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Auditory perceptual learning is not affected by anticipatory anxiety in the healthy population except for highly anxious individuals: EEG evidence

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HIGHLIGHTS

- Anxious hypervigilance sensitizes early brain responses to unrelated stimuli.
- Perceptual learning is affected only in individuals with high state or trait anxiety.
- Differences in the modulation of neural processes confirm anxiety as a dimensional construct.

ABSTRACT

Objective: A recent neurocomputational model proposed that anxious hypervigilance impedes perceptual learning. This view is supported by the observed modulation of the mismatch negativity (MMN), a biomarker of implicit perceptual learning processes, in anxiety disorders. However, other studies found that anxious states sensitize brain responses with no impact on perceptual learning. The present research aimed to elucidate the impact of anticipatory anxiety on early stimulus processing in the healthy population.
Methods: We used electroencephalography to investigate the impact of unpredictable threat on the amplitude of the MMN and other components of the auditory evoked response in healthy participants during a passive auditory oddball task.
Results: We found a general sensitization of early components of the auditory evoked response and changes in subjective and autonomic measures of anxiety during threat periods. The MMN amplitude did not differ during threat, compared to safe periods. However, this difference was modulated by the level of state or trait anxiety.
Conclusion: We propose that anxiety sensitizes early brain responses to unspecific environmental stimuli but affects implicit perceptual learning processes only when an individual is located at the higher end of the anxiety spectrum.
Significance: This view might distinguish between an adaptive role of anxiety on processing efficiency and its detrimental impact on implicit perceptual learning observed in psychiatric conditions.

1. Introduction

The adaptive interplay between perception and emotional states is fundamental for optimal goal-oriented behaviour in complex and volatile environments. Essential to this process is the capacity to screen out irrelevant sensory information and detect stimuli that are relevant or can constitute a threat. Anxiety serves this purpose via affective, cognitive and physiological changes that create a state of hypervigilance in response to unpredictable threats in novel and uncertain settings (Grupe and Nitschke, 2013). Evolutionarily, anxiety increases the odds of survival in threatening situations (Kalin and Shelton, 1989), but it can become maladaptive if sustained over time and associated to otherwise innocuous stimuli. This is the case in psychopathological conditions such as PTSD and anxiety disorders (Cisler and Koster, 2010; Newport and Nemeroff, 2000). A putative disruptive effect of anxiety on cognitive functions, and related performance impairments, is also described in the healthy population by nowadays widespread and influential theories (Eysenck et al., 2007; Eysenck and Derakshan, 2011). In the framework of cognitive neurosciences, anxiety-induced hypervigilance is considered to impact

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sensory-perceptual processing through the sensitisation of neural responses to environmental stimuli (see Jafari et al., 2017; Robinson et al., 2011 for recent reviews).

According to a recent neurocomputational model, anxious hypervigilance would impede perceptual learning by increasing the synaptic gain of prediction error signals while down-regulating descending prediction pathways. This mechanism is suggested to tap into early stimulus processing and could underlie the detrimental effects of anxiety on higher-order cognitive processes (Cornwell et al., 2017). This model is ascribed to the predictive coding framework (Friston, 2009) and considers the mismatch negativity (MMN, e.g. Näätänen et al., 2004), a neuro-electric response to violations of statistical regularities in the sensory environment, as a marker of implicit perceptual learning processes in the form of precision-weighted prediction error signal (Garrido et al., 2009b). It is worth mentioning that the definition of perceptual learning in this context, in terms of attenuation of responses encoding prediction errors (e.g. Friston, 2009), refers to an implicit process and differs from a definition of explicit learning of perceptual features through training associated with long-term neural plasticity (e.g. Schwartz et al., 2002; Yotsumoto et al., 2008).

Several studies support the idea of an impact of anxiety on implicit perceptual learning: increased MMN amplitude has been observed in individuals affected by PTSD (e.g. Ge et al., 2011) and correlates with dispositional anxiety (Hansenne et al., 2003). Moreover, a study using magnetoencephalography (MEG), has reported increased responses to stimulus deviance under threat of electric shock (Cornwell et al., 2007).

Despite this evidence, contradicting results come from other research that elicit anxious states and use electroencephalography (EEG): in these cases, a difference in the amplitude of the MMN was either not found (Ermutlu et al., 2005), observed only in response to a specific type of stimulus deviancy (Simoens et al., 2007) or found to correlate with state anxiety only in an emotionally negative context (Schirmer and Escoffier, 2010). Additionally, several studies reported higher brain responses to environmental stimuli at early and middle latencies of the sensory event-related potential (ERP) during anxious states in the auditory and visual domains, independently of the stimulus type (e.g. Ermutlu et al., 2005; Qi et al., 2018; Scaife et al., 2006; Shackman et al., 2011). However, these studies did not use threat of electric shock to induce anticipatory anxiety as in Cornwell et al. (2017) or their focus did not encompass both general sensory processes and perceptual learning markers (i.e. the MMN).

In the present study, we tried to shed light on the ambiguous findings concerning the effect of anticipatory anxiety on perceptual learning and early stimulus processing. Specifically, we used EEG to measure the amplitude of the MMN under threat of electric shock during a passive oddball task (as Cornwell et al., 2017, 2007), as well as the amplitude of early components of the auditory-evoked response. In addition to subjective self-reports, which are commonly used in the above-mentioned studies, we measured changes in the electrodermal activity in response to periods of threat to provide a marker of the autonomic response to the anxiety-induction procedure (Folkins, 1970; Nomikos et al., 1968). Finally, we investigated whether an anxious state had a different impact on perceptual learning and early sensory processing compared to the one of anxiety measured as a trait.

