



HAL
open science

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

E. Fucci, O. Abdoun, A. Lutz

► To cite this version:

E. Fucci, O. Abdoun, A. Lutz. Auditory perceptual learning is not affected by anticipatory anxiety in the healthy population except for highly anxious individuals: EEG evidence. *Clinical Neurophysiology*, 2019, 130, pp.1135 - 1143. 10.1016/j.clinph.2019.04.010 . hal-03484417

HAL Id: hal-03484417

<https://hal.science/hal-03484417>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

3

4 Fucci E., Abdoun O., Lutz, A.

5

6 Lyon Neuroscience Research Centre, INSERM U1028, CNRS UMR5292, Lyon 1 University, Lyon, France

7

8 **Corresponding author:**

9 Antoine Lutz

10 Lyon Neuroscience Research Center, DYCOG Team, INSERM U1028 – CNRS UMR5292, Centre

11 Hospitalier Le Vinatier (Bât. 452), 95 Bd Pinel, 69500 Bron, France

12 Tel.: +33-4-72-13-89-08

13 E-mail: antoine.lutz@inserm.fr

14

15

16

17

18 **Abstract**

19 *Objective:* A recent neurocomputational model proposed that anxious hypervigilance impedes
20 perceptual learning. This view is supported by the observed modulation of the mismatch
21 negativity (MMN), a biomarker of implicit perceptual learning processes, in anxiety disorders.
22 However, other studies found that anxious states sensitize brain responses with no impact on
23 perceptual learning. The present research aimed to elucidate the impact of anticipatory anxiety on
24 early stimulus processing in the healthy population.

25 *Methods:* We used electroencephalography to investigate the impact of unpredictable threat on
26 the amplitude of the MMN and other components of the auditory evoked response in healthy
27 participants during a passive auditory oddball task.

28 *Results:* We found a general sensitization of early components of the auditory evoked response
29 and changes in subjective and autonomic measures of anxiety during threat periods. The MMN
30 amplitude did not differ during threat, compared to safe periods. However, this difference was
31 modulated by the level of state or trait anxiety.

32 *Conclusion:* We propose that anxiety sensitizes early brain responses to unspecific environmental
33 stimuli but affects implicit perceptual learning processes only when an individual is located at the
34 higher end of the anxiety spectrum.

35 *Significance:* This view might distinguish between an adaptive role of anxiety on processing
36 efficiency and its detrimental impact on implicit perceptual learning observed in psychiatric
37 conditions.

38

39 **Keywords:** MMN, N1, EEG, threat, anxiety, perceptual learning.

40

41

42 **Highlights**

- 43
- 44 • Anxious hypervigilance sensitizes early brain responses to unrelated stimuli.
 - 45 • Perceptual learning is affected only in individuals with high state or trait anxiety.
 - 46 • Differences in the modulation of neural processes confirm anxiety as a dimensional
47 construct.
- 48

49 1. Introduction

50

51 The adaptive interplay between perception and emotional states is fundamental for optimal goal-
52 oriented behaviour in complex and volatile environments. Essential to this process is the capacity
53 to screen out irrelevant sensory information and detect stimuli that are relevant or can constitute
54 a threat. Anxiety serves this purpose via affective, cognitive and physiological changes that create
55 a state of hypervigilance in response to unpredictable threats in novel and uncertain settings
56 (Grupe and Nitschke, 2013). Evolutionarily, anxiety increases the odds of survival in threatening
57 situations (Kalin and Shelton, 1989), but it can become maladaptive if sustained over time and
58 associated to otherwise innocuous stimuli. This is the case in psychopathological conditions such
59 as PTSD and anxiety disorders (Cisler and Koster, 2010; Newport and Nemeroff, 2000). A putative
60 disruptive effect of anxiety on cognitive functions, and related performance impairments, is also
61 described in the healthy population by nowadays widespread and influential theories (Eysenck et
62 al., 2007; Eysenck and Derakshan, 2011). In the framework of cognitive neurosciences, anxiety-
63 induced hypervigilance is considered to impact sensory-perceptual processing through the
64 sensitisation of neural responses to environmental stimuli (see Jafari et al., 2017; Robinson et al.,
65 2011 for recent reviews).

66 According to a recent neurocomputational model, anxious hypervigilance would impede
67 perceptual learning by increasing the synaptic gain of prediction error signals while down-
68 regulating descending prediction pathways. This mechanism is suggested to tap into early stimulus
69 processing and could underlie the detrimental effects of anxiety on higher-order cognitive
70 processes (Cornwell et al., 2017). This model is ascribed to the predictive coding framework
71 (Friston, 2009) and considers the mismatch negativity (MMN, e.g. Näätänen et al., 2004), a neuro-
72 electric response to violations of statistical regularities in the sensory environment, as a marker of

73 implicit perceptual learning processes in the form of precision-weighted prediction error signal
74 (Garrido et al., 2009b). It is worth mentioning that the definition of perceptual learning in this
75 context, in terms of attenuation of responses encoding prediction errors (e.g. Friston, 2009), refers
76 to an implicit process and differs from a definition of explicit learning of perceptual features
77 through training associated with long-term neural plasticity (e.g. Schwartz et al., 2002; Yotsumoto
78 et al., 2008).

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

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

95 In the present study, we tried to shed light on the ambiguous findings concerning the effect of
96 anticipatory anxiety on perceptual learning and early stimulus processing. Specifically, we used

97 EEG to measure the amplitude of the MMN under threat of electric shock during a passive oddball
98 task (as Cornwell et al., 2017, 2007), as well as the amplitude of early components of the auditory-
99 evoked response. In addition to subjective self-reports, which are commonly used in the above-
100 mentioned studies, we measured changes in the electrodermal activity in response to periods of
101 threat to provide a marker of the autonomic response to the anxiety-induction procedure (Folkins,
102 1970; Nomikos et al., 1968). Finally, we investigated whether an anxious state had a different
103 impact on perceptual learning and early sensory processing compared to the one of anxiety
104 measured as a trait.

