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# In exogenous attention, time is the clue: Brain and heart interactions to survive threatening stimuli

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# Abstract

The capture of exogenous attention by negative stimuli has been interpreted as adaptive for survival in a diverse and changing environment. In the present paper, we investigate the neural responses towards two discrete negative emotions with different biological meanings, disgust and fear, and its potential relationships with heart rate variability (HRV) as an index of emotional regulation. With that aim, 30 participants performed a digit categorization task while fear, disgust and neutral distractor pictures were presented. Resting HRV at baseline, behavioral responses, and event-related potentials were recorded. Whereas P1 amplitudes were highest to fear distractors, the disgust stimulation led to augmented P2 amplitudes compared to the rest of distractors. Interestingly, increased N2 amplitudes were also found to disgust distractors, but only in high HRV participants. Neural source estimation data point to the involvement of the insula in this exogenous attentional response to disgust. Additionally, disgust distractors provoked longer reaction times than fear and neutral distractors in the high HRV group. Present findings are interpreted in evolutionary terms suggesting that exogenous attention is captured by negative stimuli following a different time course for fear and disgust. Possible HRV influences on neural mechanisms underlying exogenous attention are discussed considering the potential important role of this variable in emotional regulation processes.

# Introduction

To process the great amount of sensorial stimulation that continuously surrounds the individual a fast and precise brain selection is required in order to identify relevant signals from the environment such as those are important for survival to face them with an appropriate action (e.g.,[1]). Growing experimental evidence coming from both electrophysiological [2–7] and behavioral studies [8–11] has consistently shown that threatening information is capable to efficiently attract attentional resources in a rapid and automatic way (i.e., exogenous attention) when these stimuli appeared as distractors in a given visual task (for a review see [12]).

A new line of evidence has focused its efforts on exploring exogenous attentional responses to each type of negative-arousing events (i.e., fearful and disgusting) considering them as separate categories due to the subjective feelings related to each of them, their biological meaning, **Competing interests:** The authors have declared that no competing interests exist.

and even their neural substrate and effect on the peripheral nervous system are segregated [13–15]. Indeed, exogenous attention to affective events triggers fast neural responses reflected by enhanced amplitudes to threatening distractors in event-related potential ERP components within the first 200 ms (P1, P2 and N2) from the stimulus onset [14]. In this sense, previous ERP studies have found neural indices (P2 wave) describing that disgust distractors are more efficient at attracting automatic attention than fearful distractors [14]. This segregated pattern between disgust and fear was also found when neural activation within visual regions (i.e., cuneus) was measured. More recently, Zhang and colleagues [16] using a dot-probe paradigm showed a clear attentional modulation of the N1 component in response to disgust stimuli being interpreted as a rapid suppression of attention to diminish risk of contamination.

With respect to peripheral physiological responses, research has consistently found that disgust produces greater heart rate (HR) deceleration compared to fear and neutral stimuli [17– 20]. In fact, it has been proposed that this greater HR deceleration to disgusting stimuli would be specifically associated with the involvement of parasympathetic activation [17]. We have previously shown that startle and HR responses during fear and disgust pictures are modulated by vagally mediated heart rate variability (HRV). Participants with high HRV showed the expected startle magnitude increase to unpleasant foreground while the group with low HRV did not [21, 22], and deeper cardiac deceleration to disgusting compared to fear-evoking or neutral distractors [23].

The importance of the bidirectional interactions between the heart and brain has been known for over 100 years [24]. HRV has been proposed as an index of the dynamics of brainheart connections [25]. HRV refers to the change in the time interval between successive heartbeats due mainly to the influence of the two branches of the autonomic nervous system on the heart. The analysis of such variability provides information on its underlying physiological mechanisms. Thus, by applying frequency domain based methods three frequency bands can be identified in short-term (5–10 minute) recordings, being the high frequency (HF: 0.15–0.4 Hz) component linked to parasympathetic activity [22]. Specifically, vagal regulation of the heart indicates highly functional prefrontal inhibition of subcortical structures since the neural circuits bidirectionally connecting the prefrontal cortex with subcortical structures are linked to the heart via the vagus nerve [26-28]. High HRV has been associated with better affective and attentional regulation as indicated by, for example, larger orienting responses but faster habituation to nonthreatening stimuli [29] and adaptive emotional startle modulation [30]. However, low HRV has been related to hyperactive subcortical activity, which results in poor self-regulatory functions, such as the failure to recognize safety cues or to habituate to novel, neutral stimuli [26, 29, 31, 32].

Closely connected to the present study, HRV has been recently related to the capture of automatic attention by emotional stimuli. Park et al. [33] asked their participants to detect a target letter among a string of letters superimposed on either fearful or neutral distractor faces. Their results showed that neutral and fearful faces interfered with the performance of the primary task in the low HRV group whereas in the high HRV group the interference was observed only to the fearful faces. Park et al. [34] showed faster attentional engagement to fearful faces in low HRV than in high HRV participants what was considered dysfunctional. These findings together suggest that only high HRV participants showed an adaptive response.

Despite ERPs are considered as a suitable tool to explore rapid neural responses occurring at early attentional processing stages, such as exogenous attention, its study to characterize segregated neural substrates related to fear and disgust as a function of individual differences in resting HRV has not been explored. Furthermore, the use of mixed experimental paradigms in studies on exogenous attention to disgust and fear stimuli has led to obtain inconclusive outcomes that hinder the possibility to shed light on the underlying mechanisms for explaining this segregation still under debate.

Therefore, the present experiment will examine whether negative stimuli (i.e., fearful vs. disgusting) can be differently prioritized in the attentional processing at a neural level occurring "automatically" and whether they could be modulated by HRV influences. Neural responses will be recorded using a high-temporal resolution technique (ERPs) to characterize temporal dynamics of exogenous attention toward emotional distractors during a concurrent but distinct target distractor paradigm. The use of this paradigm where target stimulation (on which voluntary attention should be devoted to accomplish a given task) and task-irrelevant information (emotional distractors) are distinct but appear at the same time has been considered optimal to investigate attentional capture mechanisms [12]. Advanced source estimation tools will also be applied. On these findings we will try to build an explanation of how brain–heart connections may modulate the triggering of exogenous attention to different types of relevant environmental events, specifically when threat-related stimulation appears (fearful vs. disgust).

# Methods

# Subjects

Thirty undergraduate students (14 male) from the Universidad de Jaén, with an age range of 18–26 years old (mean = 21.67, standard deviation = 2.22), voluntarily participated in this experiment. All subjects gave written informed consent and reported normal or corrected-to-normal visual acuity. The Ethics Committee of the Universidad de Jaén approved the study.

