the experiment and during picture presentations. Prior to each condition of the experiment, participants were instructed about the upcoming experimental context, the type of pictures in this condition and the colors of the signals that predicted a specific picture category. In addition, participants were asked to provide written informed consent. At the end of the session, the EEG sensors and heart rate strap were removed and each participant was asked to view each picture once more as long as desired and to press a button to terminate picture presentation. After the slide offset, the participant evaluated his/her subjective experience of valence and arousal (SAM; Bradley and Lang, 1994). At the end of the rating session, participants were asked to assess post hoc how sure they have been that no spider picture would be presented in the safe and in a non-phobic threat condition on a 100-point Likert scale ranging from I was not sure (0) to I was very sure (100).[1]

Apparatus

Electrophysiological data were collected from the scalp using a 256-channel system (Electrical Geodesics, Inc.). Scalp impedance was kept below 30 kΩ for each sensor. EEG data were continuously recorded in the 0.1–100 Hz frequency range with a sampling rate of 250 Hz. The vertex sensor served as a reference electrode. Continuous EEG data were low pass filtered at 40 Hz using digital filtering before stimulus synchronized epochs were extracted from 120 ms before to 1000 ms after picture onset. The raw EEG epochs were passed through a computerized artifact detection algorithm (Junghöfer *et al.*, 2000). Eye movement and blink artifacts were reduced using a regression based procedure as implemented in BioSig (Schloegl *et al.*, 2007). On average, the analyses of ERPs during picture viewing were based on 96 valid trials (s.d. = 15) for the non-phobic threat block, 94 valid trials (s.d. = 14) for the phobic threat block and 46 valid trials (s.d. = 7.5) for the safe condition. Analyses of the ERPs during processing of the signal cues were based on 100 valid trials (s.d. = 13), 95 valid trials (s.d. = 15) and 48 valid trials (s.d. = 8.5) for the non-phobic threat, the phobic threat and the safe blocks, respectively. The percentage of valid trials was significantly larger in the non-phobic threat when compared with the other two blocks; *t*s (49) > 2.0, *P*s < 0.05. Data were baseline corrected using a 100 ms baseline before the onset of pictures (ERPs elicited by pictures) or cues (ERPs elicited by signal sues) and converted to the average reference.

Heart rate was assessed with wireless heart rate monitoring system Polar RS800CX (Polar Electro Oy, Kempele, Finland).[2]

ERP data analysis

Following prior research with this paradigm (Schupp *et al.*, 2003; Michalowski *et al.*, 2009), a two-step procedure was used to identify relevant ERP components. In the first step, repeated measures analysis of variance (ANOVAs) including Picture or Cue Category (unpleasant *vs* spider *vs* neutral) and Group (spider phobics *vs* controls) and post-hoc comparisons between emotional and neutral stimuli were calculated for each time point and each single sensor to identify the spatial and temporal characteristics of the ERP modulation as a function of Picture/Cue Category and Group. To avoid false positives and to assure a more stringent alpha-level adjustment, significant effects were only considered meaningful when observed for at least eight continuous data points (32 ms) and two neighboring sensors. These statistical waveform analyses and visual inspection revealed differences between the phobia group and non-fearful control participants in the time window of the P1 and differences in the EPN, LPP and SPN components between emotional (unpleasant and phobia relevant) and neutral stimuli. In the second step, mean amplitudes averaged within the time windows and sensor clusters that indicated the significant P1 group effects and emotional modulation of the EPN/LPP/SPN components were included in further statistical analyses. The effects

[1] In general, even at post-hoc assessment, our participants reported that they felt largely confident that they would not see spider pictures during the safe ($M = 84$, range: 0–100) and the non-phobic threat conditions ($M = 90$, range: 0100).

[2] The heart rate data were computed on the basis of 5-min heart rate sequences assessed at baseline and during the three blocked picture presentations. Each of the four sequences were preprocessed for artifacts using the Polar Precision Performance™ Software and analyzed for average heart rate with the HRV Analysis program (Niskanen *et al.*, 2004). Statistical analyses were performed using ANOVAs including the within-factor Condition (safe *vs* non-phobic threat *vs* phobic threat) and the between-factor Group (phobics *vs* controls). These analyses indicated that when compared with the safe condition, the phobic threat condition led to increased heart rate in the spider phobia and decreased heart rate in the control group, Condition x Group, $F(1,39) = 5.0$, $P < 0.05$. Comparing safe and non-phobic threat condition did not reveal any significant effects of Condition, $F(1,40) < 1$, ns, and Condition x Group, $F(1,40) = 3.8$, $P = 0.06$.