105

106

107 **2. Materials and Methods**

108

109 **2.1 Subjects**

110 Thirty-six healthy individuals (52 ± 7.6 years old, 17 females, right-handed, 3 ± 2.33 years of higher
111 education, all white Caucasians) participated in the study. Subjects were recruited from the local
112 community to participate as controls in a broader project that investigated the effects of
113 mindfulness meditation on cognitive and emotional processes. For a detailed description of the
114 recruitment procedure, as well as inclusion and exclusion criteria, readers can refer to the project
115 manual (Abdoun et al., 2018, available online at <https://osf.io/dbwch>). Regarding the present
116 study, relevant exclusion criteria were the following: use of psychoactive medication, history of
117 neurological or psychiatric conditions, history of chronic pain or other conditions involving
118 sensitisation to pain, personal or family history of epilepsy, severe hearing loss. All participants
119 were affiliated to social security, provided written informed consent before the start of the study

120 and were paid for their participation. Ethical approval was obtained from the appropriate regional
121 ethics committee on Human Research (CPP Sud-Est IV, 2015-A01472-47). Each subject completed
122 the trait subscale of the State Trait Anxiety Inventory (STAI, [Spielberger, 1970]) before
123 participating in the experiment.

124

125 ***2.2 Task design and stimuli***

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

143 much they were distracted during the block and how much they were listening to the auditory
144 stimuli (see [Supplementary Information](#) for the specific questions asked).

145

146 **2.3 Electric-shock stimuli and intensity work-up procedure**

147 In line with the procedure described in Schmitz and Grillon (2012), electrodes from a direct current
148 stimulator were placed on the participant's lower wrist. Participants were asked to rate delivered
149 electric stimuli on a scale from 1 to 5 (1 = barely felt, 5 = very uncomfortable). Stimuli were
150 presented at intensities starting from 2mA and up to 16mA (duration = 100ms), until the
151 participant rated the stimulus 4 out of 5 on the scale. If the subject's threshold reached 16mA,
152 stimuli were delivered at this maximal intensity. In our sample, the mean shock intensity was
153 8.29mA (SD = 4.41). Five shocks were delivered randomly throughout the two blocks. No more
154 than two shocks were delivered during the same threat period. Subjects were told that the
155 number of delivered shocks could vary randomly and that the experimenter had no control over
156 their frequency.

157

158 **2.4 EEG recordings**

159 EEG was recorded at 512 Hz using the ActiveTwo system (BioSemi, Amsterdam, Netherlands),
160 consisting of 64 active electrodes that were placed in an EEG cap according to the standard 10/20
161 system. The horizontal and vertical EOG was measured by placing electrodes on the outer canthi
162 and above and below the subject's left eye. All electrodes were kept within an offset of 50 mV (+/-
163 25 mV) using the Biosemi ActiView data acquisition system for measuring signal quality.
164 Additionally, recordings were performed in a highly shielded Faraday chamber (see [Figure S2](#) for
165 an example of raw EEG recording).

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

190

191 **2.6 Event-related potentials**

192 Statistical analyses were performed using R Studio (version 3.4.2 [R core team, 2017]). For the
193 analysis of event-related potentials (ERPs), only standard stimuli that directly preceded a deviant
194 were considered. The average number of standards was 52.25 and 51.42 for safe and threat
195 conditions (SD = 6.06 and 5.70 respectively) and the average number of deviants was 52.24 and
196 51.62 (SD = 6.03 and 5.43).

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

205 Additionally, we performed analysis on the amplitude of classical auditory ERP components, such
206 as the N1 and P2 (Picton et al., 1974), on the frontal ROI. Single-subject amplitudes for each
207 condition (safe and threat), session and stimulus (standard and deviant) were extracted from a
208 20ms time-window centred around the most negative peak between 90 and 200ms for the N1,
209 and around the most positive peak between 160 and 300ms for the P2.

210 For each of the three components of interest (MMN, N1, P2) we tested the effect of condition
211 (threat and safe periods) and stimulus type (for N1 and P2) using linear mixed-effects models (R
212 package lme4, [Bates et al., 2014]) that allow for unbalanced designs (e.g. missing data from one
213 session for a subject) and the inclusion of random effects such as, in the present case, session and

214 block order information for each observation. Mixed-effects models were evaluated with an
215 ANOVA analysis of variance (Type II Wald chi-square test). Normality of residuals and
216 heteroskedasticity have been visually checked using residual plots and QQ plots and verified for all
217 models. Paired t-tests were used as post-hoc tests, comparing least-squared means, and were
218 corrected for multiple comparisons using Tukey honestly significant difference test (HSD). We
219 report, in the results section, estimates of effect size in the form of pseudo-R² as proposed by
220 Nakagawa and Schielzeth (2013). Notice that the calculation of effect sizes in linear mixed models
221 is not unambiguous and should be handled with consideration.

222 Finally, we performed an additional analysis looking for time-electrode pairs where the MMN
223 amplitude differed significantly between safe and threat periods. We corrected for multiple
224 comparison using a non-parametric, permutation-based, cluster-level statistical test as
225 implemented in the Matlab toolbox Fieldtrip (Oostenveld et al., 2011) (cluster-defining threshold =
226 0.001; cluster-level threshold = 0.05; 10,000 permutations).

227

228 **2.7 Skin conductance data acquisition and analysis**

229 For the recording of electrodermal activity, two passive electrodes were placed on the
230 participant's non-dominant hand, on the volar surface of the distal phalange of the 2nd and 3rd
231 fingers, using an electrode paste specifically designed for the recording of electrodermal activity
232 (GEL101, Biopac; isotonic, 0.05 molar NaCl, electrode paste). Data were recorded using the 16Hz
233 coupler provided with the ActiveTwo system (BioSemi, Amsterdam, Netherlands) with a sampling
234 rate of 250Hz. Data were down-sampled at 25Hz and analysed with the Matlab software Ledalab V
235 3.4.9 (www.ledalab.de) applying Continuous Decomposition Analysis (Benedek and Kaernbach,
236 2010), separating the tonic electrodermal activity throughout a block from the phasic activity. Our
237 measure of interest was the event-related phasic activity after the onset of auditory cues

238 preceding safe and threat periods. Data were visually inspected and sessions where very weak or
239 no phasic response was present were excluded from further analysis. Following this inspection,
240 three subjects and six single sessions were excluded due to lack of data (equipment failure) or the
241 lack of phasic responses. Subsequently, skin conductance responses (SCRs) were calculated for
242 each subject and session over a 1 to 5 seconds window after stimulus onset (threat or safe cue)
243 with a minimum threshold of 0.01 microSiemens (μS). Here we report the average phasic driver
244 activity underlying raw SCRs deconvolved into tonic and phasic components. The latter was
245 integrated and averaged over the selected time-window to produce the measure of interest.
246 Finally, all values were log-transformed to improve the normality of the distributions.