2. Materials and methods

2.1. Subjects

Thirty-six healthy individuals (52 ± 7.6 years old, 17 females, right-handed, 3 ± 2.33 years of higher education, all white Caucasians) participated in the study. Subjects were recruited from the local community to participate as controls in a broader project that investigated the effects of mindfulness meditation on cognitive and emotional processes. For a detailed description of the recruitment procedure, as well as inclusion and exclusion criteria, readers can refer to the project manual (Abdoun et al., 2018, available online at https://osf.io/dbwch). Regarding the present study, relevant exclusion criteria were the following: use of psychoactive medication, history of neurological or psychiatric conditions, history of chronic pain or other conditions involving sensitisation to pain, personal or family history of epilepsy, severe hearing loss. All participants were affiliated to social security, provided written informed consent before the start of the study and were paid for their participation. Ethical approval was obtained from the appropriate regional ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47). Each subject completed the trait subscale of the State Trait Anxiety Inventory (STAI, [Spielberger et al., 1983]) before participating in the experiment.

2.2. Task design and stimuli

Subjects participated to a passive auditory oddball paradigm (e.g. Näätänen et al., 2004), consisting of sequences of standard tones (880 Hz; 80 ms duration; 10 ms rise and fall) of variable length, followed by a frequency deviant (988 Hz; 20% of all auditory stimuli) presented binaurally (fix Inter-stimulus interval [I.S.I] = 500 ms). The overall paradigm consisted of six blocks over two experimental sessions (which took place at 10.30 am and 2 pm, respectively) with three different experimental conditions: two different meditation practices and one control condition (one block per condition in each session). In the present report, we analysed data from the control condition only. The sequence of blocks was randomised within a session and the block order has been considered in the statistical analysis. During a block, subjects were asked to watch a silent documentary and ignore the auditory stimuli. As in Cornwell et al. (2007), short oddball sequences were embedded in alternating 30 s periods (8 periods per block) in which participants were informed of the possibility of receiving an electric shock (threat periods, n = 4) or that no shocks would have been delivered (safe periods, n = 4). The information was conveyed by auditory cues at the beginning of each period, before the oddball sequence. The same amount of standard and deviant stimuli was delivered during safe and threat periods (n = 56 deviants and n = 224 standards when combining four periods). After each block, participants were asked to answer, on a 7-point Likert-item, how much anxiety they felt during threat and safe periods, as well as how much they were distracted during the block and how much they were listening to the auditory stimuli (see Supplementary Information for the specific questions asked).

2.3. Electric-shock stimuli and intensity work-up procedure

In line with the procedure described in Schmitz and Grillon (2012), electrodes from a direct current stimulator were placed on the participant's lower wrist. Participants were asked to rate delivered electric stimuli on a scale from 1 to 5 (1 = barely felt, 5 = very uncomfortable). Stimuli were presented at intensities starting from 2 mA and up to 16 mA (duration = 100 ms), until the participant rated the stimulus 4 out of 5 on the scale. If the subject's threshold reached 16 mA, stimuli were delivered at this maximal intensity. In our sample, the mean shock intensity was 8.29 mA (SD = 4.41). Five shocks were delivered randomly throughout the two blocks. No more than two shocks were delivered during the same threat period. Subjects were told that the number of delivered shocks could vary randomly and that the experimenter had no control over their frequency.

2.4. EEG recordings

EEG was recorded at 512 Hz using the ActiveTwo system (BioSemi, Amsterdam, Netherlands), consisting of 64 active electrodes that were placed in an EEG cap according to the standard 10/20 system. The horizontal and vertical EOG was measured by placing electrodes on the outer canthi and above and below the subject's left eye. All electrodes were kept within an offset of 50 mV (±25 mV) using the Biosemi ActiView data acquisition system for measuring signal quality. Additionally, recordings were performed in a highly shielded Faraday chamber (see Fig. S2 for an example of raw EEG recording).

Pre-processing was done using EEGLAB (Delorme and Makeig, 2004) and in-house Matlab scripts (version R2015a). The EEG signal was downsampled to 250 Hz and re-referenced offline using the electrodes placed at the level of the mastoids (average activity of the two channels). Data were visually inspected to identify bad channels, which were marked for subsequent interpolation. Independent Component Analysis (ICA) was applied, separately for the two sessions, to the continuous data using the Runica algorithm (Makeig et al., 2002). Recordings that underwent ICA were manually cleared of big artefacts, filtered between 1 and 20 Hz and did not comprise channels that would have been subsequently interpolated. Resulting ICA matrices were then transferred to the original raw data and ICA components were visually inspected to remove blinks and saccades. Data were high-pass filtered at 2 Hz to avoid contamination of slow frequencies and drifts in the signal caused by sweating during the stress periods. Previously marked bad channels were interpolated and 50 Hz noise was removed using the CleanLine algorithm. Epochs were created between −200 and 500 ms after stimulus onset for standard and deviant stimuli and baseline-corrected (−100 ms baseline). The epoched data were visually inspected and epochs including artefacts (comprising those caused by the electric shock stimuli) were manually removed. Visual inspection was completed by an automatic rejection of those epochs that included data points exceeding a ±70 μV amplitude threshold. All outer ring channels were rejected due to occasional high-frequency noise caused by muscle-related artefacts for some subjects, leading to 41 channels remaining (see Fig. S1 for a visual layout). For each subject, epoched data from one session was removed if the number of deviants, after rejection, was lower than thirty-five for the safe or threat condition. All data from two subjects, and the second session from one subject, were excluded from further analysis because of not enough epochs after pre-processing. Finally, a low-pass filter of 20 Hz was applied to the epoched data for the analysis of the evoked responses.

2.5. Event-related potentials

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). For the analysis of event-related potentials (ERPs), only standard stimuli that directly preceded a deviant were considered. The average number of standards was 52.25 and 51.42 for safe and threat conditions (SD = 6.06 and 5.70 respectively) and the average number of deviants was 52.24 and 51.62 (SD = 6.03 and 5.43).