#### Stimuli and procedure

The experimental paradigm used in this experiment comprised of the presentation of visual stimuli which were composed of two different elements that appeared at the same time on a computer screen: 1) thirty emotional pictures which were used as task-irrelevant stimuli (distractors); and 2) a set of two digits located at the center of each picture being the elements to which participants were asked to voluntarily attend for performing an experimental task (targets). Thus, all participants completed a digit categorization task while they were exposed to three types of distractor pictures: fearful (F), disgusting (D), and emotionally neutral (N). Emotional pictures were selected from two main sources, the International Affective Picture System (IAPS) [35] and Emomadrid [36] on the basis of an independent rating study. Ten pictures conveying fear (IAPS 1525, 1932, 2692, 6190, 6244, 6350, 6510, 9622 and Emomadrid 0578, 0579), disgust (IAPS 9373, 9830 and Emomadrid 0563, 0564, 0569, 0574, 0586 and supplemented with similar pictures found from publicly available sources) and neutral (IAPS 1910, 2512, 2580, 7000 and Emomadrid 0334, 0337, 0338, 0339, 0414, 0584) affective meaning were used. The size for all stimuli was 75.17° (width) and 55.92° (height). Each of these pictures contained two central digits (4.93° height) colored in yellow and outlined in solid black so they were clearly distinguished from the background. As illustrated in Fig 1, each picture was displayed on the screen for 350 ms and stimulus onset asynchrony was always 3000 ms. The experimental task was exclusively related to the central digits, which could be both even, both odd or one even and the other odd. Participants had to categorize them "as accurately and rapidly as possible", as congruent or incongruent (in even/odd condition) by pressing different buttons. One key was pressed by the participants if both digits were even or if both were odd (i.e., if they were "congruent"), and a different key if one central digit was even and the other was odd (i.e., if they were "incongruent"). Twenty combinations of digits were composed, half of them being congruent and the other half incongruent. The whole experimental procedure





included a total of 120 trials (40 trials for each type of emotional distractor) divided into three blocks (fear, disgust, and neutral). The same combination of digits was repeated across emotional conditions in order to ensure that task difficulty was the same for F, N, and D and were presented in semi-random order into each block of trials in such a way that the congruent or incongruent conditions never appeared more than twice consecutively. The order of the blocks was counterbalanced across subjects. Each picture was presented through a CRT screen four times along the study (twice for both congruent and incongruent trials). Participants were placed in an electrically shielded, sound-attenuated room and they were instructed to continuously look at a fixation mark located in the center of the screen and to blink only after a beep that sounded 1300 ms after each stimulus onset.

Images used as distractors were selected from an independent pilot study according to their assessments in valence and arousal (the two main dimensions explaining the principal variance of emotional information), which were similar for fear and disgust categories. Additionally, a subjective criterion was also applied to select pictures representing either fear or disgust images avoiding stimuli combining both emotions.

	Fear	Disgust	Neutral	p-value
Valence	2.066 (.501)	1.761 (.386)	3.264 (.241)	< .001
Arousal	4.130 (.378)	3.466 (.458)	2.735 (.274)	< .001
Fearfulness	3.240 (.876)	1.329 (.335)	1.040 (.119)	< .001
Disgustingness	1.316 (.381)	3.323 (.675)	1.109 (.146)	< .001

Table 1. Means and standard deviations (in parenthesis) for the valence, arousal, fearfulness and disgustingness of the emotional distractors (fear, disgust neutral) evaluated by the whole sample of participants.

Information about ANOVA p-values for each statistical contrast is included.

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After the recording session, participants filled out a multidimensional scale for each picture in order to confirm that their assessments on the valence (1, negative to 5, positive), arousal (1, relaxing to 5, arousing), fearfulness (1, minimum to 5, maximum), and disgustingness (1, minimum to 5, maximum) content of the stimulation were those assumed a priori (see Table 1). One-way repeated measured ANOVAs were performed using stimuli (three levels: D, N, and F) as a factor. In order to test the significance of pairwise contrasts, a Bonferroni test was applied. Fearfulness was significantly higher for F than for D stimuli, and disgustingness was significantly higher for F than for D stimuli (p < 0.05 in both cases). Both valence and arousal were higher for F than for D pictures (p < 0.01 in both cases). N stimuli were significantly lower in fearfulness, disgustingness, valence, and arousal than were F and D stimuli (p < 0.01).

#### EEG recording and pre-processing

Continuous electroencephalographic (EEG) activity was recorded using an electrode cap (ElectroCap International) with 28 homogeneously distributed scalp electrodes. All electrodes were referenced to the nose tip electrode. Electrooculographic (EOG) data were recorded supra- and infra-orbitally (vertical EOG), as well as from the left versus right orbital rim (horizontal EOG). Electrode impedances were kept below 5 k $\Omega$ . An online bandpass filter from 0.3 Hz to 40 KHz was used (3 dB points for -6dB/octave roll-off), and the digitization sampling rate was set to 500 Hz. Off-line pre-processing was performed using Brain Vision Analyzer software (Brain Products). The continuous EEG recording was divided into 900 ms epochs for each trial, beginning 200 ms before stimulus onset. Baseline correction was made using the 200 ms period prior to the onset of the stimulus. Trials in which subjects responded errone-ously or did not respond were eliminated. A careful visual inspection was then carried out where epochs with eye movements or blinks were eliminated. This artifact and error rejection led to the average acceptance of 27 disgusting, 27.9 neutral, and 27 fearful distractor trials. The number of trials did not statistically differ among distractor types. The ERP averages were categorized according to each distractor type: fear, disgust and neutral.

# HRV recording and pre-processing

Resting HRV was obtained from the electrocardiogram (ECG) recorded during seven minutes of baseline preceding the experimental task and the EEG recording (a longer period than the one minute recommended as the minimum necessary according to the Task Force guidelines [37]). The ECG was recorded through a Biopac MP100 system using three Ag-AgCl electrodes placed following lead II using a sampling rate of at 1000 Hz and the beat-to-beat HR data were extracted through Acknowledge 3.9 software. The frequency domain measure of high frequency (HF: 0.15–0.4) power was used to index vagally mediated HRV. To obtain this index, spectral analyses using an autoregressive algorithm following the Task Force guidelines [37]

were performed on the HR data using a custom HRV package. Then, spectral estimates of power ( $ms^2$ ) of HF were transformed logarithmically (base 10) to normalize the distribution of scores. Participants were split in two groups on the basis of their baseline logHF [median = 4.94; low HRV = 3.9 (s.d. = 0.93); high HRV = 5.7 (s.d. = 0.48)] as it has been recommended [38] and extensively used [21, 23, 34, 39].

#### Data analysis

Behavioral analysis. Mean reaction times (RTs) of correct responses and error rates derived from the task were analyzed. Repeated-measures ANOVAs on each measure were computed using emotional pictures (three levels: F, D, and N) and group of HRV (two levels: high and low) as factors. The Greenhouse–Geisser epsilon correction was applied to adjust the degrees of freedom of the F ratios where necessary, and post hoc comparisons to determine the significance of pairwise contrasts were performed using the Bonferroni procedure (alpha < 0.05). As a measure of effect size, partial  $\eta$ -square ( $\eta^2_p$ ) is reported for significant effects.

**ERP** analysis. Detection and quantification of ERP components was carried out through covariance-matrix-based temporal principal component analysis (tPCA) explaining most of the brain electrical activity variance. This technique has been strongly recommended for these tasks since its application avoids the subjectivity of selecting "time windows of interest" based on visual inspection for analyses of grand-averaged ERPs. It can lead to several types of misinterpretation, especially when high-density montages are employed (see [40] for a more detailed description of the tPCA procedure and its advantages). The main advantage of tPCA is that it represents each ERP component with its "clean" shape, extracting and quantifying it free of the influences of adjacent or subjacent components [40, 41]. Indeed, the waveform recorded at a site on the head over a period of several hundreds of milliseconds represents a complex superposition of different overlapping electrical potentials. Such recordings can stymie visual inspection. In brief, tPCA computes the covariance between all ERP time points, which tends to be high between those time points involved in the same component, and low between those belonging to different components. The solution is therefore a set of independent factors made up of highly covarying time points, which ideally correspond to ERP components. Temporal factor scores, the tPCA-derived parameter in which extracted temporal factors may be quantified, is linearly related to amplitude. In the present study, the decision on the number of components to select was based on the scree test [42]. Extracted components were submitted to promax rotation, as recently recommended [43].