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

254

255 **2.8 Self-reports and regression analysis**

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

260 Finally, we investigated the relationships between answers to self-report questions and third-
261 person variables (e.g. ERP components amplitude and SCRs), as well as between trait (STAI

262 questionnaire scores) and state measures. To minimize the number of statistical tests and allow
263 for unbalanced designs (e.g. SCR or EEG data missing for some subjects), we used linear mixed
264 models entering independent variables and factors as fixed effects, as well as session and block
265 order information as random effects for all the fitted models. Eventual interactions between an
266 independent variable and levels of a factor were explored post-hoc comparing the regression
267 slopes between each factor level using the function “lstmrends” (R package “lsmeans”, Lenth, 2016).
268 In the context of interactions, we tested whether a specific slope for one factor level was different
269 from zero using the function “sim_slopes” (R package “jtools”, Long, 2018;
270 <https://www.jtools.jacob-long.com>).

271

272 **3. Results**

273

274 **3.1 Manipulation of anxiety**

275 Participants underwent two experimental sessions (2 to 3 hours apart) where they were exposed
276 to two conditions during the EEG recordings. A THREAT condition, when the participant was
277 informed of the possibility of receiving an electric shock, and a SAFE condition, when no shock was
278 delivered, were alternated during the block. Self-reported anxiety was significantly higher during
279 THREAT, compared to SAFE condition ($\chi^2(1) = 72.54$; $p < 0.001$) and was generally lower in the
280 second session ($\chi^2(1) = 11.54$; $p < 0.001$) [Figure 1.A; Pseudo- $R^2 = 0.56$, Pseudo- R^2 (fixed effects) =
281 0.26; see [Figure S3.B](#) for data distribution and additional descriptive statistics]. No interaction was
282 present between condition and session. For some sessions (16 out of 72) participants reported no
283 difference in anxiety between conditions. We decided to keep these observations in further
284 analyses because in several sessions (8 out of 16) self-reported anxiety was higher than 1.

285 Nonetheless, additional analyses on the MMN amplitude were performed excluding these
286 observations (see results section 3.2).

287 Skin conductance responses (SCRs) were significantly higher during THREAT, compared to SAFE
288 condition ($\chi^2(1) = 5.3$; $p = 0.02$) and were lower in the second session ($\chi^2(1) = 35.45$; $p < 0.001$)
289 [Figure 1.B; Pseudo- $R^2 = 0.45$, Pseudo- R^2 (fixed effects) = 0.06; see [Figure S3.B](#) for data distribution
290 and additional descriptive statistics]. No interaction was present between condition and session.
291 Higher self-reported anxiety significantly predicted higher SCRs ($\chi^2(1) = 15.23$; $p < 0.001$; $\beta = 0.22$ [
292 95% c.i. = 0.11, 0.34]) [Figure 1.C; Pseudo- $R^2 = 0.45$, Pseudo- R^2 (fixed effects) = 0.11]. Lower
293 subjective discomfort thresholds to the electric shocks predicted higher SCRs ($\chi^2(1) = 6.64$; $p =$
294 0.009 ; $\beta = -0.07$ [95% c.i. = -0.13, -0.02]) [Figure 1.C; Pseudo- $R^2 = 0.47$, Pseudo- R^2 (fixed effects) =
295 0.08]. For the last two regression models, condition and session were entered as random effects.

296

297 **3.2 MMN amplitude**

298 Our main question was to investigate whether the MMN amplitude was modulated by the threat
299 of electric shock. As no interaction between condition and session was found on self-reported
300 anxiety or SCRs, we did not test this interaction in the model on the MMN amplitude, but rather
301 included session as a random effect. Figure 2.A and 2.B show the time-course of the mean
302 amplitude of the difference waveforms, across participants and sessions, and topographies at the
303 MMN time-window for the SAFE and THREAT conditions. There was no effect of condition on the
304 MMN amplitude when all observations were included ($\chi^2(1) = 7 \times 10^{-4}$; $p = 0.97$) [Figure 2.A;
305 Pseudo- $R^2 = 0.04$, Pseudo- R^2 (fixed effects) = 0; see [Figure S3.C](#) for data distribution and additional
306 descriptive statistics], as well as excluding observations with no difference in self-reported anxiety
307 ($\chi^2(1) = 0.03$; $p = 0.84$) [Pseudo- $R^2 = 0.04$, Pseudo- R^2 (fixed effects) = 0]. To rule out a possible bias

308 from focusing on a frontal ROI, as well as to explore a possible effect of condition on the MMN in
309 unconventional scalp locations, we performed an electrode-wise cluster-based analysis in time
310 and space dimensions. We did not find any significant cluster of electrodes that showed a
311 difference between the two experimental conditions at any time point of the difference
312 waveform. Additionally, we explored a possible relation between self-reported anxiety and the
313 MMN amplitude. In this case, we found a significant interaction between anxiety and condition (χ^2
314 (1) = 3.75; $p = 0.05$) showing that higher self-reported anxiety predicted lower MMN amplitude in
315 the SAFE condition and higher MMN amplitude in the THREAT condition [Figure 2.D; Pseudo- $R^2 =$
316 0.06, Pseudo- R^2 (fixed effects) = 0.03]. Nonetheless, none of the two slope coefficients were
317 significantly higher than zero ($\beta = 0.31$ [95% c.i. = -0.02, 0.63]; $p = 0.2$ and $\beta = -0.09$ [95% c.i. = -
318 0.33, 0.15]; $p = 0.51$ for SAFE and THREAT conditions respectively). Finally, we explored a
319 relationship between the SCRs and MMN amplitudes. No main effect or interaction between SCRs
320 and MMN resulted from this regression model (Figure 2.D).