To measure the MMN, we calculated difference waveforms from the grand average across all subjects, separately for each of the two experimental sessions and for each condition (safe and threat). We implemented an a priori region of interest (ROI) that included the channel Fz and four surrounding channels (see Fig. S1 for a visual layout), consistent with previous literature (e.g. Duncan et al., 2009; Näätänen et al., 2011). The MMN amplitude was calculated based on a 20 ms time-window centred around the most negative peak of the difference waveform for each condition (safe and threat) and session between 90 and 200 ms after stimulus onset. Amplitude values for each subject were extracted within this identified time-window.

Additionally, we performed analysis on the amplitude of classical auditory ERP components, such as the N1 and P2 (Picton et al., 1974), on the frontal ROI. Single-subject amplitudes for each condition (safe and threat), session and stimulus (standard and deviant) were extracted from a 20 ms time-window centred around the most negative peak between 90 and 200 ms for the N1, and around the most positive peak between 160 and 300 ms for the P2.

For each of the three components of interest (MMN, N1, P2) we tested the effect of condition (threat and safe periods) and stimulus type (for N1 and P2) using linear mixed-effects models (R package lme4, [Bates et al., 2014]) that allow for unbalanced designs (e.g. missing data from one session for a subject) and the inclusion of random effects such as, in the present case, session and block order information for each observation. Mixed-effects models were evaluated with an ANOVA analysis of variance (Type II Wald chi-square test). Normality of residuals and heteroskedasticity have been visually checked using residual plots and QQ plots and verified for all models. Paired *t*-tests were used as post-hoc tests, comparing least-squared means, and were corrected for multiple comparisons using Tukey honestly significant difference test (HSD). We report, in the results section, estimates of effect size in the form of pseudo-R^2 as proposed by Nakagawa and Schielzeth (2013). Notice that the calculation of effect sizes in linear mixed models is not unambiguous and should be handled with consideration.

Finally, we performed an additional analysis looking for time-electrode pairs where the MMN amplitude differed significantly between safe and threat periods. We corrected for multiple comparison using a non-parametric, permutation-based, cluster-level statistical test as implemented in the Matlab toolbox Fieldtrip (Oostenveld et al., 2011) (cluster-defining threshold = 0.001; cluster-level threshold = 0.05; 10,000 permutations).

2.6. Skin conductance data acquisition and analysis

For the recording of electrodermal activity, two passive electrodes were placed on the participant's non-dominant hand, on the volar surface of the distal phalange of the 2nd and 3rd fingers, using an electrode paste specifically designed for the recording of electrodermal activity (GEL101, Biopac; isotonic, 0.05 molar NaCl, electrode paste). Data were recorded using the 16 Hz coupler provided with the ActiveTwo system (BioSemi, Amsterdam, Netherlands) with a sampling rate of 250 Hz. Data were down-sampled at 25 Hz and analysed with the Matlab software Ledalab V 3.4.9 (www.ledalab.de) applying Continuous Decomposition Analysis (Benedek and Kaernbach, 2010), separating the tonic electrodermal activity throughout a block from the phasic activity. Our measure of interest was the event-related phasic activity after the onset of auditory cues preceding safe and threat periods. Data were visually inspected and sessions where very weak or no phasic response was present were excluded from further analysis. Following this inspection, three subjects and six single sessions were excluded due to lack of data (equipment failure) or the lack of phasic responses. Subsequently, skin conductance responses (SCRs) were calculated for each subject and session over a 1–5 s window after stimulus onset (threat or safe cue) with a minimum threshold of 0.01 microSiemens (μS). Here we report the average phasic driver activity underlying raw SCRs deconvolved into tonic and phasic components. The latter was integrated and averaged over the selected time-window to produce the measure of interest. Finally, all values were log-transformed to improve the normality of the distributions.

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). We used linear mixed models to test the effect of condition (safe and threat) and session on the log-transformed SCRs. The information about block order and auditory cue order within a block were entered in the model as random effects. Mixed-effects models were evaluated using an ANOVA analysis of variance (Type II Wald chi-square test). Paired *t*-tests, corrected for multiple comparisons using Tukey honestly significant difference test (HSD), were used as post-hoc tests comparing least-squared means.

2.7. Self-reports and regression analysis

Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). The analysis of condition (safe and threat) and session effects on self-reported anxiety was performed using linear mixed models and treating Likert items as interval data. As in previously described models, the information on block order was entered as a random effect.

Finally, we investigated the relationships between answers to self-report questions and third-person variables (e.g. ERP components amplitude and SCRs), as well as between trait (STAI questionnaire scores) and state measures. To minimize the number of statistical tests and allow for unbalanced designs (e.g. SCR or EEG data missing for some subjects), we used linear mixed models entering independent variables and factors as fixed effects, as well as session and block order information as random effects for all the fitted models. Eventual interactions between an independent variable and levels of a factor were explored post-hoc comparing the regression slopes between each factor level using the function "lstrends" (R package "lsmeans", Lenth, 2016). In the context of interactions, we tested whether a specific slope for one factor level was different from zero using the function "sim_slopes" (R package "jtools", Long, 2018; https://www.jtools.jacob-long.com).

3. Results

3.1. Manipulation of anxiety

Participants underwent two experimental sessions (2–3 h apart) where they were exposed to two conditions during the EEG recordings. A THREAT condition, when the participant was informed of the possibility of receiving an electric shock, and a SAFE condition, when no shock was delivered, were alternated during the block. Self-reported anxiety was significantly higher during THREAT, compared to SAFE condition (χ^2 (1) = 72.54; $p < 0.001$) and was generally lower in the second session (χ^2 (1) = 11.54; $p < 0.001$) [Fig. 1A; Pseudo-R^2 = 0.56, Pseudo-R^2 (fixed effects) = 0.26; see Fig. S3B for data distribution and additional descriptive statistics]. No interaction was present between condition and session. For some sessions (16 out of 72) participants reported no difference in anxiety between conditions. We decided to keep these observations in further analyses because in several sessions (8 out of 16) self-reported anxiety was higher than 1. Nonetheless, additional analyses on the MMN amplitude were performed excluding these observations (see results Section 3.2).