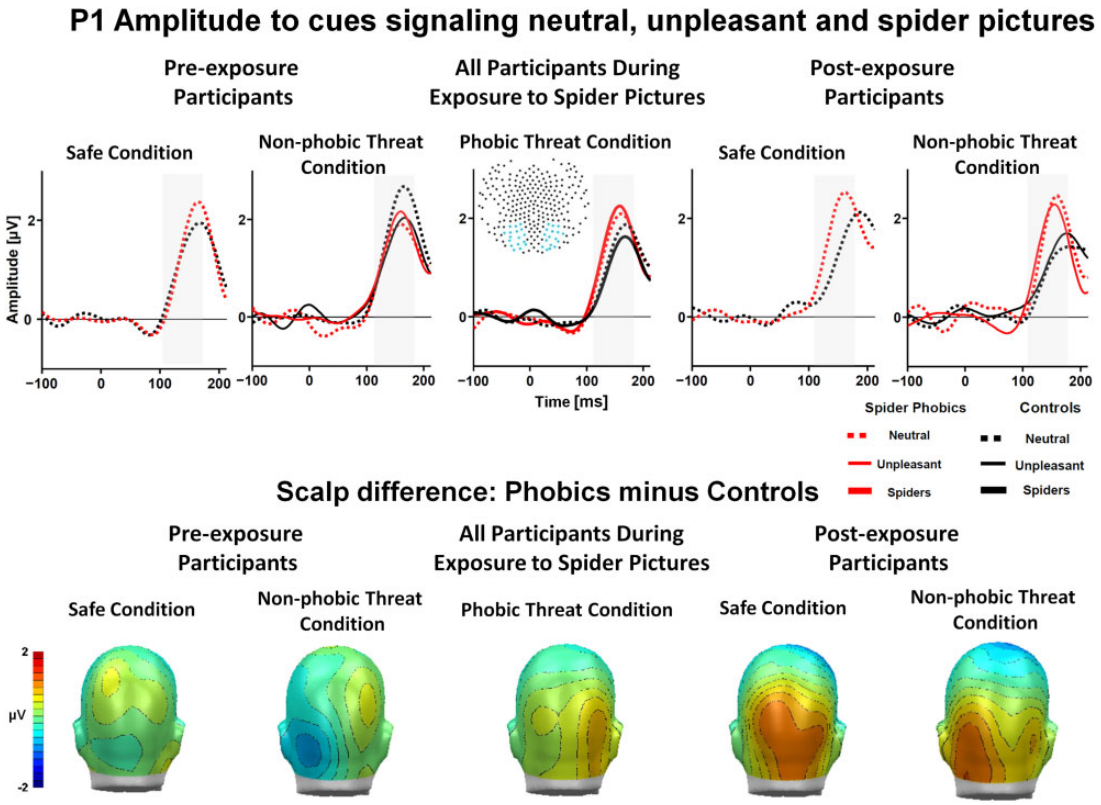

Fig. 1 Hypervigilance effect (P1) in spider fearful individuals viewing cues signaling phobia-relevant and phobia-irrelevant pictures. Grand-averaged ERPs elicited over posterior sensors (see inlet) before, during and after the exposure to spider pictures displayed for single cue categories, conditions and groups. The bottom panel illustrates scalp potential difference maps (spider phobics minus controls) for each condition as a function of presentation order. Shaded areas and head plots are selected in time interval of the P1 (120-160 ms).

showed different topographical distributions and temporal dynamics of the components depending on whether they were triggered by signal cues or pictures. With respect to pictures, the early ERP components were scored in posterior sensor clusters in the time windows from 120 to 180 ms (P1, Figure 2) and 200–300 ms (EPN, Figure 5, top), whereas the LPP was assessed in the time window 352–652 ms in centro-parietal sensor clusters (Figure 5, bottom).[3] With respect to signal cues predicting emotional and neutral pictures, the P1 was analyzed in the time window 120–160 ms, the EPN in the time window 180–300 ms in posterior sensor clusters (Figures 1 and 3, top), the LPP in the time window 300–552 ms in centro-parietal sensor clusters (Figure 3, bottom) and the SPN was scored within the time window 800–1000 ms for a centro-frontal sensor cluster (Figure 4).[4]

To replicate previous findings on attention effects during processing of phobia-relevant stimuli in spider phobics, separate statistical analyses of the P1, EPN, LPP and SPN were carried out for the phobic threat condition by calculating repeated measures ANOVAs including Picture/Cue Category (spider *vs* neutral) and Laterality (right *vs* left) as within-factors and Group (phobics *vs* controls) as a between-factor. To determine the effects of presentation order on the P1, we further calculated separate 2 × 2 ANOVAs for the safe block with the between group factors Group (spider phobics *vs* controls) and Order (pre-exposure *vs* post-exposure participants). We also analyzed P1-amplitudes to neutral and unpleasant contents in the non-phobic threat block in a 2 × 2 × 2 factorial design including both between group variables Group and Oder and—in addition—as within subject variable Picture/Cue Category (unpleasant *vs* neutral). Laterality was added as an additional within-factor in these analyses. These analyses were followed up by four ANOVAs for the neutral and non-phobic threat conditions separately in pre- and post-exposure participants. Because the factor "order" varied across participants, each of the four analyses mentioned above included a different number of subjects. These analyses were performed with Picture/Cue Category (unpleasant *vs* neutral, only in the non-phobic threat condition) and Laterality as within-factors and Group (spider phobics *vs* controls) as a between-factor. With respect to the EPN, LPP and SPN during the exposure to phobia-irrelevant stimuli, we compared ERPs to stimuli presented during the non-phobic threat condition using repeated measures ANOVAs including Picture/Cue Category (unpleasant *vs* neutral) and Laterality as within-factors and Group and Order (pre-exposure *vs* post-exposure participants) as a between-factors. Follow-up tests compared contents from the phobic threat and non-phobic threat blocks (spider *vs* unpleasant stimuli and neutral phobic threat *vs* neutral non-phobic threat stimuli).

[3] The P1 sensor clusters: 93, 94, 95, 96, 97, 98, 103, 104, 105, 106, 107, 108, in the left hemisphere and 151, 152, 160, 161, 169, 170, 177, 178, 189, 190, 200, 201 in the right hemisphere. The EPN sensor clusters: 106, 107, 108, 109, 113, 114, 115, 116, 117, 118, 122, 123, 124, 125,134, 135, 136 in the left hemisphere and 127, 138, 139, 140, 148, 149, 150, 151, 157, 158, 159, 160, 166, 167, 168, 169, 176 in the right hemisphere. The LPP sensor clusters: 45, 52, 53, 59, 60, 66, 72, 77, 78, 79, 80, 88, 89, in the left hemisphere and 130, 131, 132, 142, 143, 144, 154, 155, 163, 164, 173, 183, 184 in the right hemisphere.