321

322 **3.3 N1 and P2 amplitude**

323 We investigated the impact of threat of electric shock on components of the auditory evoked
324 response that are related to early sensory processing for standard and deviant stimuli. Again, we
325 included session as a random effect in the tested models. Figure 3.A shows the time-course of the
326 auditory evoked responses across participants and sessions for standard and deviant stimuli
327 during THREAT and SAFE condition. Figure 3.B shows the respective topographies at the N1 and P2
328 time-windows. The model tested at the N1 latency showed how the N1 amplitude increases
329 during THREAT, compared to the SAFE condition (χ^2 (1) = 11.16; $p < 0.001$). A main effect of
330 stimulus was present, representing the MMN (χ^2 (1) = 67; $p < 0.001$), while there was no

331 interaction between stimulus and condition [Figure 3.C; Pseudo-R² = 0.71, Pseudo-R² (fixed effects)
332 = 0.08; see [Figure S3.D](#) for data distribution and additional descriptive statistics]. At the P2 latency,
333 the tested model resulted in an interaction between stimulus and condition (χ^2 (1) = 6.07; p =
334 0.01) [Figure 3.D; Pseudo-R² = 0.39, Pseudo-R² (fixed effects) = 0.02]. At this latency, the amplitude
335 of the evoked response increases during the THREAT condition only for deviant stimuli (t-ratio
336 (231) = -2.33; p = 0.02 for deviants and t-ratio (231) = 1.15; p = 0.25 for standards) and a difference
337 between standard and deviant stimuli is present during the SAFE condition only (t-ratio (231) =
338 2.84; p = 0.004 for safe and t-ratio (231) = -0.64; p = 0.52 for threat conditions). Additionally, we
339 tested whether self-reported anxiety and the amplitude of SCRs mediated the effect of condition
340 on the N1 amplitude. In this case, we did not find any relation between self-reported anxiety, or
341 SCRs, and N1 amplitude during threat or safe conditions.

342

343 **3.3 Modulation of MMN and N1 amplitude by trait anxiety and attention**

344 We investigated the relation between trait anxiety, derived from the STAI questionnaire scores,
345 and the amplitude of the MMN and N1 components of the auditory evoked response during SAFE
346 or THREAT conditions. Averaged trait anxiety scores across participants were 39.39 (SD = 9.06).
347 We found a significant interaction between STAI scores and condition in predicting the MMN
348 amplitude (χ^2 (1) = 4.54; p = 0.03) [Figure 4; Pseudo-R² = 0.07, Pseudo-R² (fixed effects) = 0.03]. As
349 for the interaction between self-reported anxiety and MMN amplitude, a higher score in trait
350 anxiety was related to decreased MMN amplitude in the safe condition and increased amplitude in
351 the threat condition. Nonetheless, when the two slopes coefficients were tested, none was
352 significantly different than zero (β = 0.03 [95% c.i. = -0.01, 0.08]; p = 0.23 and β = -0.03 [95% c.i. = -
353 0.08, 0.01]; p = 0.24 for SAFE and THREAT conditions respectively). We conducted an additional

354 analysis to confirm the validity of this effect. Specifically, we extracted data from participants
355 scoring low or high in the STAI questionnaire (1st quartile $n = 8$, 4th quartile $n = 8$) and added this
356 information as a fixed effect in a linear mixed model testing an interaction between condition
357 (safe vs threat) and group (low vs high anxiety). We found a significant interaction between
358 condition and group ($\chi^2(1) = 3.98$; $p = 0.04$). Post-hoc tests did not yield any significant result. In
359 the same way as for the self-reported anxiety, no relation was found between STAI scores and N1
360 amplitude.

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

367

368 **4. Discussion**

369

370 The main aim of the present study was to clarify the impact of anticipatory anxiety on early
371 sensory processing. We investigated whether an induced anxious state affects brain correlates of
372 perceptual learning (i.e. the MMN amplitude) or results in a general sensitisation of neural early
373 stimulus processing. Contrary to previous EEG studies, we relied on threat of electric shock as a
374 well-established state anxiety manipulation procedure, to provide results that are comparable
375 with recent findings (Cornwell et al., 2017) and account for limitations of other methods (Robinson
376 et al., 2013 for a review). Participants reported higher levels of anxiety during periods of threat,

377 compared to safe periods. Additionally, electrodermal activity was affected by electric shock
378 threat, resulting in higher skin conductance responses (SCRs) to auditory cues introducing threat,
379 compared to safe periods. These results confirm the involvement of the sympathetic branch of the
380 autonomic nervous system in the anticipation of unpredictable noxious stimuli (Epstein and
381 Roupenian, 1970). Moreover, SRCs and self-reports of state anxiety were strongly related in this
382 paradigm, highlighting a high degree of specificity of electrodermal activity compared to other
383 physiological measures. In a previous study, for instance, measures of salivary cortisol, a widely
384 used marker of stress, did not correlate with subjective ratings (Simoens et al., 2007).