As previously mentioned, the analyses required that the ERPs be recorded at 28 globally distributed scalp points. Signal overlapping may also occur at the space domain. At any given time point, several neural processes (and hence, several electrical signals) may concur, and the recording at any scalp location at that moment is the electrical balance of these different neural processes. Thus, ERP components frequently behave differently in some scalp areas to others (e.g., present opposite polarity). While tPCA allows solving temporal overlapping of ERP components, spatial PCA (sPCA) separates ERP components along the space. In this sense, each spatial factor would ideally reflect one of the concurrent neural processes underlying each temporal factor. Therefore, this configuring and quantifying scalp region system is preferable to an a priori subdivision into fixed scalp regions for all components, as sPCA demarcates scalp regions according to the real behavior of each scalp-point recording (basically, each region or spatial factor is formed with scalp points where recordings tend to covary). Consequently, the shape of the sPCA-configured regions is functionally based, and scarcely resembles the shape of the traditional, geometrically configured regions. sPCAs were carried out for each of the temporal factors. This regional grouping was determined through a covariance matrix-based spatial PCA. Moreover, each spatial factor can be quantified through the *spatial factor score*, a single parameter that reflects the amplitude of the whole spatial factor. Additionally, in this case, the decision on the number of factors to extract was based on the scree test. Extracted spatial factors were submitted to promax rotation. This analysis procedure, comprising of both tPCA and sPCA, has been recommended for exploring emotional processing through ERPs [44].

Finally, repeated-measures ANOVAs on temporospatial factor scores were carried out with respect to emotional pictures (three levels: F, D, and N) and HRV group (two levels: high and low). The Greenhouse–Geisser epsilon correction was applied to adjust the degrees of freedom of the F ratios where necessary, and post hoc comparisons to determine the significance of pairwise contrasts were performed using the Bonferroni procedure (alpha < 0.05). Effect sizes were also reported using the partial  $\eta$ -square ( $\eta^2_p$ ) method.

Source estimation analysis. In order to three-dimensionally explore cortical regions that could account for the experimental effects at the scalp level, exact low-resolution brain electromagnetic tomography (eLORETA) [45, 46] was applied to relevant temporal factor scores in accordance with the ANOVA results, as it will be explained later. eLORETA is a 3D, discrete linear solution for the EEG inverse problem [47] which refers to a three-shell spherical model registered to the MNI305 digitized structural human brain atlas template. Solutions are given, therefore, in three coordinates: "x" is the distance in millimeters to the right (+) or left (-) of midline; "y" is the distance anterior (+) or posterior (-) to the anterior commissure; and "z" is the distance above (+) or below (-) a horizontal plane through the anterior and posterior commissures. Although, in general, solutions provided by EEG-based source location algorithms should be interpreted with caution due to their potential error margins, LORETA solutions have shown significant correspondence with those provided by hemodynamic procedures in the same tasks [48-50]. In the present experiment, we tried to minimize this potential error margin using the tPCA-derived factor scores instead of voltages. This strategy has provided more accurate source estimation analyses [2, 51]. In its current version, eLORETA computes the current density at each of 6239 voxels mainly located in the cortical gray matter and the hippocampus of the digitized Montreal Neurological Institute (MNI) standard brain.

Therefore, in order to identify the brain regions underlying exogenous attention processes triggered by emotional stimulation, three-dimensional current density estimates for relevant temporal factor scores that were sensitive to experimental manipulations according to ERP results were computed for each participant and each experimental condition. Subsequently, the voxel-based whole-brain eLORETA-images (6239 voxels) were compared among three experimental conditions (F, D, and N: emotional distractors). To that aim, eLORETA built-in voxelwise randomization tests (5000 permutations) based on a statistical non-parametric mapping methodology were used. As explained by Nichols and Holmes [52], the non-parametric methodology inherently avoids multiple comparison-derived problems and does not require any assumption of normality. Voxels that showed significant differences between conditions (log-F-ratio statistic, two-tailed corrected p < 0.05) were located in anatomical regions and Brodmann areas (BAs). In order to explore exogenous attentional processing related to the three types of emotional distractors (three levels: F, D, and N) and the two groups of HRV (two levels: high and low), current densities of different regions of interest (ROIs; radius = 5 mm) were submitted to ANOVAs.

#### Results

#### **Behavioral results**

Average values for RTs and error rates for each emotional distractor are shown in <u>Table 2</u>. Two separate repeated-measures ANOVAs were conducted on RTs and error rates including

		Disgust	Neutral	Fear	
RTs	High HRV	1163.209 (259.847)	1079.277 (223.196)	1112.146 (243.435)	
	Low HRV	1006.353 (198.167)	1038.759 (176.714)	956.964 (187.165)	
	Total	1084.781 (240.660)	1059.018 (198.870)	1034.555 (227.482)	
Errors Rates	High HRV	7.867 (4.138)	5.667 (2.895)	6.933 (3.693)	
	Low HRV	7.133 (3.248)	5.933 (4.234)	6.333 (4.467)	
	Total	7.500 (3.674)	5.800 (3.566)	6.633 (4.038)	

	Table 2. Means and standard deviations	(in	parenthesis	) of RTs an	d errors rates	to disgust	t, neutral a	nd fearful	distractors
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emotional distractor (three levels: F, D, and N) and HRV group (two levels: high and low) as factors. Although both RTs and error rates for D stimuli were slowest and highest, as it can be observed in Fig 2, a significant main effect of emotional distractor was only found for error rates [F(1.91,53.53) = 3.297, p = .047,  $\eta^2 = 0.105$ ] but not for RTs [F(1.82,50.85) = 3.075, p = .06]. Disgusting distractors provoked higher error rates than neutral distractors (p < 0.05). There was no significant main effect for HRV group (RTs [F(1.28) = 2.413, p = .132]; error rates [F(1.28) = .093, p = .763]). Finally, the interaction between emotional distractor and HRV was significant for RTs [F(1.82,50.85) = 5.419, p = .009,  $\eta^2 = .162$ ] but not for error rates [F(1.91,53.53) = .336, p = .706]. Posterior analysis conducted on this interaction revealed slower RTs to D distractors compared to N (p = .01) and F stimuli (p = .04) in the high HRV group. Additionally, low HRV group showed faster RTs to F distractors compared to D (p = .048) and N (p = .01).

#### **ERP** results

Grand averages related to exogenous attentional brain responses for the three emotional distractors, once the baseline value (pre-stimulus recording) has been subtracted from each ERP, are displayed in Fig 3. This figure mainly shows ERP activity (P1, P2, and N2) where the most relevant experimental effects related to attentional capture processes are clearly appreciable. These effects will be subsequently detailed.

As a consequence of the tPCA application, eight temporal factors (TFs) were extracted from the ERPs (see Fig 4). Extracted factors explained 83.79% of the total variance. According to the factor peak latency and topography distribution, TF8 and TF6 (peaking at 138 and 228 ms, respectively) were identified at fronto-central and centro-parietal sites of the scalp and associated with ERP components signaled in the grand averages as P1 and P2 (see Fig 3). Furthermore, TF7 (peaking at 176 ms), maximal at frontal scalp sites, was related to N2 (Figs 3 and 4).