[4] The P1 was analyzed in two clusters comprising the following sensors: 96, 97, 98, 105, 106, 107, 108, 113, 114, 115, 116, 121, 122, 123, 133, 134, 135 in the left hemisphere and 150, 151, 152, 157, 158, 159, 160, 161, 166, 167, 168, 169, 170, 174, 175, 176, 177 in the right hemisphere. The EPN sensor clusters included 168, 169, 176, 177, 178, 188, 189, 190, 199, 200, 201, 208, 209 and 92, 93, 94, 95, 102, 103, 104, 105, 106, 111, 112, 113, 114. The LPP was analyzed within two sensor clusters: 45, 53, 60, 66, 72, 76, 77, 78, 79, 80, 85, 86, 87, 88, 89 in the left hemisphere and 130, 131, 132, 142, 143, 144, 153, 154, 155, 162, 163, 164, 171, 172, 173 in the right hemisphere. The SPN was analyzed within a centro-frontal sensor cluster including the following sensors 6, 7, 8, 9, 15, 16, 17, 23, 24, 43, 44, 52, 184, 185, 186, 197, 198, 207.

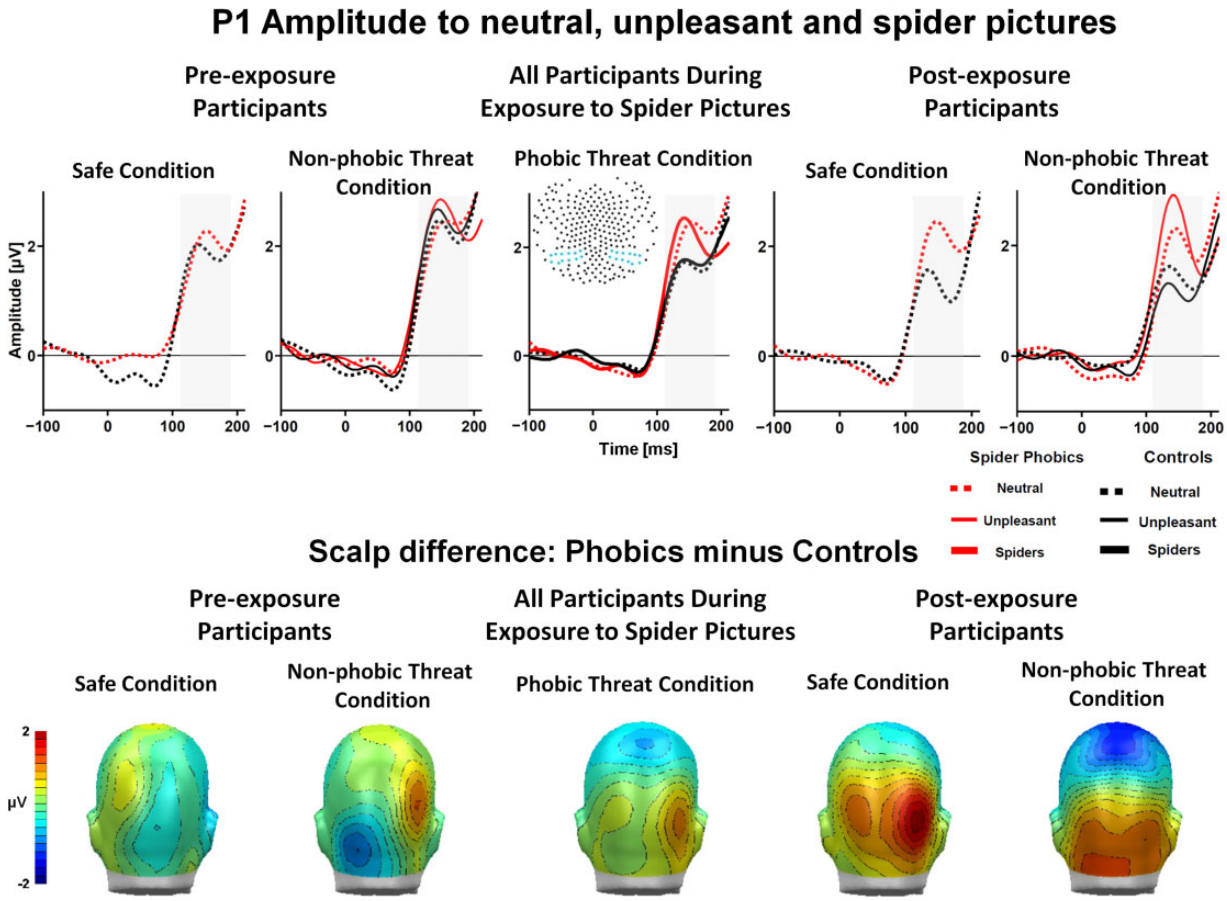

Fig. 2 P1 hypervigilance effect in spider fearful individuals exposed to pictures of naturalistic scenes. The top panel highlights grand-averaged ERP waveforms elicited across posterior channels (see inlet) during viewing of single picture categories before, during and after the exposure to spider pictures displayed as a function of group. The bottom graphs illustrate scalp potential difference maps (spider phobics minus controls) for single experimental conditions and presentation orders. Shaded areas and head plots are selected in time interval of the P1 (120-180 ms).

RESULTS

P1

Signal cues (colored fixation crosses) presented during the phobic threat condition

In the phobic threat condition, repeated measures ANOVA revealed that the P1 was more pronounced in spider-phobic than control individuals, Group, $F(1, 48) = 4.4$, $P < 0.5$, $\eta_p2 = 0.08$ (Figure 1, middle). These group differences were identical for cues signaling the occurrence of neutral and spider pictures, Cue Category, $F(1, 48) < 1$, ns; Cue Category × Group, $F(1, 48) = 1.8$, $P = 0.19$, $\eta_p2 = 0.04$.