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

391 Although we can maintain, based on the above-mentioned results, that the experimental
392 paradigm effectively manipulated levels of anticipatory anxiety, we did not find a difference in the
393 amplitude of the MMN between safe and threat periods. This result held true regardless of
394 whether a difference in MMN amplitude was tested in a canonical frontal ROI or using an
395 electrode-wise cluster-based approach. No effect of the experimental manipulation was found
396 when subjects that did not report any difference in anticipatory anxiety between conditions were
397 excluded from the analysis. The findings are in line with previous studies that either did not find
398 differences in MMN amplitude to frequency deviants at the level of scalp EEG (Ermutlu et al.,
399 2005; Simoens et al., 2007) or found that state anxiety modulates differences in MMN in negative,
400 but not neutral contexts (Schirmer and Escoffier, 2010). Our results contradict previous studies

401 that reported increased brain responses to auditory deviants after the induction of an anxious
402 state (Cornwell et al., 2017, 2007; Elling et al., 2011). Elling et al. (2011) used EEG to measure the
403 MMN amplitude during a cold pressure task (CPT); the MMN increased right after the application
404 of the stressor. Beside the ambiguity on the CPT effectiveness in inducing anticipatory anxiety (e.g.
405 Robinson et al., 2013), the statistical analysis implemented in this study is questionable. The MMN
406 amplitude after the stressor application was compared, using an a priori contrast, to the average
407 amplitude of measures at other nine time-points combined. This approach can increase the
408 probability of false positives since the two conditions tested differ in terms of signal-to-noise ratio.
409 Cornwell et al. (2007) used MEG to locate brain regions of increased response to stimulus
410 deviance under threat of electric shock. Greater activity in several regions was found to correlate
411 with differences in self-reported anticipatory anxiety. Nonetheless, a relatively lax threshold for
412 detecting regions of activity was used (at least two contiguous voxels with the probability of the
413 average t statistic $p < 0.05$, with no correction for multiple comparisons). Cornwell et al. (2017)
414 replicated the previous MEG results, but restricting the analysis on a priori regions of interest that
415 are part of a neuroanatomical model of the MMN (Garrido et al., 2009a). Within specific sources,
416 they found an interaction between treatment (benzodiazepine) and condition (safe and threat) on
417 the magnetic equivalent of the MMN. The authors, however, do not report results on the direction
418 of the interaction and one could presume that the response to deviants was higher in threat,
419 compared to safe periods, in the placebo condition, whereas the opposite was true when subjects
420 underwent a pharmacological treatment.

421 A possible reason underlying the different results between the present EEG study and previous
422 MEG studies could come from the role of attention in modulating the size of prediction error
423 signals, described in different sensory domains (Feldman and Friston, 2010; Kok et al., 2012). In
424 the cited research, subjects underwent a passive oddball task, but were not instructed to ignore

425 the auditory stimuli (the information is not present in the reports). In the present study,
426 participants were instructed to watch a silent movie and ignore the auditory stimulation.
427 However, we did not find any significant relation between self-reported attention to the auditory
428 stimuli and the MMN amplitude. As we did not conceive the paradigm to elucidate this question,
429 we can hypothesize that attentional shifts during the oddball session were not that consistent to
430 determine a modulation of the MMN.

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

437 Despite the lack of replication of studies that propose a general effect of anticipatory anxiety on
438 perceptual learning, we hypothesize that this effect could be present for subjects with high
439 degrees of state or trait anxiety. Specifically, we found a different modulatory effect of self-
440 reported, as well as trait anxiety, on the MMN amplitude in the threat and safe conditions. The
441 observed interactions point towards a possible difference in the MMN during threat, compared to
442 safe periods, in subjects that scored high in the trait anxiety measure, as well as in those who
443 reported high levels of state anxiety. This is in line with views of anxiety as a dimensional construct
444 (Endler and Kocovski, 2001) and neurophysiological accounts of disfunctions in executive networks
445 related to high levels of trait anxiety (Sylvester et al., 2012). The putative impact of anxiety on
446 perceptual learning as a function of the degree of trait and state severity can also explain the
447 relative consistency found in studies that investigated the modulation of MMN amplitude by
448 anxiety-related psychopathologies and dispositional anxiety (e.g. Bangel et al., 2017; Chen et al.,

449 2016; Ge et al., 2011; Hansenne et al., 2003). The present findings raised a methodological
450 consideration: when explored separately, no relationship was found between state or trait anxiety
451 and the amplitude of the MMN in either safe or threat conditions. This result suggests that the
452 MMN could be used as a marker of trait-anxiety only when one is contrasting the modulatory
453 effect of trait-anxiety in a neutral compared to an anxiogenic state.

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

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

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

484

485 **Conflict of interest**

486 The authors have no conflict of interests.

487

488 **Acknowledgments**

489 This study was supported by a European Research Council grant ERC-Consolidator 617739-
490 BRAINandMINDFULNESS to Antoine Lutz.