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Fig 3. Grand averages related to exogenous attentional ERP responses (P1, P2 and N2) for the three emotional distractors at Oz (a) and Fz (b). https://doi.org/10.1371/journal.pone.0243117.g003

Subsequently, the sPCA extracted three spatial factors for each temporal factor, except for TF5 and TF6, where only two spatial factors were extracted. Therefore, the temporospatial PCA yielded a total of 22 factor combinations. Repeated-measures ANOVAs on each temporospatial factor were carried out for exploring exogenous attention (i.e., P1, P2, N2 at different scalp areas) triggered by emotional distractors (three levels: F, D, and N) with respect to the HRV group (two levels: high and low).

Table 3 also provides the statistical details of these analyses including main effects of emotional distractor and the interaction effects between emotional distractor by HRV group. As can be appreciated in this table, a clear effect related to the emotional content conveyed by distractor pictures was revealed for both P1 and P2 components. Specifically, posterior scalp regions of P1 (corresponding to SF1 and SF2) showed a significant main effect of emotional distractor [SF1: F(1.97,55.26) = 5.729, p = .006;  $\eta^2 = 0.170$ ; SF2: F(1.95,54.65) = 3.429, p = .041;  $\eta^2 = 0.109$ ], with higher amplitudes for trials including fearful distractors than neutral ones (p < .05). The main effect of emotional distractor also reached significant results for P2 [SF2: F (1.99,55.696) = 3.710, p = .031;  $\eta^2 = 0.117$ ], showing a complementary pattern in which brain amplitudes at frontal regions were higher for disgusting compared to neutral distractors (p = .050). However, no interaction effects involving HRV were found for these ERP components.

Finally, with respect to N2, different scalp regions reached statistical significance for the interaction between emotional distractor by HRV group [SF1: F(1.97,55.18) = 5.462, p = .007;



Fig 4. Temporal factors extracted through the application of the tPCA.

 $\eta^2 = 0.163$ ; SF2: F(1.9,53.27) = 4.225, p = .021;  $\eta^2 = 0.131$ ; SF3: F(1.89,52.90) = 6.125, p = .005;  $\eta^2 = 0.179$ ]. Post hoc tests showed enhanced N2 amplitudes for disgusting compared to fearful emotional distractors. This pattern was only exhibited for the high HRV group (p < 0.01; see Fig 5a and 5b). Although the N2 amplitude was different between fearful compared to neutral distractors, it did not reveal significant differences for any scalp regions (p = 1). Furthermore, high HRV subjects exhibited frontal N2 augmented amplitudes for both disgust and neutral distractors compared to low HRV group (p < 0.05). No other significant data were found on the rest of the ERP components with respect to this interaction effect. Finally, a main effect of HRV group (F(1,28) = 4.294, p = .048, eta = .133) was found for N2, which presented a higher amplitude in high HRV than low HRV individuals. Mainly both frontal and central regions were sensitive to this comparison.

Table 3. Description and statistical results for the temporal factors sensitive to experimental manipulations extracted by temporospatial principal component analysis.

Temporal Peak factor	Peak (ms)	Spatial factor: scalp distribution	ANOVAs	ANOVAs	Post-hoc tests	
			(Distractor type, d.f. = 2, 56)	(Distractor type x HRV group, d.f. = 2, 56)		
TF8 (P1)	138	SF1 Parietooccipital	F = 5.729, p = 0.006	F = 0.812, p = 0.4	<b>F</b> > <b>N</b>	
		SF2 Temporoparietal	F = 3.429, p = 0.041	F = 0.129, p = 0.9		
		SF3 Centroparietal	F = 2.170, p = 0.124	F = 0.084, p = 0.9		
TF7 (N2)	176	SF1 Frontal	F = 0.478, p = 0.6	F = 5.461, p = 0.007	High HRV: D > F	
		SF2 Frontocentral	F = 1.022, p = 0.4	F = 4.225, p = 0.021	High HRV D > Low HRV D	
		SF3 Centroparietal	F = 0.139, p = 0.8	F = 6.125, p = 0.005	High HRV N > Low HRV N	
TF6 (P2)	228	SF1 Posterior	F = 1.483, p = 0.2	F = 1.134, p = 0.3		
		SF2 Frontal	F = 3.710, p = 0.031	F = 1.204, p = 0.3	D > N	

TF: temporal factor; SF: spatial factor; d.f.: degrees of freedom; High HRV: High Heart Rate Variability Group; Low HRV: Low Heart Rate Variability Group; F: Fearful; D: Disgust; N: Neutral.

Post-hoc results are shared by all spatial factor belonging to each temporal factor.

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# Source estimation results on N2

In order to three-dimensionally estimate cortical regions that could account for the experimental effects observed in N2 regarding the interaction between emotional distractor by HRV group, a final analytical step was computed. To achieve this, N2 TF scores of each subject, electrode, and condition were submitted to eLORETA. Then, the voxel-based whole-brain eLOR-ETA-images (6329 voxels) were compared among the three emotional distractor conditions for the whole sample of participants. To this aim, statistical non-parametric randomization tests were performed. According to the computed comparisons related to N2 activation, disgusting distractors were associated with higher activity than neutral distractors in several



Fig 6. Insula activation to disgusting distractors (low vs. high HRV). Average current densities for each condition are also shown. (D, disgusting distractors; F, fear-evoking distractors; N, neutral distractors). Error bars represent standard errors.

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voxels within BA13 (insula; MNI coordinates: x = 35, y = 5, z = 15). This effect was only statistically significant for high HRV subjects (see Fig 6). Activation differences among the remainder of the distractor conditions did not reach significance. No other ROIs were sensitive regarding this interaction between emotional distractor by HRV group.

### Discussion

The current study points out that to understand the differential effect of fearful and disgusting stimulation on exogenous attention it is important to consider the time course of its different subprocesses. Fear seems to be processed at a very early stage such as 100 ms after stimulus onset, producing a rapid response in the whole sample of participants. Disgust would also capture exogenous attention at a very early phase, although later than fear. In fact, disgusting distractors attracted exogenous attention resources more efficiently than fear at 200 ms after stimulus onset, as reflected by its effects on the N2 and P2 components of the ERPs. Interestingly, the augmented N2 response to disgust distractors was only present in those participants having a high HRV level.

These apparently puzzling results can well be understood from an evolutionary perspective, which is in agreement with previous proposals describing that exogenous attentional involves different functional phases or processes (see a review in [12]). Prior studies have distinguished different ERP components (peak latency from 100 to 250 ms) in response to visual stimulation reflecting the temporal dynamics of exogenous attention towards emotional events (e.g., [2, 5]). Early functional phases or processes of exogenous attention would be related to a greater mobilization of processing resources toward negatively valenced stimuli indicating probably a negativity bias, which would have adaptive and evolutionary advantages for survival (see reviews, [12, 53]). This effect would confirm the biological importance of emotional stimuli compared to neutral [4, 6, 54, 55]. On the contrary, during later phases, attentional resources would be directed preferentially to positive and neutral events that do not require such an urgent response as negative stimuli do [55]. However, a direct comparison between present data and this previous evidence cannot be made for different reasons: 1) experimental paradigms were different; 2) we did not include positive stimuli; 3) in previous investigations negative pictures used depicted only fear-related but not disgust-related content. Even though, our results are not exclusive with those reported by other studies, but rather are complementary.