Signal cues (colored fixation crosses) presented before and after the phobic threat condition

Overall, ANOVAs calculated for the non-phobic threat condition resulted in a significant Order × Group interaction, $F(1, 46) = 5.6$, $P < 0.05$, $\eta_p2 = 0.11$. Follow-up comparisons performed for pre-exposure participants did not reveal significant differences between phobics and controls in the P1 amplitude during the non-phobic threat condition, Group, $F(1, 25) < 1$, ns (Figure 1, left), Cue Category and Cue Category × Group, $Fs < 2.3$, ns. However, larger P1 in the spider phobia than in the control group was found during the non-phobic threat condition in post-exposure participants, Group, $F(1, 21) = 12.2$, $P < 0.01$, $\eta_p2 = 0.37$ (Figure 1, right), Cue Category and Cue Category × Group, $Fs < 1$, ns.

Overall, ANOVAs calculated for the safe condition did not reveal significant Order × Group interaction, $F(1, 46) = 1.7$, $P = 0.19$, $\eta_p2 = 0.04$. However, follow-up tests showed similar P1 in the pre-exposure spider phobia and control groups, Group, $F(1, 24) < 1$, ns, and a trend toward significantly greater P1 amplitudes in post-exposure phobia when compared with control participants, Group, $Fs(1, 22) < 3.7$, $P = 0.068$, $\eta_p2 = 0.14$ (Figure 1, left and right).

Pictures presented during the phobic threat condition

During the phobic threat condition, the P1 to neutral and spider pictures was significantly larger in spider-phobic than in control subjects, Group, $F(1,48) = 4.2$, $P < 0.05$, $\eta_p2 = 0.08$, replicating our previous findings (Figure 2, middle). The P1 was enhanced in phobic participants for both phobic and neutral pictures, Picture Category and Picture Category × Group, $Fs(1,48) < 1$, ns.

Pictures presented before and after the phobic threat condition

According to the overall analyses calculated for the non-phobic threat condition, there was no significant Order × Group interaction, $F(1, 46) = 2.3$, $P = 0.14$, $\eta_p2 = 0.05$. However, follow-up tests revealed that the P1 effects observed for pictures in the non-phobic threat block corresponded with the P1 findings to the signal cues. That is, no significant P1 differences between phobics and controls were found in pre-exposure participants, Group, $F(1, 25) < 1$, ns, but greater P1 response was found in post-exposure phobia when compared with control participants, Group, $F(1, 21) = 5.6$, $P < 0.05$, $\eta_p2 = 0.21$ (Figure 2, left and right). The overall ANOVAs revealed greater P1 amplitudes for unpleasant when compared with neutral pictures, Picture Category, $F(1, 46) = 8.2$, $P < 0.01$, $\eta_p2 = 0.15$, but no significant

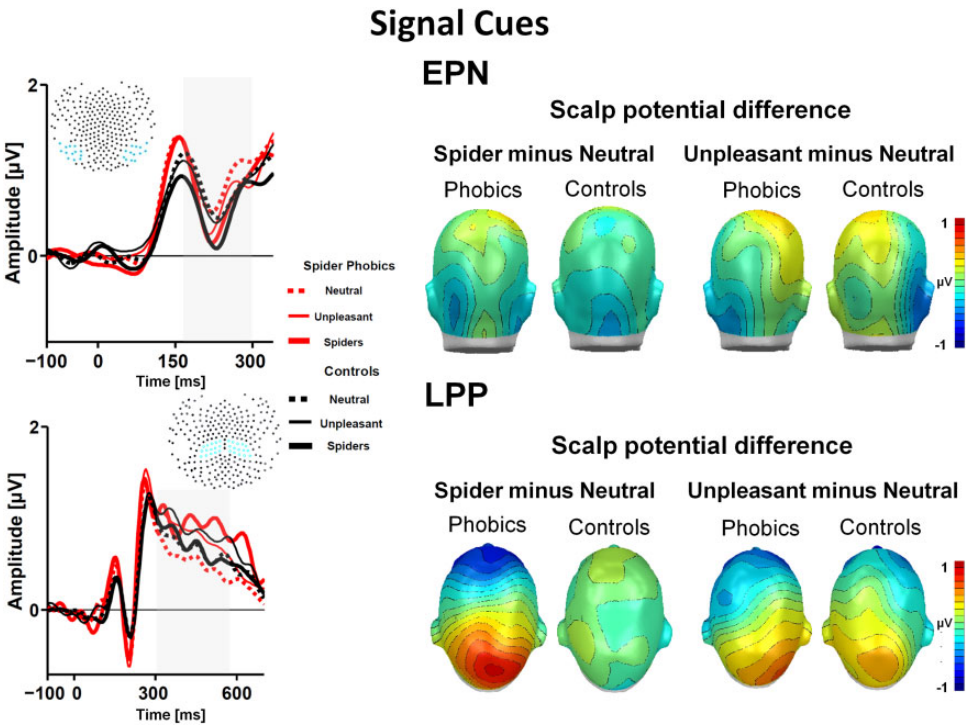

Fig. 3 EPN and LPP selective attention effects during the encoding of cues instructed for neutral, unpleasant and spider pictures. The top panel highlights ERP waveforms grand-averaged across pre- and post-exposure participants elicited by the three cue categories over posterior channels (left, see inlet) and topographical ERP difference maps (spider minus neutral and unpleasant minus neutral) displaying the activity averaged in the time window from 180 to 300 ms on a back view of a model head (right) as a function of group. The bottom panel illustrates grand-averaged ERP waveforms elicited by the three cue categories over centro-parietal channel clusters (left, see inlet) and topographical ERP difference maps (spider minus neutral and unpleasant minus neutral) displaying the activity averaged from 300 to 552 ms on a top view of a model head (right) as a function of group.