Skin conductance responses (SCRs) were significantly higher during THREAT, compared to SAFE condition (χ^2 (1) = 5.3; $p = 0.02$) and were lower in the second session (χ^2 (1) = 35.45; $p < 0.001$) [Fig. 1B; Pseudo-R^2 = 0.45, Pseudo-R^2 (fixed effects) = 0.06; see Fig. S3B for data distribution and additional descriptive statistics]. No interaction was present between condition and session. Higher self-reported anxiety significantly predicted higher SCRs (χ^2 (1) = 15.23; $p < 0.001$; $\beta = 0.22$ [95% c.i. = 0.11, 0.34]) [Fig. 1C; Pseudo-R^2 = 0.45, Pseudo-R^2 (fixed effects) = 0.11]. Lower subjective discomfort thresholds to the electric shocks predicted higher SCRs ($\chi 2$ (1) = 6.64; $p = 0.009$; $\beta = -0.07$ [95% c.i. = −0.13, −0.02]) [Fig. 1C; Pseudo-R^2 = 0.47, Pseudo-R^2 (fixed effects) = 0.08]. For the last two regression models, condition and session were entered as random effects.

3.2. MMN amplitude

Our main question was to investigate whether the MMN amplitude was modulated by the threat of electric shock. As no interaction between condition and session was found on self-reported anxiety or SCRs, we did not test this interaction in the model on the MMN amplitude, but rather included session as a random effect. Fig. 2A and B show the time-course of the mean amplitude of the difference waveforms, across participants and sessions, and topographies at the MMN time-window for the SAFE and THREAT conditions. There was no effect of condition on the MMN amplitude when all observations where included (χ^2 (1) = 7×10^{-4}; $p = 0.97$) [Fig. 2A; Pseudo-R^2 = 0.04, Pseudo-R^2 (fixed effects) = 0; see Fig. S3C for data distribution and additional descriptive statistics], as well as excluding observations with no difference in self-reported anxiety (χ^2 (1) = 0.03; $p = 0.84$) [Pseudo-R^2 = 0.04, Pseudo-R^2 (fixed effects) = 0]. To rule out a possible bias from focusing on a frontal ROI, as well as to explore a possible effect of condition on the MMN in unconventional scalp locations, we performed an electrode-wise cluster-based analysis in time and space dimensions. We did not find any significant cluster of electrodes that showed a difference between the two experimental conditions at any time point of the difference waveform. Additionally, we explored a possible relation between self-reported anxiety and the MMN amplitude. In this case, we found a significant interaction between anxiety and condition (χ^2 (1) = 3.75; $p = 0.05$) showing that higher self-reported anxiety predicted lower MMN amplitude in the SAFE condition and higher MMN amplitude in the THREAT condition [Fig. 2.D; Pseudo-R^2 = 0.06, Pseudo-R^2 (fixed effects) = 0.03]. Nonetheless, none of the two slope coefficients were significantly higher than zero ($\beta = 0.31$ [95% c.i. = −0.02, 0.63]; $p = 0.2$ and $\beta = -0.09$ [95% c.i. = −0.33, 0.15]; $p = 0.51$ for SAFE and THREAT conditions respectively). Finally, we explored a relationship between the SCRs and MMN amplitudes. No main effect or interaction between SCRs and MMN resulted from this regression model (Fig. 2.D).

3.3. N1 and P2 amplitude

We investigated the impact of threat of electric shock on components of the auditory evoked response that are related to early sensory processing for standard and deviant stimuli. Again, we included session as a random effect in the tested models. Fig. 3A shows the time-course of the auditory evoked responses across participants and sessions for standard and deviant stimuli during THREAT and SAFE condition. Fig. 3B shows the respective topographies at the N1 and P2 time-windows. The model tested at the N1 latency showed how the N1 amplitude increases during THREAT, compared to the SAFE condition (χ^2 (1) = 11.16; $p < 0.001$). A main effect of stimulus was present, representing the MMN (χ^2 (1) = 67; $p < 0.001$), while there was no interaction between stimulus and condition [Fig. 3C; Pseudo-R^2 = 0.71, Pseudo-R^2 (fixed effects) = 0.08; see Fig. S3D for data distribution and additional descriptive statistics]. At the P2 latency, the tested model resulted in an interaction between stimulus and condition (χ^2 (1) = 6.07; $p = 0.01$) [Fig. 3D; Pseudo-R^2 = 0.39, Pseudo-R^2 (fixed effects) = 0.02]. At this latency, the amplitude of the evoked response increases during the THREAT condition only for deviant stimuli (t-ratio (231) = −2.33; $p = 0.02$ for deviants and t-ratio (231) = 1.15; $p = 0.25$ for standards) and a difference between standard and deviant stimuli is present during the SAFE condition only (t-ratio (231) = 2.84; $p = 0.004$ for safe and t-ratio (231) = −0.64; $p = 0.52$ for threat conditions). Additionally, we tested whether self-reported anxiety and