491

- 493 Abdoun, O., Zorn, J., Fucci, E., Perraud, E., Aarts, K., Lutz, A., 2018. Brain & Mindfulness project manual.
494 OSF. <https://osf.io/dbwch/>
- 495 Bangel, K.A., Buschbach, S. van, Smit, D.J.A., Mazaheri, A., Olff, M., 2017. Aberrant brain response after
496 auditory deviance in PTSD compared to trauma controls: An EEG study. *Sci. Rep.* 7, 16596.
497 <https://doi.org/10.1038/s41598-017-16669-8>
- 498 Bates, D., Mächler, M., Bolker, B., Walker, S., 2014. Fitting linear mixed-effects models using lme4. *ArXiv*
499 Prepr. ArXiv14065823.
- 500 Benedek, M., Kaernbach, C., 2010. A continuous measure of phasic electrodermal activity. *J. Neurosci.*
501 *Methods* 190, 80–91. <https://doi.org/10.1016/j.jneumeth.2010.04.028>
- 502 Chen, C., Hu, C.-H., Cheng, Y., 2016. Mismatch negativity (MMN) stands at the crossroads between explicit
503 and implicit emotional processing. *Hum. Brain Mapp.* 38, 140–150.
504 <https://doi.org/10.1002/hbm.23349>
- 505 Cisler, J.M., Koster, E.H.W., 2010. Mechanisms of attentional biases towards threat in anxiety disorders: An
506 integrative review. *Clin. Psychol. Rev.* 30, 203–216. <https://doi.org/10.1016/j.cpr.2009.11.003>
- 507 Cornwell, B.R., Baas, J.M.P., Johnson, L., Holroyd, T., Carver, F.W., Lissek, S., Grillon, C., 2007. Neural
508 responses to auditory stimulus deviance under threat of electric shock revealed by spatially-filtered
509 magnetoencephalography. *NeuroImage* 37, 282–289.
510 <https://doi.org/10.1016/j.neuroimage.2007.04.055>
- 511 Cornwell, B.R., Garrido, M.I., Overstreet, C., Pine, D.S., Grillon, C., 2017. The Unpredictive Brain Under
512 Threat: A Neurocomputational Account of Anxious Hypervigilance. *Biol. Psychiatry* 82, 447–454.
513 <https://doi.org/10.1016/j.biopsych.2017.06.031>
- 514 Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics
515 including independent component analysis. *J. Neurosci. Methods* 134, 9–21.
516 <https://doi.org/10.1016/j.jneumeth.2003.10.009>
- 517 Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Näätänen, R., Polich, J., Reinvang, I., Van
518 Petten, C., 2009. Event-related potentials in clinical research: Guidelines for eliciting, recording, and
519 quantifying mismatch negativity, P300, and N400. *Clin. Neurophysiol.* 120, 1883–1908.
520 <https://doi.org/10.1016/j.clinph.2009.07.045>
- 521 Elling, L., Steinberg, C., Bröckelmann, A.-K., Dobel, C., Bölte, J., Junghofer, M., 2011. Acute Stress Alters
522 Auditory Selective Attention in Humans Independent of HPA: A Study of Evoked Potentials. *PLOS*
523 *ONE* 6, e18009. <https://doi.org/10.1371/journal.pone.0018009>
- 524 Ender, N.S., Kocovski, N.L., 2001. State and trait anxiety revisited. *J. Anxiety Disord.* 15, 231–245.
525 [https://doi.org/10.1016/S0887-6185\(01\)00060-3](https://doi.org/10.1016/S0887-6185(01)00060-3)
- 526 Epstein, S., 1971. Heart rate, skin conductance, and intensity ratings during experimentally induced anxiety:
527 habituation within and among days. *Psychophysiology* 8, 319–331. <https://doi.org/10.1111/j.1469-8986.1971.tb00462.x>
- 529 Epstein, S., Roupelian, A., 1970. Heart rate and skin conductance during experimentally induced anxiety:
530 The effect of uncertainty about receiving a noxious stimulus. *J. Pers. Soc. Psychol.* 16, 20.
- 531 Ermutlu, M.N., Karamürsel, S., Ugur, E.H., Senturk, L., Gokhan, N., 2005. Effects of cold stress on early and
532 late stimulus gating. *Psychiatry Res.* 136, 201–209. <https://doi.org/10.1016/j.psychres.2003.03.002>
- 533 Eysenck, M.W., Derakshan, N., 2011. New perspectives in attentional control theory. *Personal. Individ.*
534 *Differ.* 50, 955–960. <https://doi.org/10.1016/j.paid.2010.08.019>

- 535 Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance:
536 Attentional control theory. *Emotion* 7, 336–353. <https://doi.org/10.1037/1528-3542.7.2.336>
- 537 Feldman, H., Friston, K.J., 2010. Attention, Uncertainty, and Free-Energy. *Front. Hum. Neurosci.* 4.
538 <https://doi.org/10.3389/fnhum.2010.00215>
- 539 Folkins, C.H., 1970. Temporal factors and the cognitive mediators of stress reaction. *J. Pers. Soc. Psychol.*
540 14, 173–184. <https://doi.org/10.1037/h0028688>
- 541 Friston, K., 2009. The free-energy principle: a rough guide to the brain? *Trends Cogn. Sci.* 13, 293–301.
542 <https://doi.org/10.1016/j.tics.2009.04.005>
- 543 Garrido, M.I., Kilner, J.M., Kiebel, S.J., Friston, K.J., 2009a. Dynamic Causal Modeling of the Response to
544 Frequency Deviants. *J. Neurophysiol.* 101, 2620–2631. <https://doi.org/10.1152/jn.90291.2008>
- 545 Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009b. The mismatch negativity: a review of
546 underlying mechanisms. *Clin. Neurophysiol.* 120, 453–463.
547 <https://doi.org/10.1016/j.clinph.2008.11.029>
- 548 Ge, Y., Wu, J., Sun, X., Zhang, K., 2011. Enhanced mismatch negativity in adolescents with posttraumatic
549 stress disorder (PTSD). *Int. J. Psychophysiol.* 79, 231–235.
550 <https://doi.org/10.1016/j.ijpsycho.2010.10.012>
- 551 Grupe, D.W., Nitschke, J.B., 2013. Uncertainty and anticipation in anxiety: an integrated neurobiological
552 and psychological perspective. *Nat. Rev. Neurosci.* 14, 488–501. <https://doi.org/10.1038/nrn3524>
- 553 Hansenne, M., Pinto, E., Scantamburlo, G., Renard, B., Reggers, J., Fuchs, S., Pitchot, W., Anseau, M., 2003.
554 Harm avoidance is related to mismatch negativity (MMN) amplitude in healthy subjects. *Personal.*
555 *Individ. Differ.* 34, 1039–1048. [https://doi.org/10.1016/S0191-8869\(02\)00088-0](https://doi.org/10.1016/S0191-8869(02)00088-0)
- 556 Huotilainen, M., Winkler, I., Alho, K., Escera, C., Virtanen, J., Ilmoniemi, R.J., Jääskeläinen, I.P., Pekkonen, E.,
557 Näätänen, R., 1998. Combined mapping of human auditory EEG and MEG responses.
558 *Electroencephalogr. Clin. Neurophysiol. Potentials Sect.* 108, 370–379.
559 [https://doi.org/10.1016/S0168-5597\(98\)00017-3](https://doi.org/10.1016/S0168-5597(98)00017-3)
- 560 Jafari, Z., Kolb, B.E., Mohajerani, M.H., 2017. Effect of acute stress on auditory processing: a systematic
561 review of human studies. *Rev. Neurosci.* 28, 1–13. <https://doi.org/10.1515/revneuro-2016-0043>
- 562 Kalin, N.H., Shelton, S.E., 1989. Defensive behaviors in infant rhesus monkeys: environmental cues and
563 neurochemical regulation. *Science* 243, 1718–1721. <https://doi.org/10.1126/science.2564702>
- 564 Kok, P., Rahnev, D., Jehee, J.F.M., Lau, H.C., Lange, D., P, F., 2012. Attention Reverses the Effect of
565 Prediction in Silencing Sensory Signals. *Cereb. Cortex* 22, 2197–2206.
566 <https://doi.org/10.1093/cercor/bhr310>
- 567 Lenth, R.V., 2016. Least-Squares Means: The R Package lsmeans. *J. Stat. Softw.* 69.
568 <https://doi.org/10.18637/jss.v069.i01>
- 569 Long, J.A., 2018. jtools: Analysis and Presentation of Social Scientific Data.
- 570 Makeig, S., Westerfield, M., Jung, T.-P., Enghoff, S., Townsend, J., Courchesne, E., Sejnowski, T.J., 2002.
571 Dynamic Brain Sources of Visual Evoked Responses. *Science* 295, 690–694.
572 <https://doi.org/10.1126/science.1066168>
- 573 Näätänen, R., Kujala, T., Winkler, I., 2011. Auditory processing that leads to conscious perception: A unique
574 window to central auditory processing opened by the mismatch negativity and related responses:
575 Auditory processing that leads to conscious perception. *Psychophysiology* 48, 4–22.
576 <https://doi.org/10.1111/j.1469-8986.2010.01114.x>
- 577 Näätänen, R., Pakarinen, S., Rinne, T., Takegata, R., 2004. The mismatch negativity (MMN): towards the
578 optimal paradigm. *Clin. Neurophysiol.* 115, 140–144. <https://doi.org/10.1016/j.clinph.2003.04.001>