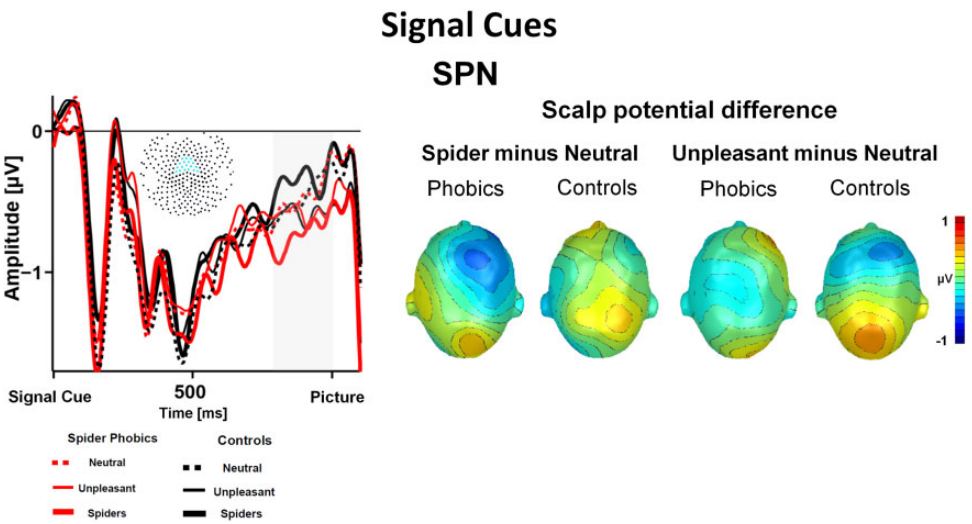

Fig. 4 SPN anticipatory attention effects for cues signaling neutral, unpleasant and spider pictures. The left panel highlights ERP waveforms grand-averaged across pre- and post-exposure participants elicited over centro-frontal channels by the three cue categories in the spider phobia and control groups. Shaded area indicates the analyzed SPN time interval (800–1000 ms). The right panel illustrates topographical ERP difference maps (spider *vs* neutral and unpleasant *vs* neutral) scored in the time window 800–1000 ms on the top view of a model head as a function of group.

Picture Category × Group and Picture Category × Order effects, *F*s (1, 46) < 1, ns.

The P1 effects observed in the safe condition were similar to those found during the non-phobic threat block, Order × Group, F (1, 46) = 1.5, $P = 0.23$, $\eta_p2 = 0.03$, as well as Group, $F(1, 24) < 1$, ns and Group, $F(1,22) = 4.6$, $P < 0.05$, $\eta_p2 = 0.17$, for pre- and post-exposure participants, respectively (Figure 2, left and right).

Selective attention effects during the encoding of signal cues (colored fixation crosses)

EPN. The EPN component was less pronounced during the encoding of safety-cues when compared with the cues signaling spider pictures, Cue Category, $F(1,48) = 4.6$, $P < 0.05$, $\eta_p2 = 0.09$, and those predicting unpleasant pictures, Cue Category, $F(1,48) = 3.5$, $P = 0.066$, $\eta_p2 = 0.07$ (Figure 3, top). Overall, ANOVAs did not indicate any significant

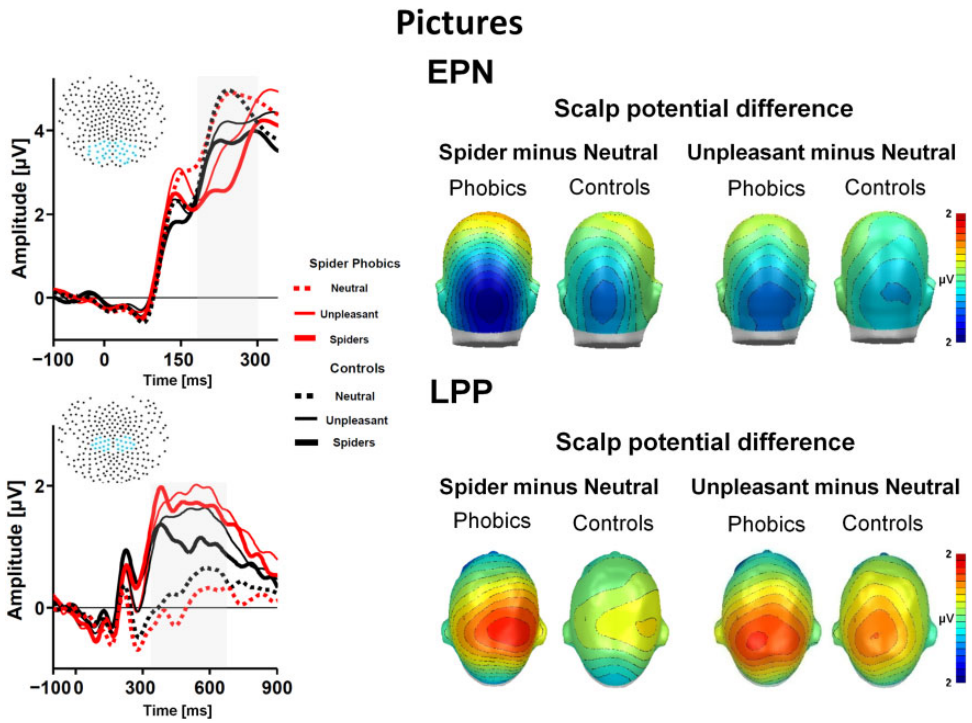

Fig. 5 The Picture Category × Group effects as revealed by the EPN and LPP components elicited during picture viewing. The figure highlights ERP waveforms grand-averaged across pre- and post-exposure participants elicited over posterior (top left) and centro-parietal channel clusters (bottom left) during viewing of neutral, unpleasant and spider pictures as well as topographical ERP difference maps (spider minus neutral and unpleasant minus neutral) displayed as a function of group. Shaded areas and head plots are selected in time intervals of the EPN (200-300 ms) and LPP (352-652 ms).

effects of Group, Group × Cue Category and Group × Cue Category × Laterality, $Fs(1,48) < 1$, ns. The emotional modulation of the EPN was similar in the pre- and post-exposure participants, Cue Category × Order and Cue Category × Group × Order, $F\ (1,\ 46) < 1$, ns. We did not find any significant EPN differences comparing safety-cues presented during the phobic and non-phobic threat conditions, Cue Category, Group and Group × Cue Category, $Fs < 1$, ns.