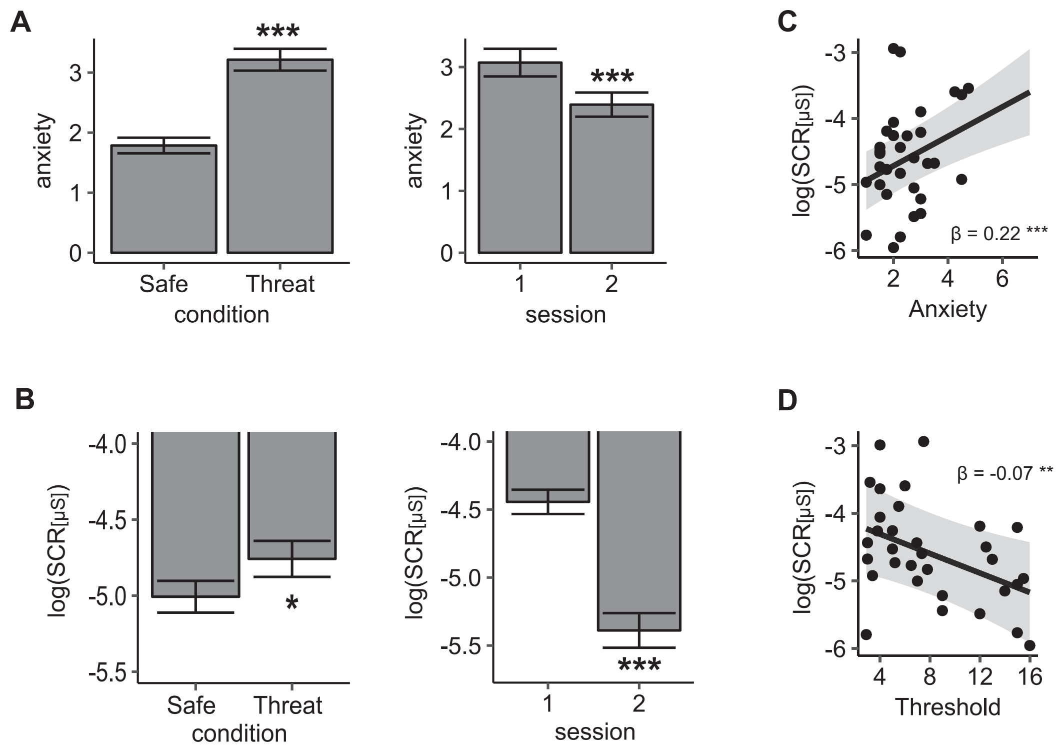

Fig. 1. Threat of electric shock increases anticipatory anxiety as measured by self-reports and skin conductance responses. (A) Mean values of self-reported anxiety during threat and safe periods (left) and during session 1 and 2 (right). (B) Mean amplitude of the phasic component of the log-transformed skin conductance responses (SCRs, estimated using continuous decomposition analysis) after threat and safe cues (left) and during session 1 and 2 (right). For (A) and (B), error bars represent standard errors of the mean. (C) Scatter plot for single-subject mean values of self-reported anxiety and SCRs amplitude. The regression line and coefficient β are derived from a linear mixed model including SCRs and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. (D) Scatter plot for single-subject subjective pain threshold and mean SCRs amplitude. The regression line and coefficient β are derived from a linear mixed model including threshold and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. For (C) and (D) the grey area around the regression line indicates 95% confidence intervals. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$ as a result of paired *t*-tests (Tukey HSD corrected).

the amplitude of SCRs mediated the effect of condition on the N1 amplitude. In this case, we did not find any relation between self-reported anxiety, or SCRs, and N1 amplitude during threat or safe conditions.

3.4. Modulation of MMN and N1 amplitude by trait anxiety and attention

We investigated the relation between trait anxiety, derived from the STAI questionnaire scores, and the amplitude of the MMN and N1 components of the auditory evoked response during SAFE or THREAT conditions. Averaged trait anxiety scores across participants were 39.39 (SD = 9.06). We found a significant interaction between STAI scores and condition in predicting the MMN amplitude (χ^2 (1) = 4.54; p = 0.03) [Fig. 4; Pseudo-R^2 = 0.07, Pseudo-R^2 (fixed effects) = 0.03]. As for the interaction between self-reported anxiety and MMN amplitude, a higher score in trait anxiety was related to decreased MMN amplitude in the safe condition and increased amplitude in the threat condition. Nonetheless, when the two slopes coefficients were tested, none was significantly different than zero (β = 0.03 [95% c.i. = −0.01, 0.08]; p = 0.23 and β = −0.03 [95% c.i. = −0.08, 0.01]; p = 0.24 for SAFE and THREAT conditions respectively). We conducted an additional analysis to confirm the validity of this effect. Specifically, we extracted data from participants scoring low or high in the STAI questionnaire (1st quartile n = 8, 4th quartile n = 8) and added this information as a fixed effect in a linear mixed model testing an interaction between condition (safe vs threat) and group (low vs high anxiety). We found a significant interaction between condition and group (χ^2 (1) = 3.98; p = 0.04). Post-hoc tests did not yield any significant result. In the same way as for the self-reported anxiety, no relation was found between STAI scores and N1 amplitude.

Finally, we explored whether a modulation of the MMN and N1 amplitude was related to self-report measures of distraction and attention to sounds. More specifically, participants were asked, at the end of each block, to which degree they have got distracted from the task (i.e. watching a movie) and to which degree they were listening to sounds during the task. No interaction or main effect was present when we tested whether attention to sounds or general distraction during the block predicted higher MMN or N1 amplitude.

4. Discussion

The main aim of the present study was to clarify the impact of anticipatory anxiety on early sensory processing. We investigated whether an induced anxious state affects brain correlates of perceptual learning (i.e. the MMN amplitude) or results in a general sensitisation of neural early stimulus processing. Contrary to previous EEG studies, we relied on threat of electric shock as a well-established state anxiety manipulation procedure, to provide results that are comparable with recent findings (Cornwell et al., 2017) and account for limitations of other methods (Robinson et al., 2013 for a review). Participants reported higher levels of anxiety during periods of threat, compared to safe periods. Additionally, electrodermal activity was affected by electric shock threat, resulting in higher skin conductance responses (SCRs) to auditory cues introducing threat, compared to safe periods. These results confirm the involvement of the sympathetic branch of the autonomic nervous system in the anticipation of unpredictable noxious