According to the statistical results, fearful distractors elicited the largest posterior P1 amplitudes. It has been indicated that fear eliciting stimulation signals an imminent threat that calls for an immediate and fast response while disgust stimuli do not. In support of this idea, previous studies on exogenous attention have reported enhanced parieto-occipital P1 amplitudes to fear evoking stimuli used as distractors [3, 56, 57]. In the same line, attentional effects to disgust stimuli have not been reflected in P1 amplitude, which has been interpreted as its effects occur later [58]. Different findings converge to propose that higher P1 amplitudes would reflect amplification of sensory processing (as a subprocess belonging to exogenous attention) to fear stimulation gaining access for awareness and processing it to a deeper extent [5]. This enhancement of attentional resources to fearful events would involve a clear adaptative advantage in biological terms, playing a crucial role for survival [1]. In this sense, sensory visual cortices would increase their neural activity mediated by top–down attention mechanisms where both the amygdala and ventral prefrontal regions would generate rapid saliency signals for fear stimulation [59–61].

On the other hand, ERP components peaking around 200 ms showed an increase of attention resources for processing disgusting distractors. Specifically, P2 component was characterized by two spatial components (frontal and posterior) through spatial principal component analyses. Although the posterior P2 wave showed no modulations regarding exogenous attention, disgust distractors elicited larger anterior P2 amplitudes than neutral distractors. Furthermore, disgust distractors produced larger N2 amplitudes than fearful stimuli, but this modulation was only true for the high HRV group. Several investigations have found similar modulations in P2 showing greater sensitivity toward negative events, considering this component as a neural index of exogenous attention [55, 62, 63]. Prior studies have highlighted that disgust is a kind of event capable of attracting automatic attention resources even more efficiently than fear [14]. Although this effect was also found around 200 ms after stimulus onset, N2 modulations was not previously reported and possible influences of HRV on neural responses linked to exogenous attention has not been described yet.

The selective enhancement of exogenous attention to negatively valenced distractors (i.e, fearful and disgusting) deserves further consideration. When the organism is involved in the performance of a given task and a potentially threatening distractor appears, the most adaptive response is to do a quick evaluation to explore whether such new stimulus seems to be dangerous in order to initiate a fight or flight response [1]. However, in the case that the outcome of such initial evaluation does not indicate an imminent danger, but the stimulus includes ambiguous information, as happens with disgusting stimuli that can bring death (e.g., illness) or life (e.g., edible food), the most adaptive response would be mobilize attentional resources to analyze it more deeply. Our findings suggest that this attentional adaptive response is evident for high HRV participants as shown by both enhanced N2 amplitudes and slower RTs to disgusting distractors compared to fearful ones. Also disgusting provoked higher error rates than neutral distractors. N2 family deflections have been described as emotion-sensitive ERP waves showing enhanced allocation of exogenous attention resources toward negative stimulation compared to neutral ones [62, 64]. In a previous study, we also found that disgusting distractors capture attention more efficiently than fearful distractors [14] as reflected by neural responses peaking around 200 ms after stimulus onset. Other studies have offered evidence indirectly supporting the suggestion that disgusting distractors capture exogenous attention with latency responses around 200 ms. Van Hooff et al. [11] manipulated the temporal interval between cue onset (disgust, fear, or neutral picture) and target showing that targets presented 200 ms after disgust cue onset were identified less accurately and more slowly than targets presented after fear or neutral cues, indicating a more efficient capture of attention by disgust than by fear cues. Similarly, other studies focused on the study on automatic attention to negative stimulation (disgust and fear), have described longer RTs to targets that appeared 200 ms after the disgusting pictures [65]. Although ERPs were not recorded and the methodology used in their study does not allow exploration of the time course of the differential responses to fear and disgust, it has been suggested that attentional response for fearful pictures seems to

occur earlier and more automatically than for disgusting events, since just the quick registration of their rough content is enough to trigger the appropriate fight or flight reaction [65].

The influence of HRV on the very early phase of the exogenous attentional processing (i.e., P1 ERP deflection) was not observed. However, an interesting effect was evident in a later phase, as reflected by the augmentation of N2 amplitudes to disgust distractors, only for the high HRV group. Our results also indicated that this enhancement of N2 seem to be related to neural activity within the insula. These effect involving participants characterized by a high level of HRV was also prominent at the behavioral level. RTs for trials including disgust distractors were longer compared to neutral and fear ones. No effect of HRV was detected in the error rates.

This pattern of results regarding the role of HRV can also be interpreted from an evolutionary perspective. Following present results, the HRV may play an important role only once that fear stimuli (related with imminent threat) have been processed, when individuals (i.e., high HRV group) may become involved into a more detailed exploration of disgusting stimuli, as reflected by RTs and N2. However, low HRV participants did not show the same attentional pattern. They seem not to be able to disengage their initial attentional response to fear distractors as manifested by their short RT responses, which is typical of hypervigilance responses [34]. Similar results have previously been reported by our group. A deeper cardiac deceleration was found to disgusting distractors compared to fear and neutral ones in an exogenous attention task only in high HRV participants. The low HRV group showed no differences in cardiac deceleration to the three types of emotional distractors [23]. However, early attentional responses to threat are required to face with this kind of stimulation for survival. In this case, higher neural responses were detected in P1when fearful distractors appeared across all participants, regardless of their HRV level.

As it mentioned, neural activity within the insula was related to the enhanced N2 during disgust distractor trials for high HRV individuals. The insula has been associated with the processing of negative emotional stimuli [12, 66, 67], especially with the emotion of disgust [13] as well as with interoception and bodily signals' processing [68, 69]. Importantly, recently the insula has also been suggested as a key structure in two relevant models for the interpretation of our findings. On one side, Carretié [12] included the insula as one of the three main brain areas (together with the amygdala and ventral prefrontal cortex) responsible for the first phase of exogenous attention, called "preattention". During this phase, a fast evaluation of the environment based on low-level stimulus features is conducted in order to detect relevant stimulation and to trigger reorienting processes. Also, Shafer et al. [70] included the insula between those brain areas that reflect automaticity in the emotional processing. On the other side, the relationship between HRV and cerebral blood flow responses elicited by different kind of emotional states such as happiness, sadness, disgust neutral has been previously explored [24]. Their results showed an association between HRV and activity in the insula, but the specific role of each specific emotion on this heart and brain link was not explored. Smith et al. [71] presented a version of the Neurovisceral Integration Model in which the nervous system structures that contribute to vagal control are organized in an eight-level hierarchy, increasing the range and complexity of function at each level. The insula plays a primary role at level six, where the structures implicated in the vagal regulation based on perceptual representation of one's current somatic/visceral state are included. Taking into consideration the role of the insula indicated by these authors from different perspectives, it could be suggested that this structure may be contributing to the preattention phase by offering important information about the current bodily state that may help to regulate vagal control as well as the attentional responses.