LPP. As illustrated in the bottom panel of Figure 3, cues signaling spider pictures elicited larger LPP amplitudes than safety-cues, Cue Category, $F(1,48) = 9.2$, $P < 0.01$, $\eta_p 2 = 0.16$. Importantly, this effect was significantly larger in the phobia than in the control group, Group × Cue Category, $F(1,48) = 6.6$, $P < 0.05$, $\eta_p 2 = 0.12$. Again in correspondence with the results obtained for picture processing, cues signaling unpleasant pictures elicited larger LPP amplitudes than safety cues, Cue Category, $F(1,48) = 12.6$, $P < 0.001$, $\eta_p 2 = 0.21$. This latter effect did not differ significantly as a function of group, Group × Cue Category, $F(1,48) < 1$, ns, and it was similar in the pre- and post-exposure participants, Cue Category × Order and Cue Category × Group × Order, $Fs\ (1,\ 46) < 2$, ns. Finally, spider-phobic individuals responded with similar LPPs to cues signaling spider and unpleasant pictures, Cue Category, $F(1,24) < 1$, ns, whereas in the control group, there was a trend toward greater LPPs for cues predicting unpleasant than spider pictures, Cue Category, $F(1,24) = 3.5$, $P = 0.080$, $\eta_p 2 = 0.12$. There were no significant differences for safety-cues in the phobic and non-phobic threat conditions, Cue Category and Cue Category × Group, $Fs(1,48) < 1$, ns.

SPN. Comparing the SPN for spider and neutral pictures in both groups showed a trend toward a significant Cue Category × Group effect, $F\ (1,\ 48) = 2.8$, $P = 0.10$, $\eta_p 2 = 0.054$. Follow-up tests revealed that cues signaling spider pictures elicited larger SPN than those signaling neutral pictures in the spider phobia but not in the control group, Cue Category, $F\ (1,\ 24) = 10.0$, $P < 0.01$, $\eta_p 2 = 0.294$ and $F\ (1,\ 24) < 1$, ns, for spider phobics and controls, respectively (Figure 4). Moreover, cues signaling unpleasant pictures elicited significantly more pronounced SPN than neutral cues in both experimental groups, Cue Category, $F\ (1,\ 48) = 8.16$, $P < 0.01$, $\eta_p 2 = 0.145$, and Cue Category × Group, $F\ (1,\ 48) < 1$, ns, these effects did not differ for pre- and post-exposure individuals, Cue Category × Order and Cue Category × Group × Order, $Fs\ (1,\ 46) < 2$, $Ps \geq 1.7$. There were no other significant SPN effects, $Fs < 2$, $Ps > 0.17$.

Selective attention effects during picture encoding

EPN. As illustrated in the top panel of Figure 5,[5] spider pictures evoked a larger EPN than neutral pictures, $F(1,48) = 41.9$, $P < 0.001$, $\eta_p 2 = 0.47$, significantly larger in spider phobics than in controls, Group × Picture Category, $F(1,48) = 6.1$, $P < 0.05$, $\eta_p 2 = 0.11$. Moreover, replicating previous findings, unpleasant pictures also elicited a significantly larger EPN than neutral pictures, $F(1,48) = 13.2$, $P < 0.001$, $\eta_p 2 = 0.22$, a pattern that was comparable in both groups, Group × Picture Category, $F(1,48) < 1$, ns, Group × Picture Category × Laterality, $F(1,48) < 1$, ns and did not differ between the pre- and post-exposure participants, Picture Category × Order and Picture Category × Group × Order, $Fs\ (1,\ 46) < 1.8$, ns. Finally, comparing the EPN with spider and unpleasant pictures revealed that spider pictures elicited significantly greater EPN than unpleasant pictures in spider-phobic subjects, $F(1,24) = 4.7$, $P < 0.05$, $\eta_p 2 = 0.16$, but did not differ from the EPN evoked by unpleasant pictures in controls, $F(1,24) = 1.5$, $P = 0.23$, $\eta_p 2 = 0.06$. There were no significant

[5] Because Picture/Cue Category and Picture/Cue Category x Group effects observed for EPN, LPP and SPN were not modulated by factor Order, these components are illustrated without splitting them into pre- and post-exposure individuals.

differences in the EPN elicited by neutral pictures between the phobic-threat and non-phobic threat conditions, Picture Category and Picture Category × Group, $Fs(1,48) < 1$, ns.

LPP. Spider pictures elicited significantly larger LPPs than neutral contents, $F(1,48) = 66.8$, $P < 0.001$, $\eta_p2 = 0.58$. This effect was more pronounced in spider-phobic than control individuals, Group × Picture Category, $F(1,48) = 15.2$, $P < 0.001$, $\eta_p2 = 0.24$ (see bottom panel of Figure 5). Moreover, the amplitude of the LPP was also larger for unpleasant than neutral pictures, $F(1,48) = 126.6$, $P < 0.001$, $\eta_p2 = 73$, an effect that was not affected by group, Group × Picture Category, $F(1,48) = 2.9$, $P = 0.09$, $\eta_p2 = 0.06$ and Group × Picture Category × Laterality, $F(1,48) < 1$, ns and was similar in the pre- and post-exposure participants, Picture Category × Order and Picture Category × Group × Order, Fs $(1, 46) < 1$, ns. Replicating previous results (Michalowski *et al.*, 2009), spider-phobic participants did not respond with larger LPPs to spider than to unpleasant pictures, $F(1, 24) < 1$, ns, whereas in the control group, spiders pictures elicited smaller LPPs than unpleasant pictures, $F(1, 24) = 9.5$, $P < 0.01$, $\eta_p2 = 0.28$. There were no significant differences for neutral pictures in the phobic-threat and non-phobic threat conditions, Picture Category and Picture Category × Group, $Fs(1,48) < 1.2$, ns

Viewing time, valence and arousal ratings

The valence and arousal ratings of this sample corresponded with the standard affective ratings on which the picture selection was based. As expected, pictures of spiders were rated as more arousing and unpleasant and with shorter viewing times by spider-phobic than control subjects, $ts(47) > 2.5$, $Ps < 0.01$.