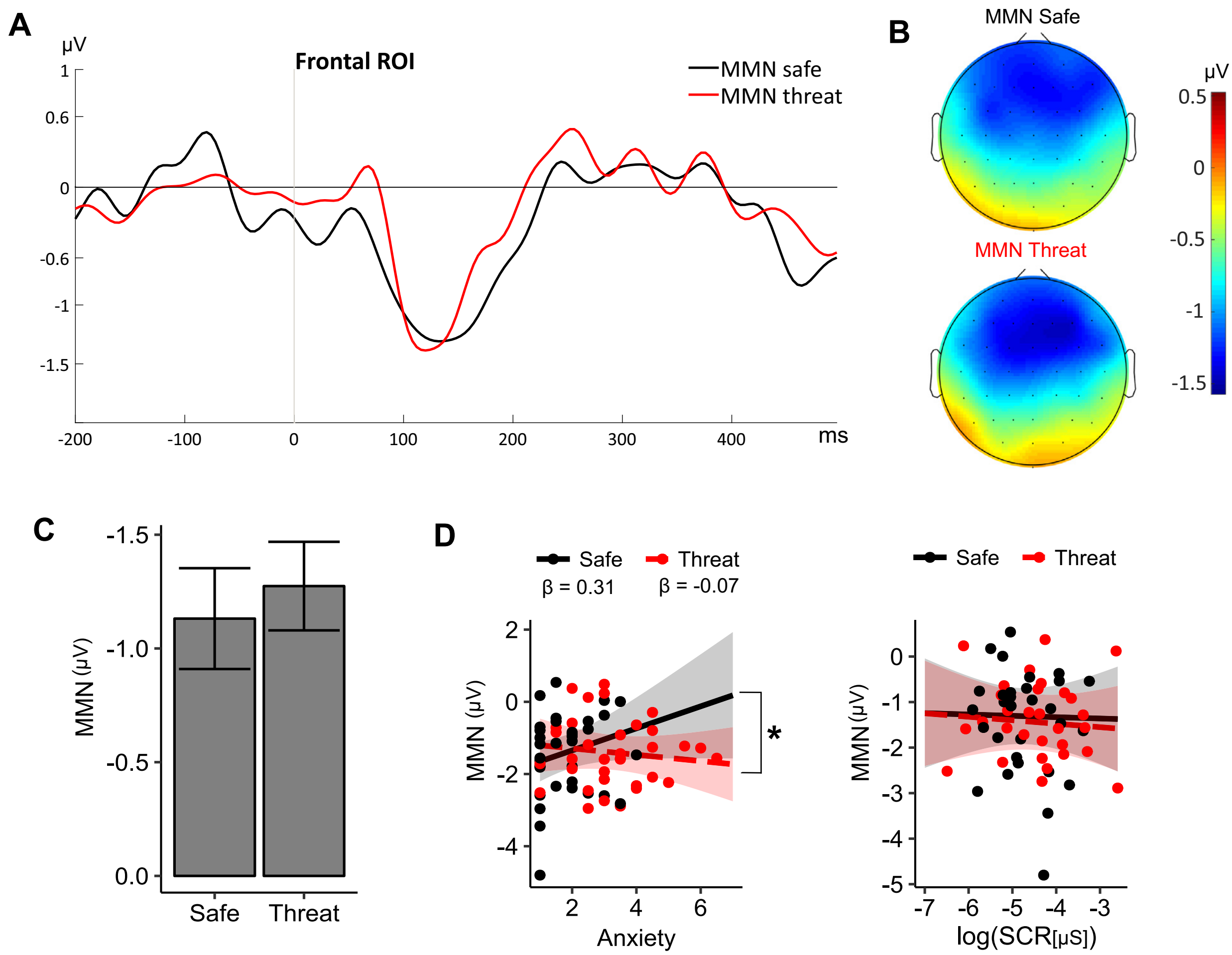

Fig. 2. Threat of electric shock does not modulate neural correlates of perceptual learning, except at high degrees of anxiety. (A) Difference (deviant minus standard, i.e. MMN) waveforms at frontal ROI (see Fig. S1) for safe and threat conditions. (B) Average voltage scalp maps of MMN in safe and threat conditions at 30 ms around peak latencies (safe = 130–150 ms; threat = 110–130 ms). (C) Mean values of MMN from (B) at frontal ROI. Error bars represent standard errors of the mean. (D) Scatter plot for single-subject mean values of self-reported anxiety and MMN amplitude (left) and mean SCRs and MMN amplitude (right) in safe and threat conditions. Regression lines and coefficients β for both plots were derived from linear mixed models that included self-reported anxiety (left) or SCRs [mean amplitude of the phasic component] (right) and condition as fixed effects and session, subject and block order as random effects. The grey and red areas around the regression lines indicate 95% confidence intervals for safe and threat conditions, respectively. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$ as a result of paired *t*-tests (Tukey HSD corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stimuli (Epstein and Roupenian, 1970). Moreover, SRCs and self-reports of state anxiety were strongly related in this paradigm, highlighting a high degree of specificity of electrodermal activity compared to other physiological measures. In a previous study, for instance, measures of salivary cortisol, a widely used marker of stress, did not correlate with subjective ratings (Simoens et al., 2007).

Both the average self-reported anxiety and SCRs decreased from the first to the second experimental session. Despite a well-known relation between repetitive exposure to stressors and habituation of electrodermal activity (Epstein, 1971), an alternative explanation for these results could be found in an effect of general fatigue and in the fact that the second session took place within an hour after lunch. However, the general decrease in anxiety between the first and second session did not modulate or disrupt the induction of an anxious state during the threat periods.