579 Nakagawa, S., Schielzeth, H., 2013. A general and simple method for obtaining R^2 from generalized linear
580 mixed-effects models. *Methods Ecol. Evol.* 4, 133–142. <https://doi.org/10.1111/j.2041->
581 210x.2012.00261.x

582 Newport, D.J., Nemeroff, C.B., 2000. Neurobiology of posttraumatic stress disorder. *Curr. Opin. Neurobiol.*
583 10, 211–218. [https://doi.org/10.1016/S0959-4388\(00\)00080-5](https://doi.org/10.1016/S0959-4388(00)00080-5)

584 Nomikos, M.S., Opton Jr., E., Averill, J.R., 1968. Surprise versus suspense in the production of stress
585 reaction. *J. Pers. Soc. Psychol.* 8, 204–208. <https://doi.org/10.1037/h0025274>

586 Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open Source Software for Advanced
587 Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Comput Intell Neurosci.* 2011,
588 156869. <https://doi.org/10.1155/2011/156869>

589 Pacheco-Unguetti, A.P., Acosta, A., Callejas, A., Lupiáñez, J., 2010. Attention and Anxiety: Different
590 Attentional Functioning Under State and Trait Anxiety. *Psychol. Sci.* 21, 298–304.
591 <https://doi.org/10.1177/0956797609359624>

592 Picton, T.W., Hillyard, S.A., Krausz, H.I., Galambos, R., 1974. Human auditory evoked potentials. I:
593 Evaluation of components. *Electroencephalogr. Clin. Neurophysiol.* 36, 179–190.
594 [https://doi.org/10.1016/0013-4694\(74\)90155-2](https://doi.org/10.1016/0013-4694(74)90155-2)

595 Qi, M., Gao, H., Liu, G., 2018. The effect of mild acute psychological stress on attention processing: an ERP
596 study. *Exp. Brain Res.* 236, 2061–2071. <https://doi.org/10.1007/s00221-018-5283-6>

597 R core team, 2017. R: A language and environment for statistical computing. *R Found. Stat. Comput.* Vienna
598 Austria.

599 Robinson, O.J., Letkiewicz, A.M., Overstreet, C., Ernst, M., Grillon, C., 2011. The effect of induced anxiety on
600 cognition: threat of shock enhances aversive processing in healthy individuals. *Cogn. Affect. Behav.*
601 *Neurosci.* 11, 217–227. <https://doi.org/10.3758/s13415-011-0030-5>

602 Robinson, O.J., Vytal, K., Cornwell, B.R., Grillon, C., 2013. The impact of anxiety upon cognition:
603 perspectives from human threat of shock studies. *Front. Hum. Neurosci.* 7.
604 <https://doi.org/10.3389/fnhum.2013.00203>

605 Scaife, J.C., Groves, J., Langley, R.W., Bradshaw, C.M., Szabadi, E., 2006a. Sensitivity of late-latency auditory
606 and somatosensory evoked potentials to threat of electric shock and the sedative drugs diazepam
607 and diphenhydramine in human volunteers. *J. Psychopharmacol.* 20, 485–495.
608 <https://doi.org/10.1177/0269881105059343>

609 Scaife, J.C., Groves, J., Langley, R.W., Bradshaw, C.M., Szabadi, E., 2006b. Sensitivity of late-latency auditory
610 and somatosensory evoked potentials to threat of electric shock and the sedative drugs diazepam
611 and diphenhydramine in human volunteers. *J. Psychopharmacol.* 20, 485–495.
612 <https://doi.org/10.1177/0269881105059343>

613 Schirmer, A., Escoffier, N., 2010. Emotional MMN: Anxiety and heart rate correlate with the ERP signature
614 for auditory change detection. *Clin. Neurophysiol.* 121, 53–59.
615 <https://doi.org/10.1016/j.clinph.2009.09.029>

616 Schwartz, S., Maquet, P., Frith, C., 2002. Neural correlates of perceptual learning: A functional MRI study of
617 visual texture discrimination. *Proc. Natl. Acad. Sci.* 99, 17137–17142.
618 <https://doi.org/10.1073/pnas.242414599>

619 Shackman, A.J., Maxwell, J.S., McMenemy, B.W., Greischar, L.L., Davidson, R.J., 2011a. Stress Potentiates
620 Early and Attenuates Late Stages of Visual Processing. *J. Neurosci.* 31, 1156–1161.
621 <https://doi.org/10.1523/JNEUROSCI.3384-10.2011>