DISCUSSION

The purpose of this study was to examine the temporal dynamics of visual attention in spider-phobic and non-phobic volunteers exposed to neutral, unpleasant and phobia-relevant pictures as well as to perceptually simple cues that signaled one of the three mentioned picture categories. Moreover, we investigated the influence of spider fear on the vigilance and selective attention effects under safe as well as phobic and non-phobic threatening contexts. Providing a millisecond time resolution of dynamic brain activity, ERP measures replicated previous findings regarding the preferential picture processing in spider-phobic participants at distinct processing stages. The P1 was the first ERP component revealing group differences between spider-phobic and non-phobic control participants.

Increased P1 to all visual stimuli during pre-encounter defense

In a context where phobic objects could occur, spider phobics showed a greater P1 than controls for all pictures. This general hypervigilance effect was maintained once the individuals had made the experience that spider pictures might be presented in this experiment. At the same time, spider-phobic and non-fearful control individuals did not differ in their P1 to neutral and unpleasant pictures prior to the exposure of phobia-relevant objects. Even though these exposure effects do not seem particularly strong, they appear to be fairly consistent: Similar effects were observed for perceptually simple cues that signaled the occurrence of the pictures, i.e. no group differences in the P1 prior to the phobic threat context and increased P1 to all signal cues during or after the context in which spider pictures were presented suggesting that the early P1 effect is not driven by the perceptual features of the stimuli, an argument that is also supported by the fact that both groups viewed stimuli that were physically identical. Instead, the increased P1 in spider phobics undergoing phobia-relevant exposure seem to reflect hypervigilance and increased attention to all visual images that occur in a potentially threatening context.

The results of this study are strikingly similar to our previous findings of increased P1 in spider phobics to all visual stimuli when spider pictures might occur (Michalowski *et al.*, 2009). This study clearly demonstrates that this hypervigilance is indeed an index of pre-encounter defense. If spider-phobic individuals did not expect the occurrence of any phobic objects (like in the safe or non-phobic threat condition prior to the exposure of spider pictures), no group differences in the P1-amplitude were observed. Even the occurrence of unpleasant but not phobia-relevant scenes did not increase the P1-amplitude in specific-phobic individuals. In contrast, from the moment, when spider-phobic individuals were informed that spider pictures might be part of the experiment creating a phobia-relevant context, increased P1-amplitudes to all visual stimuli were observed in the phobic individuals. This increased hypervigilance generalized to other contexts even though spider phobics were explicitly told that the upcoming context would not include spider pictures. Thus, once sensitized by the phobic stimuli, the instruction that a context is safe did not abolish the hypervigilance to external cues. This is in line with animal data showing strong sensitization effects after exposure to aversive stimuli (Rau *et al.*, 2005; Rau and Fanselow, 2009). Moreover, considering these previous animal findings, one could speculate that such hypervigilance after exposure to the phobic objects might also facilitate fear conditioning to other stimuli and might promote generalization of fear which might be an important mechanism in the maintenance of anxiety disorders (see Lissek *et al.*, 2009).

Preferential processing of threat pictures and threat-associated cues: EPN

At later processing stages, spider-phobic individuals showed enhanced encoding of spider pictures. When compared with non-fearful controls, spider phobics showed increased selective attention effects for spider pictures, as indexed by greater EPN, replicating previous findings (Kopp and Altmann, 2005; Michalowski *et al.*, 2009). In contrast to P1, neutral stimuli elicited comparable EPN amplitudes in both groups suggesting that enhanced EPN to spider pictures in spider phobics might be related to increased emotional salience of these stimuli for this group (Schupp *et al.*, 2006). Supporting this view, EPN to spider pictures was not larger than the EPN elicited by other unpleasant, i.e. emotionally relevant pictures in spider-phobic participants. Some studies suggest that perceptual features of the stimuli (e.g. figure ground configurations) might seriously confound emotional EPN effects (Bradley *et al.*, 2007; Wiens *et al.*, 2011; Löw *et al.*, 2013). However, the early modulatory ERP effects observed in this study cannot be explained solely by differences in physical stimulus characteristics because both groups (spider phobics and controls) were exposed to physically identical stimuli. Furthermore, visual signals that predicted the occurrence of unpleasant and spider pictures also elicited larger EPN amplitudes than cues that predicted neutral stimuli even though the signal cue differed only in color and the assignment of colors to threat and safety pictures. Considering previous research on simple stimulus identification (for review, see Harter and Aine, 1984), these early ERP effects might indicate a color-based visual selection of threat-signaling cues and speak for a top-down modulation of threat-related stimulus encoding. In contrast to the stimulus identification studies, this study did not use an explicit instruction to attend to one specific stimulus type. The lack of an explicit attention instruction and the removal of almost all features facilitating the differentiation between threat and safety cues might be responsible for the fact that the early modulatory ERP effects observed for simple cues

were much smaller than those observed for natural scenes. Future replication studies should check the reliability of this finding.