Although we can maintain, based on the above-mentioned results, that the experimental paradigm effectively manipulated levels of anticipatory anxiety, we did not find a difference in the amplitude of the MMN between safe and threat periods. This result held true regardless of whether a difference in MMN amplitude was tested in a canonical frontal ROI or using an electrode-wise cluster-based approach. No effect of the experimental manipulation was found when subjects that did not report any difference in anticipatory anxiety between conditions were excluded from the analysis. The findings are in line with previous studies that either did not find differences in MMN amplitude to frequency deviants at the level of scalp EEG (Ermutlu et al., 2005; Simoens et al., 2007) or found that state anxiety modulates differences in MMN in negative, but not neutral contexts (Schirmer and Escoffier, 2010). Our results contradict previous studies that reported increased brain responses to auditory deviants after the induction of an anxious state (Cornwell et al., 2017, 2007; Elling et al., 2011). Elling et al. (2011) used EEG to measure the MMN amplitude during a cold pressure task (CPT); the MMN increased right after the application of the stressor. Beside the ambiguity on the CPT effectiveness in inducing anticipatory anxiety (e.g. Robinson et al., 2013), the statistical analysis implemented in this study is questionable. The MMN amplitude after the stressor application was compared, using an a priori contrast, to the average amplitude of measures at other nine time-points combined. This approach can increase the probability of false positives since the two conditions tested differ in terms of signal-to-noise ratio. Cornwell et al. (2007) used MEG to locate brain regions of

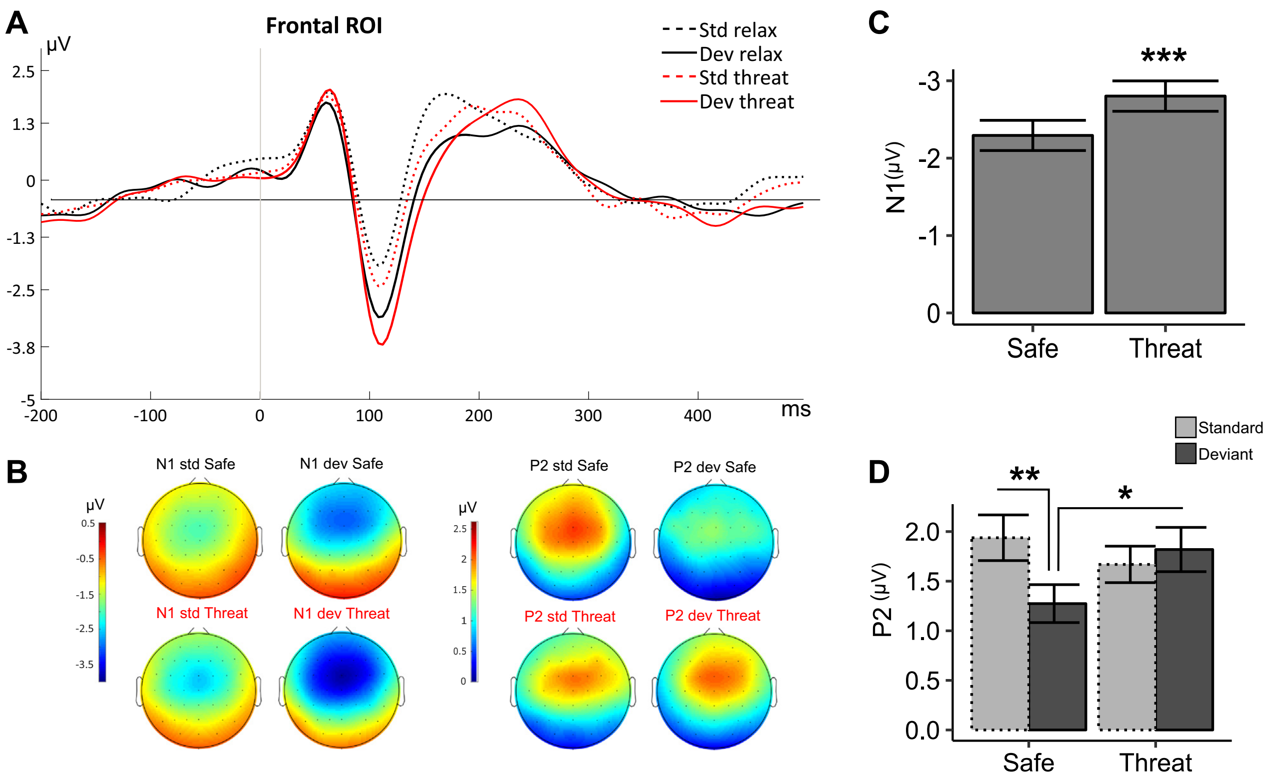

Fig. 3. Threat of electric shock increases the amplitude of neural correlates of early sensory processing. (A) Average auditory-evoked responses to standard (solid lines) and deviant (dashed lines) stimuli at frontal ROI (see Fig. S1) during safe and threat conditions. (B) Average voltage scalp maps of standard and deviant stimuli in safe and threat conditions at 30 ms around peak latencies for the N1 (30–200 ms) and P2 (160–300 ms) components of the auditory evoked response. (C) Mean values of N1 amplitude from (B) at frontal ROI for safe and threat conditions, combining standard and deviant stimuli. (D) Mean values of P2 amplitude from (B) at frontal ROI for safe and threat conditions and separately for standard and deviant stimuli. For (C) and (D), error bars represent standard errors of the mean. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$ as a result of paired *t*-tests (Tukey HSD corrected).

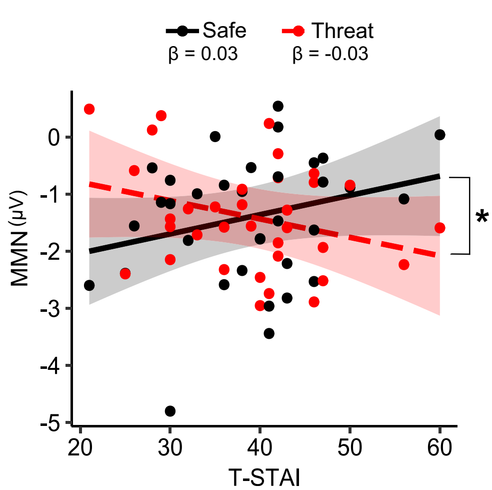

Fig. 4. High degrees of trait anxiety modulate the neural correlates of perceptual learning under threat of electric shock. Scatter plot for single-subject mean values of trait anxiety (T-STAI score) and MMN amplitude in safe and threat conditions. The regression lines and coefficients β are derived from a linear mixed model including T-STAI score and condition (safe, threat) as fixed effects and session, block order and subjects as random effects. The grey and red areas around the regression lines indicate 95% confidence intervals for safe and threat conditions, respectively. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$ as a result of paired *t*-tests (Tukey HSD corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