Vagally mediated HRV has been structurally and functionally linked to emotional regulation. It has been argued that prefrontal, anterior cingulated, and insula cortices constitutes a neural network with bidirectional communication with the amygdala and other structures implicated in emotional regulation as well as autonomic regulation of the heart [25]. In this way, HRV becomes an index of emotion, cognition, and health related physiological processes. Regarding emotional regulation, it has been found that high HRV is associated with context appropriate emotional responses, for example, under a startle emotional modulation paradigm [22] or to phasic HR responses in addition to behavioral and self-reported emotional responses [23, 39, 72, 73]. Low HRV, however, has previously been related to poor emotional regulation, hypervigilance, and exaggerated responses to innocuous stimuli [21, 22, 31]. This maladaptive pattern of responses is consistent with faster RTs shown to trials containing fearful distractors and the absence of a N2 response related to disgusting stimuli in the present study in the low HRV participants. Although resting HRV can be understood as a trait like measure, it is not included in the characteristics that have been repeatedly associated with negativity bias to negative stimuli. However, the findings of the present study suggest that HRV may be a more informative index of underlying processes of exogenous attention to emotional stimuli than trait anxiety or disgust sensitivity (see S1 File), which posits as a potential tool that may help to understand and disentangle inconsistencies in the previous literature.

Although exposed findings offer relevant evidence on the brain dynamics related to attentional capture by discrete emotions, some potential limitations need to be addressed. In this sense, valence and arousal scores were significantly more negative and arousing for fearful than disgusting distractors. Such differences in these dimensional affective characteristics between emotional stimuli (distinct from their fearfulness and disgustingness, respectively) might have some unexpected influence on attentional capture processes leading to misunderstandings. Nevertheless, although discrete emotions (as a part of affective experience) could be represented in a dimensional space [74], they have their own and intrinsic emotional meaning that makes them unique, apart from the other features. In the current context, future studies combining both discrete and dimensional approaches for representing emotional states are needed to extend knowledge on the capability of emotional stimuli for attracting automatic attention resources. On the other hand, the relatively small sample size used in the present experiment could affect statistical power. To check if our results had the necessary and significant statistical power, we carried out a series of post-hoc power analysis (see S2 File). These analyses yielded a high statistical power for the interaction effect between the type of Distractor x HRV group for each of ERP component sensitive to the experimental manipulations related to attentional capture. Finally, the study of exogenous attention towards emotional stimulation using trial by trial versus blocked presentation could lead to different modulation effects, being blocked designs more susceptible to habituation [75]. What is most important is whether this kind of stimulus presentation may lead to a differential habituation pattern in exogenous attentional responses for negative stimuli as compared to neutral. In this sense, previous studies have shown that although attentional responses were decreased during repeated and blocked presentation of emotional pictures, the amplitudes of early ERP components (between 150–300 ms) did not differ as a function of stimulus emotional meaning [76]. In addition, the prior use of the trial by trial design carried out by our group showed similar exogenous attention responses for negative (disgusting and fearful stimuli) as compared to neutral distractors as those have been found in the current study [14].

In sum, findings derived from the present investigation provide new data about how exogenous attention is captured by different types of negatively valance stimuli. A different time course for fear and disgust is shown by electrophysiological indices. Fear distractors capture automatic attention at very early processing phases (i.e., greatest P1 amplitudes) followed by an augmented modulation in the P2 component in response to disgust events. Data suggest that HRV might contribute to modulate the allocation of exogenous attentional resources for disgusting stimulation as reflected in the N2 amplitudes. Enhanced activation within the insula lead to think that this region may have a relevant role in the early stages of exogenous attention. Future research should be done to better characterize the temporal course of exogenous attention to emotional stimuli, taking into account measures of HRV as a variable that might be important when attention is automatically triggered by potential threats.

# **Supporting information**

S1 File. Results on the relationship between trait anxiety and disgust sensitivity and exogenous attention to emotional stimuli. (DOCX)

**S2** File. Analyses for checking statistical power. (DOCX)

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#### References

- Öhman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol Rev. 2001; 108(3): 483–522. https://doi.org/10.1037/0033-295x.108.3.483 PMID: 11488376
- Carretié L, Hinojosa JA, Martín-Loeches M, Mercado F, Tapia M. Automatic attention to emotional stimuli: neural correlates. Hum Brain Mapp. 2004; 22(4): 290–299. https://doi.org/10.1002/hbm.20037 PMID: 15202107
- Carretié L, Hinojosa JA, López-Martín S, Albert J, Tapia M, Pozo MA. Danger is worse when it moves: neural and behavioral indices of enhanced attentional capture by dynamic threatening stimuli. Neuropsychologia. 2009; 47(2): 364–369. https://doi.org/10.1016/j.neuropsychologia.2008.09.007 PMID: 18835285

- Doallo S, Holguin SR, Cadaveira F. Attentional load affects automatic emotional processing: evidence from event-related potentials. Neuroreport. 2006; 17: 1797–1801. <u>https://doi.org/10.1097/01.wnr</u>. 0000246325.51191.39 PMID: 17164667
- Pourtois G, Schettino A, Vuilleumier P. Brain mechanisms for emotional influences on perception and attention: what is magic and what is not. Biol Psychol. 2012; 92: 492–512. <u>https://doi.org/10.1016/j. biopsycho.2012.02.007 PMID: 22373657</u>
- 6. Pourtois G, Vuilleumier P. Dynamics of emotional effects on spatial attention in the human visual cortex. Progr Brain Res. 2006; 156: 67–91. https://doi.org/10.1016/S0079-6123(06)56004-2 PMID: 17015075
- Yuan J, Zhang Q, Chen A, Li H, Wang Q, Zhuang Z, et al. Are we sensitive to valence differences in emotionally negative stimuli? Electrophysiological evidence from an ERP study. Neuropsychologia. 2007; 45: 2764–71. https://doi.org/10.1016/j.neuropsychologia.2007.04.018 PMID: 17548095
- Alpers G. and Pauli P. Emotional pictures predominate in binocular rivalry. Cogn Emot. 2006; 20: 596– 607.
- Constantine R, McNally RJ, Hornig CD. Snake fear and the pictorial emotional Stroop paradigm. Cognit Ther Res. 2001; 25: 757–764.
- Thomas SJ, Johnstone SJ, Gonsalvez CJ. Event-related potentials during an emotional Stroop task. Int J Psychophysiol. 2007; 63: 221–231. <u>https://doi.org/10.1016/j.ijpsycho.2006.10.002</u> PMID: <u>17123655</u>
- 11. van Hooff JC, Devue C, Vieweg PE, Theeuwes J. Disgust-and not fear-evoking images hold our attention. Acta Psychol. 2013; 143(1): 1–6.
- 12. Carretié L. Exogenous (automatic) attention to emotional stimuli: a review. Cogn Affect Behav Neurosci. 2014; 14(4): 1228–1258. https://doi.org/10.3758/s13415-014-0270-2 PMID: 24683062
- Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. Nat Rev Neurosci. 2001; 2(5): 352–363. https://doi.org/10.1038/35072584 PMID: 11331919
- Carretié L, Ruiz-Padial E, López-Martín S, Albert J. Decomposing unpleasantness: differential exogenous attention to disgusting and fearful stimuli. Biol Psychol. 2011; 86(3): 247–253. https://doi.org/10. 1016/j.biopsycho.2010.12.005 PMID: 21184798
- 15. Pezzulo G, Iodice P, Barca L, Chausse P, Monceau S, Mermillod M. Increased heart rate after exercise facilitates the processing of fearful but not disgusted faces. Sci Rep. 2018; 8(1): 1–10.
- Zhang D, Liu Y, Wang L, Ai H, Luo Y. Mechanisms for attentional modulation by threatening emotions of fear, anger, and disgust. Cogn Affect Behav Neurosci. 2017; 17(1): 198–210. <u>https://doi.org/10.</u> 3758/s13415-016-0473-9 PMID: 27761806
- 17. Cisler JM, Olatunji BO, Lohr JM. Disgust, fear, and the anxiety disorders: A critical review. Clin Psychol Rev. 2009; 29(1), 34–46. https://doi.org/10.1016/j.cpr.2008.09.007 PMID: 18977061
- DePesa NS, Cassisi JE. Affective and autonomic responses to erotic images: evidence of disgustbased mechanisms in Female Sexual Interest/Arousal Disorder. J Sex Res. 2017; 54(7), 877–886. https://doi.org/10.1080/00224499.2016.1252307 PMID: 27911086
- Gilchrist PT, Vrinceanu T, Béland S, Bacon SL, Ditto B. Disgust stimuli reduce heart rate but do not contribute to vasovagal symptoms. J Behav Ther Exp Psychiatry. 2016; 51: 116–122. https://doi.org/10. 1016/j.jbtep.2016.01.005 PMID: 26851836
- Serrano MÁ, Rosell-Clari V, García-Soriano G. The Role of Perceived Control in the Psychophysiological Responses to Disgust of Subclinical OCD Women. Sensors. 2019; 19(19), 4180. <u>https://doi.org/10.</u> 3390/s19194180 PMID: 31561601
- Ruiz-Padial E, Thayer JF. Resting heart rate variability and the startle reflex to briefly presented affective pictures. Int J Psychophysiol. 2014; 94: 329–335. https://doi.org/10.1016/j.ijpsycho.2014.10.005 PMID: 25449955
- Ruiz-Padial E, Sollers JJIII, Vila J, Thayer JF. The rhythm of the heart in the blink of an eye: emotionmodulated startle magnitude covaries with heart rate variability. Psychophysiology. 2003; 40: 306–313. https://doi.org/10.1111/1469-8986.00032 PMID: 12820871
- Ruiz-Padial E, Mendoza Medialdea MT, Reyes del Paso GA, Thayer JF. Individual differences in attentional capture by pictures of fear and disgust as indexed by cardiac responses. J Psychophysiol. 2018; 32 (4): 191–201.
- Lane RD, McRae K, Reiman EM, Chen K, Ahern GL, Thayer JF. Neural correlates of heart rate variability during emotion. Neuroimage. 2009; 4(1): 213–222. https://doi.org/10.1016/j.neuroimage.2008.07. 056 PMID: 18778779
- Thayer JF, Lane RD. Claude Bernard and the heart–brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009; 33: 81–88. <u>https://doi.org/10.1016/j.neubiorev.2008.08.004</u> PMID: 18771686