Elaborated processing of threat pictures and threat-associated cues: LPPs and SPN

Replicating previous findings (Kolassa *et al.*, 2005; Kopp and Altmann, 2005; Miltner *et al.*, 2005; Michalowski *et al.*, 2009, 2014), this study showed that emotionally relevant pictures evoke significantly larger LPPs than neutral images. Moreover, specific-phobic participants responded with greater LPP amplitudes to phobia-relevant pictures than controls. This latter effect was fear specific as control pictures elicited comparable LPP amplitudes in the spider and control groups. As was previously suggested (e.g. Michalowski *et al.*, 2009), the enlarged LPP amplitudes to phobia-relevant stimuli in specific-phobic individuals might reflect a state of enhanced selective attention to feared stimuli. Importantly, in the spider phobia group, the LPP was similarly increased for other unpleasant pictures demonstrating that the selective attention capture is not specific for phobia-relevant cues. These data are consistent with results from fMRI studies, which found increased activation of the amygdala, the insula and the visual cortex to phobia-relevant pictures in animal-phobic volunteers but not in controls compared with neutral pictures. However, the same increase in activation in these areas was found for other highly arousing unpleasant pictures with no group differences (Sabatinelli *et al.*, 2005; Wendt *et al.*, 2008). Taken together, these data suggest that although phobic individuals show enhanced selective processing of their phobia-relevant cues, this increase in attention capture is not threat-specific but is rather related to the emotional relevance of these cues. Accordingly, these data do not support assumptions formulated in cognitive theories of fear and anxiety that postulate specific attentional bias toward threatening stimuli as a vulnerability factor for developing anxiety disorders (Williams *et al.*, 1997; Mathews and Mackintosh, 1998; Mogg and Bradley, 1998). Rather the current data suggest that the attention to external stimuli is driven by the emotional system in a dynamic way as would be predicted by the threat-imminence model.

This study gave clear evidence for increased LPP amplitudes during the encoding of cues signaling the occurrence of threat. Spider phobics responded with increased LPPs to cues that signaled the occurrence of spiders relative to cues signaling neutral events. Similar effects for preferential processing of threat signals were observed for the SPN, which is considered to index the cortical activation during the anticipation of relevant stimuli (Brunia and van Boxtel, 2001). Participants responded with larger SPN to cues signaling unpleasant pictures when compared with those instructed as safety cues. Moreover, spider signaling cues elicited an increased SPN in the spider phobia but not in the control group. These findings indicate that the processing of threat signals is organized with the dynamics mirroring the defense cascade. The initial unspecific facilitation of perceptual processing in the pre-encounter defense mode (P1) is followed by a shift into post-encounter defense, prompted by the identification of a threat signal (EPN and LPP). Its detection activates the anticipatory attention toward upcoming threat (SPN) and leads to autonomic and somatic responses consistent with defense preparation (cf. Öhman, 2000; Bradley, 2009). These findings are also in line with the results from fear conditioning studies, showing that visual stimuli that signal aversive electric shocks provoke greater LPP amplitudes (Baas *et al.*, 2002; Bublatzky and Schupp, 2012) and increased startle and skin conductance responses (Grillon *et al.*, 1991; Grillon and Davis, 1995; Funayama *et al.*, 2001; Olsson and Phelps, 2004; Bradley *et al.*, 2005; Weike *et al.*, 2008). Enhanced encoding of threat signaling stimuli (e.g. spider web or garden in case of spider phobics) might be associated with unpleasant post-event recollection and increased retrieval of fear memories (Cuthbert *et al.*, 2003). Resulting in an increased avoidance and reinforcing new threat-contingencies, these processes would lead to a generalization of the fear response and hinder recovery (Williams *et al.*, 1997). In this study, the effect of larger LPPs to threat-relevant pictures was most pronounced over centro-parietal sensor regions, whereas the emotional cue effect was located slightly more posterior (Figures 3 and 5). These topographical differences are in line with previous results. Specifically, in instructed threat paradigms, larger LPPs to threat signaling cues were observed over parieto-occipital regions (Baas *et al.*, 2002; Böcker *et al.*, 2004; Bublatzky and Schupp, 2012), whereas in case of pictures, the emotional LPP effect is usually most pronounced over centro-parietal regions (cf. Schupp *et al.*, 2006). The observed difference in LPP topography supports the notion of partly distinct neural substrates involved in the processing of images depicting threatening scenes and symbolic stimuli signaling threat (Funayama *et al.*, 2001; Bublatzky and Schupp, 2012; Bublatzky *et al.*, 2013).

Some limitations of this study should be mentioned. First, reducing the sample size by dividing it into the pre- and post-exposure groups limited the statistical power, which might be responsible for the failure to find significant pre/post-differences between the phobia and the control groups. Moreover, future studies may also investigate the sensitivity of the vigilance system by presenting the same pictures before and after the threatening context to all participants. As a caveat, it has to be noted that the interpretation of such within-group data will be confounded with order effects. Further, the generalizability of the present findings is limited to the sample. Our findings have been obtained with spider phobia individuals and cannot be directly transferred to other anxious populations without additional investigations. The study included only students and almost only female participants. However, we have currently no reason to suspect that men or non-students would differ in terms of the attention effects observed in our study. Finally, future studies may also benefit from examining the sensitivity of attention system among a clinical sample with specific phobias, as this might provide further information about the underlying mechanisms of the development of pathological anxiety.

Considered from the perspective of the defense cascade model, our findings indicate that after the initial hypervigilance to all stimuli, as indexed by increased P1-amplitudes, individuals with specific phobia shift into a mode of increased attention to threat-related stimuli once these stimuli are identified and encoded. This enhanced encoding is accompanied by freezing and startle potentiation, even during anticipation of the threatening event. These data clearly demonstrate that defensive behavior is organized dynamically with a close interaction between the emotional and the cognitive system shaping both stimulus encoding and response output, as would be predicted by the threat imminence or defense cascade model.

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