increased response to stimulus deviance under threat of electric shock. Greater activity in several regions was found to correlate with differences in self-reported anticipatory anxiety. Nonetheless, a relatively lax threshold for detecting regions of activity was used (at least two contiguous voxels with the probability of the average t statistic $p < 0.05$, with no correction for multiple comparisons). Cornwell et al. (2017) replicated the previous MEG results, but restricting the analysis on a priori regions of interest that are part of a neuroanatomical model of the MMN (Garrido et al., 2009a). Within specific sources, they found an interaction between treatment (benzodiazepine) and condition (safe and threat) on the magnetic equivalent of the MMN. The authors, however, do not report results on the direction of the interaction and one could presume that the response to deviants was higher in threat, compared to safe periods, in the placebo condition, whereas the opposite was true when subjects underwent a pharmacological treatment.

A possible reason underlying the different results between the present EEG study and previous MEG studies could come from the role of attention in modulating the size of prediction error signals, described in different sensory domains (Feldman and Friston, 2010; Kok et al., 2012). In the cited research, subjects underwent a passive oddball task, but were not instructed to ignore the auditory stimuli (the information is not present in the reports). In the present study, participants were instructed to watch a silent movie and ignore the auditory stimulation. However, we did not find any significant relation between self-reported attention to the auditory stimuli and the MMN amplitude. As we did not conceive the paradigm to elucidate this question, we can hypothesize that attentional shifts during the oddball session were not that consistent to determine a modulation of the MMN.

A further explanation could be found in the different statistical power and sensitivity between a source-based approach using MEG and the analysis of electric currents at the scalp level with EEG. Previous MEG studies did not report statistical analysis on sensors, hence no comparison with the present findings is possible at the scalp level. In spite of this, previous researches have described a considerable degree of correspondence between sources of MEG activity and electric MMN responses (Huotilainen et al., 1998).

Despite the lack of replication of studies that propose a general effect of anticipatory anxiety on perceptual learning, we hypothesize that this effect could be present for subjects with high degrees of state or trait anxiety. Specifically, we found a different modulatory effect of self-reported, as well as trait anxiety, on the MMN amplitude in the threat and safe conditions. The observed interactions point towards a possible difference in the MMN during threat, compared to safe periods, in subjects that scored high in the trait anxiety measure, as well as in those who reported high levels of state anxiety. This is in line with views of anxiety as a dimensional construct (Endler and Kocovski, 2001) and neurophysiological accounts of disfunctions in executive networks related to high levels of trait anxiety (Sylvester et al., 2012). The putative impact of anxiety on perceptual learning as a function of the degree of trait and state severity can also explain the relative consistency found in studies that investigated the modulation of MMN amplitude by anxiety-related psychopathologies and dispositional anxiety (e.g. Bangel et al., 2017; Chen et al., 2016; Ge et al., 2011; Hansenne et al., 2003). The present findings raised a methodological consideration: when explored separately, no relationship was found between state or trait anxiety and the amplitude of the MMN in either safe or threat conditions. This result suggests that the MMN could be used as a marker of trait-anxiety only when one is contrasting the modulatory effect of trait-anxiety in a neutral compared to an anxiogenic state.

An interesting hypothesis is that state anxiety is generally linked to alerting and hyper vigilance and does not necessarily impact more complex processes such as perceptual learning, unless high levels of state or trait anxiety are reached (Pacheco-Unguetti et al., 2010). In the present study, we found an impact of the experimental manipulation on the amplitude of early neural responses to auditory stimuli. Similarly to previous studies (Ermutlu et al., 2005; Scaife et al., 2006; White et al., 2005) we found an increased auditory N1 during threat, compared to safe periods. These results are also in line with research that reports an impact of mild stress on the sensitisation of early sensory processing in other domains (Qi et al., 2018; Shackman et al., 2011a). In the auditory domain, the increase in N1 amplitude has been related to an increase in noradrenergic activity, affecting the ability to filter out irrelevant sensory information (Ermutlu et al., 2005). Here we found that the modulation of neural correlates of early sensory processing by anticipatory anxiety is present for all stimuli at the N1 latency but is limited to auditory deviants at the P2 latency. A possible explanation is that, at later stages of sensory processing, only stimuli that are characterised by a higher degree of saliency are affected by the experimental manipulation. Nonetheless, this hypothesis remains exploratory.

Finally, contrary to the MMN, the modulation of the N1 amplitude by the experimental conditions was not mediated by self-reported or trait anxiety. In this sense, we can affirm that the sensitisation of early sensory processing by a state of hypervigilance is a robust phenomenon, which impacts brain responses even at a mild degree of anxiety.

To summarize, in the present study we sought to elucidate the influence of anticipatory anxiety on early sensory processing. We found that, contrary to recent findings, state anxiety does not modulate a common neural marker of perceptual learning, but rather sensitises early brain responses to auditory stimuli. Perceptual learning processes seem to be affected only at high levels of state and trait anxiety. Such a scenario is plausible if we consider anxiety as a dimensional construct. At mild levels of anxiety, brain responses to otherwise irrelevant stimuli are increased, an adaptive feedback to unpredictable threats in uncertain environments. However, when a state of anxiety is highly intense, or sustained across time, it affects the way the brain makes sense of the environment and learns about its features. Ultimately, such view distinguishes between an adaptive role of anxiety on processing efficiency and the detrimental impact on perceptual learning observed in psychiatric conditions.

Conflict of interest

The authors have no conflict of interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.04.010.

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