622 Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011b. The integration of
623 negative affect, pain and cognitive control in the cingulate cortex. *Nat. Rev. Neurosci.* 12, 154–167.
624 <https://doi.org/10.1038/nrn2994>

- 625 Simoens, V.L., Istók, E., Hyttinen, S., Hirvonen, A., Näätänen, R., Tervaniemi, M., 2007. Psychosocial stress
626 attenuates general sound processing and duration change detection. *Psychophysiology* 44, 30–38.
627 <https://doi.org/10.1111/j.1469-8986.2006.00476.x>
- 628 Spielberger, C., Gorsuch, R., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait*
629 *anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press
- 630 Sylvester, C.M., Corbetta, M., Raichle, M.E., Rodebaugh, T.L., Schlaggar, B.L., Sheline, Y.I., Zorumski, C.F.,
631 Lenze, E.J., 2012. Functional network dysfunction in anxiety and anxiety disorders. *Trends Neurosci.*
632 35, 527–535. <https://doi.org/10.1016/j.tins.2012.04.012>
- 633 White, P.M., Kanazawa, A., Yee, C.M., 2005. Gender and suppression of mid-latency ERP components
634 during stress. *Psychophysiology* 42, 720–725. <https://doi.org/10.1111/j.1469-8986.2005.00365.x>
- 635 Yotsumoto, Y., Watanabe, T., Sasaki, Y., 2008. Different Dynamics of Performance and Brain Activation in
636 the Time Course of Perceptual Learning. *Neuron* 57, 827–833.
637 <https://doi.org/10.1016/j.neuron.2008.02.034>

638

639

640

641 **Figure Legends**

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

656

657 **Figure 2. Threat of electric shock does not modulate neural correlates of perceptual learning,**
658 **except at high degrees of anxiety.** (A) Difference (deviant minus standard, i.e. MMN) waveforms
659 at frontal ROI (see **Figure S1**) for safe and threat conditions. (B) Average voltage scalp maps of
660 MMN in safe and threat conditions at 30ms around peak latencies (safe = 130-150ms; threat =
661 110-130ms). (C) Mean values of MMN from (B) at frontal ROI. Error bars represent standard errors
662 of the mean. (D) Scatter plot for single-subject mean values of self-reported anxiety and MMN

663 amplitude (left) and mean SCRs and MMN amplitude (right) in safe and threat conditions.
664 Regression lines and coefficients β for both plots were derived from linear mixed models that
665 included self-reported anxiety (left) or SCRs [mean amplitude of the phasic component] (right) and
666 condition as fixed effects and session, subject and block order as random effects. The grey and red
667 areas around the regression lines indicate 95% confidence intervals for safe and threat conditions,
668 respectively. *** : $p < 0.001$; ** : $p < 0.01$; * : $p < 0.05$ as a result of paired t-tests (Tukey HSD
669 corrected).

670

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

681

682 **Figure 4. High degrees of trait anxiety modulate the neural correlates of perceptual learning**
683 **under threat of electric shock.** Scatter plot for single-subject mean values of trait anxiety (T-STAI
684 score) and MMN amplitude in safe and threat conditions. The regression lines and coefficients β
685 are derived from a linear mixed model including T-STAI score and condition (safe, threat) as fixed
686 effects and session, block order and subjects as random effects. The grey and red areas around the
687 regression lines indicate 95% confidence intervals for safe and threat conditions, respectively. ***
688 : $p < 0.001$; ** : $p < 0.01$; * : $p < 0.05$ as a result of paired t-tests (Tukey HSD corrected).

689

690 **Supplementary Figures**

691

692 **Figure S1.** Visual layout of the 41 electrodes remaining after preprocessing and of the frontal
693 region of interest (grey area) used for the analyses of event-related potentials.

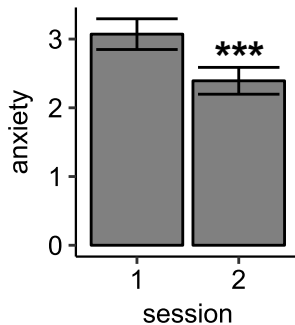
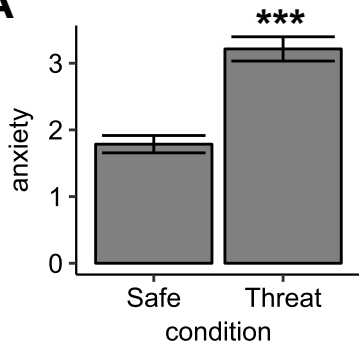
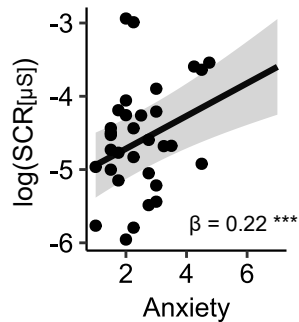
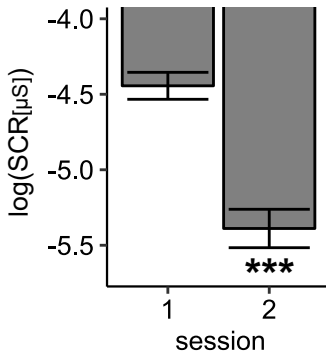
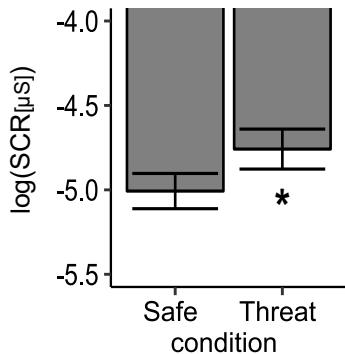
694

695 **Figure S2.** Examples of raw EEG recordings.

696

697 **Figure S3.** Raincloud plots for A) Effect of threat and safe periods (x-axis) on subjective anxiety (y-
698 axis), B) Effect of threat and safe periods (x-axis) on skin conductance responses (y-axis), C) Effect
699 of threat and safe periods (x-axis) on MMN amplitude (y-axis), D) Effect of threat and safe periods
700 (x-axis) on N1 amplitude (y-axis).

701

A**C****B****D**