- 26. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann Behav Med. 2009; 37: 141–153. https://doi.org/10.1007/s12160-009-9101-z PMID: 19424767
- Smith R, Allen JJ, Thayer JF, Lane RD. Altered functional connectivity between medial prefrontal cortex and the inferior brainstem in major depression during appraisal of subjective emotional responses: a preliminary study. Biol Psychol. 2015; 108: 13–24. <u>https://doi.org/10.1016/j.biopsycho.2015.03.007</u> PMID: 25795386
- Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. Neuroimage. 2016; 39: 44– 52. https://doi.org/10.1016/j.neuroimage.2016.05.076 PMID: 27261160
- Thayer JF, Friedman BH, Borkovec TD, Johnsen BH, Molina S. Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. Psychophysiology. 2000; 37(3): 361–368. PMID: 10860413
- Ruiz-Padial E, Vila J, Thayer JF. The effect of conscious and non-conscious presentation of biologically relevant emotion pictures on emotion modulated startle and phasic heart rate. Int J Psychophysiol. 2011; 79: 341–346. https://doi.org/10.1016/j.ijpsycho.2010.12.001 PMID: 21145923
- Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol. 2007; 74: 185–199. https://doi.org/10.1016/j.biopsycho.2005.08.009 PMID: 17069959
- Wendt J, Neubert J, Koenig J, Thayer JF Hamm AO. Resting heart rate variability is associated with inhibition of conditioned fear. Psychophysiology. 2015; 52(9): 1161–1166. <u>https://doi.org/10.1111/ psyp.12456</u> PMID: 26095980
- Park G, Vasey MW, Van Bavel JJ, Thayer JF. Cardiac vagal tone is correlated with selective attention to neutral distractors under load. Psychophysiology. 2013a; 50(4): 398–406.
- Park G, Van Bavel JJ, Vasey MW, Thayer JF. Cardiac vagal tone predicts attentional engagement to and disengagement from fearful faces. Emotion. 2013b; 13(4): 645.
- Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. Gainesville, FL: University of Florida; 2008.
- Carretié L, Tapia M, López-Martín S, Albert J. EmoMadrid: An emotional pictures database for affect research. Motiv Emot. 2019; 43(6): 929–939.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiology interpretation, and clinical use. Circulation. 1996; 93: 1043–1065. PMID: 8598068
- Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research–recommendations for experiment planning, data analysis, and data reporting. Front Psychol. 2017; 8: 213. https://doi.org/10.3389/fpsyg.2017.00213 PMID: 28265249
- Melzig C, Weike A, Hamm A, Thayer J. Individual differences in fear-potentiated startle as a function of resting heart rate variability: implications for panic disorder. Int J Psychophysiol. 2009; 71: 109–117. https://doi.org/10.1016/j.ijpsycho.2008.07.013 PMID: 18708100
- Dien J, Frishkoff G. Principal components analysis of event-related potential datasets. In: Handy T, editor. Event-Related Potentials: A Methods Handbook. Cambridge: MIT Press; 2005. pp. 189–208.
- Chapman RM, McCrary JW. EP component identification and measurement by principal components analysis. Brain Cogn. 1995; 27: 288–310. https://doi.org/10.1006/brcg.1995.1024 PMID: 7626278
- Cattell RB. The scree test for the number of factors. Multivar Behav Res. 1966; 1: 245–276. https://doi. org/10.1207/s15327906mbr0102\_10 PMID: 26828106
- Dien J. Evaluating two-step PCA of ERP data with geomin, infomax, oblimin, promax, and varimax rotations. Psychophysiology. 2010; 47: 170–183. <u>https://doi.org/10.1111/j.1469-8986.2009.00885.x</u> PMID: 19761521
- Pourtois G, Delplanque S, Michel C, Vuilleumier P. Beyond conventional event-related brain potential (ERP): exploring the time-course of visual emotion processing using topographic and principal component analyses. Brain Topogr. 2008; 20: 265–277. <u>https://doi.org/10.1007/s10548-008-0053-6</u> PMID: 18338243
- Pascual-Marqui RD. Discrete, 3D Distributed, Linear Imaging Methods of Electric Neuronal Activity. Part 1: Exact, Zero Error Localization 2007; Available at: <a href="http://arxiv.org/pdf/0710.3341">http://arxiv.org/pdf/0710.3341</a> (accessed October 17, 2007).
- Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, et al. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci. 2011; 369: 3768–3784. https://doi.org/10.1098/rsta.2011.0081 PMID: 21893527

- Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol. 2002; 24 (Suppl. D): 5–12. PMID: 12575463
- 48. Dierks T, Jelic V, Pascual-Marqui RD, Wahlund L, Julin P, Linden DE, et al. Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. Clin Neurophysiol. 2000; 11: 1817–1824. <u>https://doi.org/10.1016/s1388-2457(00)00427-2</u> PMID: 11018498
- 49. Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller HJ, et al. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage. 2004; 22: 83–94. https://doi.org/10.1016/j.neuroimage.2003.10.051 PMID: 15109999
- Vitacco D, Brandeis D, Pascual-Marqui R, Martin E. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum Brain Mapp. 2002; 17: 4–12 https://doi.org/10.1002/hbm.10038 PMID: 12203683
- Dien J, Spencer KM, Donchin E. Localization of the event-related potential novelty response as defined by principal components analysis. Cogn Brain Res. 2003; 17: 637–50. https://doi.org/10.1016/s0926-6410(03)00188-5 PMID: 14561451
- Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp. 2002; 15(1): 1–25. https://doi.org/10.1002/hbm.1058 PMID: 11747097
- Emery NJ, Amaral DG. The role of the amygdala in primate social cognition. In: Lane RD, Nadel L, editors. Cognitive Neuroscience of Emotion. New York: Oxford University Press; 2000. p. 156–191.
- Carretié L, Hinojosa JA, Mercado F, Tapia M. Cortical response to subjectively unconscious danger. NeuroImage. 2005; 24: 615–623. https://doi.org/10.1016/j.neuroimage.2004.09.009 PMID: 15652297
- Huang YX, Luo YJ. Temporal course of emotional negativity bias: an ERP study. Neurosci Lett. 2006; 398: 91–6. https://doi.org/10.1016/j.neulet.2005.12.074 PMID: 16446031
- 56. Krusemark EA, Li W. Do all threats work the same way? Divergent effects of fear and disgust on sensory perception and attention. J Neurosci. 2011; 31(9): 3429–3434. <u>https://doi.org/10.1523/JNEUROSCI.4394-10.2011 PMID: 21368054</u>
- Pourtois G, Grandjean D, Sander D, Vuilleumier P. Electrophysiological correlates of rapid spatial orientating towards fearful faces. Cereb Cortex 2004; 14: 619–633. <u>https://doi.org/10.1093/cercor/bhh023</u> PMID: 15054077
- Zimmer U, Keppel MT, Poglitsch C, Ischebeck A. ERP evidence for spatial attention being directed away from disgusting locations. Psychophysiology. 2015; 52(10): 1317–1327. https://doi.org/10.1111/ psyp.12463 PMID: 26085080
- 59. Kawasaki H, Kaufman O, Damasio H, Damasio AR, Granner M, Bakken H, et al. Single-neuron responses to emotional visual stimuli in human ventral prefrontal cortex. Nat Neurosci. 2001; 4: 15–16. https://doi.org/10.1038/82850 PMID: 11135639
- Méndez-Bértolo C, Moratti S, Toledano R, Lopez-Sosa F, Martínez-Álvarez R, Mah Y, et al. A fast pathway for fear in human amygdala. Nat Neurosci. 2016; 19: 1041–1049. https://doi.org/10.1038/nn.4324 PMID: 27294508
- Pourtois G, Spinelli L, Seeck M, Vuilleumier P. Temporal precedence of emotion over attention modulations in the lateral amygdala: intracranial evidence from a patient with temporal lobe epilepsy. Cogn Affect Behav Neurosci. 2010; 10: 83–93. https://doi.org/10.3758/CABN.10.1.83 PMID: 20233957
- Carretié L, Kessel D, Carboni A, López-Martín S, Albert J, Tapia M, et al. Exogenous attention to facial vs. non-facial emotional visual stimuli. Soc Cogn Affect Neurosci. 2013; 8: 764–773. https://doi.org/10. 1093/scan/nss068 PMID: 22689218
- Junhong H, Renlai Z, Senqi H. Effects on automatic attention due to exposure to pictures of emotional faces while performing Chinese word judgment tasks. PloS One. 2013; 8: e75386 <u>https://doi.org/10.1371/journal.pone.0075386</u> PMID: 24124486
- Eimer M, Kiss M. Attentional capture by task-irrelevant fearful faces is revealed by the N2pc component. Biol Psychol. 2007; 74: 108–112. https://doi.org/10.1016/j.biopsycho.2006.06.008 PMID: 16899334
- 65. van Hooff JC, van Buuringen M, El M'rabet I, de Gier M, van Zalingen L. Disgust-specific modulation of early attention processes. Acta Psychol. 2014; 152, 149–157. <u>https://doi.org/10.1016/j.actpsy.2014.08.</u> 009 PMID: 25226546
- Garfinkel SN, Critchley HD. Threat and the body: how the heart supports fear processing. Trends in Cognitive Sciences 2016; 20(1): 34–46. https://doi.org/10.1016/j.tics.2015.10.005 PMID: 26628111
- 67. Papagno C, Pisoni A, Mattavelli G, Casarotti A, Comi A, Fumagalli F, et al. Specific disgust processing in the left insula: new evidence from direct electrical stimulation. Neuropsychologia. 2016; 84: 29–35. https://doi.org/10.1016/j.neuropsychologia.2016.01.036 PMID: 26836143

- Craig AD. How do you feel now? The anterior insula and human awareness. Nat Rev Neurosci. 2009; 10: 59–70. https://doi.org/10.1038/nrn2555 PMID: 19096369
- Meissner K, Wittmann M. Body signals, cardiac awareness, and the perception of time. Biol Psychol. 2011; 86: 289–297. https://doi.org/10.1016/j.biopsycho.2011.01.001 PMID: 21262314
- Shafer AT, Matveychuk D, Penney T, O'Hare AJ, Stokes J, Dolcos F. Processing of emotional distraction is both automatic and modulated by attention: evidence from an event-related fMRI investigation. J Cogn Neurosci. 2012; 24(5): 1233–1252. https://doi.org/10.1162/jocn\_a\_00206 PMID: 22332805
- Smith R, Thayer JF, Khalsa SS, Lane RD. The hierarchical basis of neurovisceral integration. Neurosci Biobehav Rev. 2017; 75: 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003 PMID: 28188890
- **72.** Thayer JF, Brosschot JF. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology. 2005; 30: 1050–1058. <u>https://doi.org/10.1016/j.psyneuen.2005.04.014</u> PMID: 16005156
- 73. Visted E, Sørensen L, Osnes B, Svendsen JL, Binder PE, Schanche E. The association between self-reported difficulties in emotion regulation and heart rate variability: the salient role of not accepting negative emotions. Front Psychol. 2017; 8: 328. https://doi.org/10.3389/fpsyg.2017.00328 PMID: 28337160
- 74. Adolphs R. How should neuroscience study emotions? By distinguishing emotion states, concepts, and experiences. Soc Cog Affect Neurosci. 2017; 12 (1): 24–31.
- Carretié L, Hinojosa JA, Mercado F. Cerebral patterns of attentional habituation to emotional visual stimuli. Psychophysiology. 2003; 40: 381–388. <u>https://doi.org/10.1111/1469-8986.00041</u> PMID: 12946112
- 76. Codispoti M, Ferrari V, Bradley MM. Repetition and Event-related Potentials: Distinguishing Early and Late Processes in Affective Picture Perception. J Cogn Neurosci. 2007; 19(4): 577–586. <u>https://doi.org/ 10.1162/jocn.2007.19.4.577 PMID: 17381249</u>