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Abstract

Emotional deficits in major depressive disorder lead to changes in the distribution of attention in the visual field. We investigate the impact of unpleasant and neutral pictures, presented in central (0°) and peripheral vision (12°; 24°), in 15 depression patients (DP) and 15 matched healthy controls (HC). Heart rate, skin conductance responses (SCRs) and electroencephalogram (EEG) were recorded. A spatiotemporal principal component analysis (PCA) was applied to the EEG, and ANCOVAs controlling for participants' state- and trait-anxiety and patients' medication were performed to assess the effects of visual eccentricity and emotion. Unlike HC, DP showed for CV stimulation 1/ greater sensitivity with a response bias toward unpleasant pictures, 2/ larger SCRs, especially to unpleasant pictures, and 3/ deeper cardiac deceleration. Furthermore, eccentricity and emotion modulated cerebral components. Finally, results bring a new vista on visual capture of negative information and support methods to enlarge the attentional span of depressed patients.

Keywords

Major Depressive Disorder, Emotion, Attention, Skin conductance, Heart rate, ERPs

Introduction

The perceptual and attentional selection of emotional information allows individuals to ensure their preservation and well-being (Vuilleumier, 2015). This selectivity has been observed in near and even in far peripheral vision (PV) despite its low acuity (D'Hondt et al., 2016). Furthermore, emotional stimuli in PV interfere with information processing in central vision (CV, D'Hondt et al., 2013). Hence, PV appears to be an alert system able to detect relevant information and to summon up sufficient attentional resources to challenge the priority of a CV task. Emotional processing is manifested by brain activities (Olofsson et al., 2008) and physiological responses depending on the autonomic nervous system (ANS). Among ANS-dependant activities, skin conductance responses (SCRs), a robust indicator of physiological arousal (Critchley, 2002), have been related to attentional capture. SCR amplitude increases with emotional arousal, regardless of the valence (unpleasant or pleasant, Lang et al., 1993; Bradley et al., 2001). Thus, SCRs reflect the autonomic arousal accompanying the attentional engagement toward relevant information. Emotion also modulates the heart rate (HR), which is increased and decreased by the sympathetic and parasympathetic branches of the ANS, respectively (Berntson et al., 1997). Initial cardiac deceleration occurs in the context of environmental detection, reflecting an enhanced orienting response (Bradley, 2009). Subsequent cardiac acceleration occurs as the individual prepares for action and indicates sensory rejection and defensive arousal (Bradley et al., 2001; Bradley, 2009). Otherwise, cardiac deceleration increases in response to unpleasant cues while cardiac acceleration increases with emotional arousal (Lang et al., 1993; Bradley, 2009).

In affective disorders, impaired emotional processing within the visual space results in behavioural and physiological maladjustments. For example, major depressive disorder (MDD), which is characterised by depressed mood and loss of pleasure, is accompanied by somatic and cognitive disturbances (American Psychiatric Association & American Psychiatric Association, 2013). Patients show an attentional bias towards unpleasant

information and deficits in visual orienting and in sustained and executive attention (Paelecke-Habermann et al., 2005), which may lead to lesser PV exploration. Regarding autonomic reactivity in depression, the literature suggests either an increased reactivity to unpleasantness (Wenzler et al., 2017), or a decreased reactivity to pleasantness (Clark & Watson, 1991), or a blunted reactivity for both valences (Rottenberg et al., 2005). Moreover, a meta-analysis showed reduced physiological reactivity for unpleasant stimuli in MDD but not pleasant ones (Bylsma et al., 2008). At the cerebral level, inhibition exerted by the ventromedial prefrontal cortex (vmPFC) on the amygdala (Thayer et al., 2012) seems to be enhanced in MDD patients (Kaiser et al., 2015). Interestingly, vmPFC and medial orbitofrontal cortex (OFC) activities are negatively correlated with skin conductance (Nagai et al., 2004). Furthermore, vmPFC activity is negatively correlated with an increased HR during threat (Roy et al., 2012).

Concerning the event-related potentials, depression is associated with a reduced P300 amplitude in response to happy faces (Cavanagh & Geisler, 2006), an enhanced P300 in response to negative words (Ilardi et al., 2007), and a reduced Late Positive Potential (LPP) in response to emotional faces (Foti et al., 2010). These data reflect an attentional deficit in the late visual processing stages of emotional information in depression. Moreover, depression seems to modulate early emotional processing stages and has been associated to a reduced N100/P100 amplitude for emotional words (Dai & Feng, 2011). However, the way in which depression modulates the dynamics of visual processing of emotional information, and especially the processing of complex emotional scenes, requires further investigation.

Hence, the aim of this study was to compare the behavioural, autonomic and cerebral impact of unpleasant and neutral stimuli presented in CV and PV in MDD patients and healthy controls. To this end, standardised pictures were presented at five positions to participants who had to categorise them in terms of emotional content. Comorbidity with anxiety disorders and patients' medication were controlled. We hypothesised that, compared to healthy controls, MDD patients would be more focused on CV and exhibit a differential

reactivity to emotion. Furthermore, we expected these differences in reactivity to be associated with cerebral components identified by data-driven analysis of event-related brain activity.

Material and methods

Participants

Fifteen depressed patients (DP; 7 women) and 15 healthy controls (HC) matched on gender, age and education levels were included. DP received an MDD diagnosis on the basis of the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV, American Psychiatric Association, 2000; DATA, 1997). HC had no neurological or psychiatric antecedents. All the participants were right-handed (Hécaen, 1984), French speakers, had normal or corrected to normal vision as established by an eye examination, and fulfilled the State-Trait Anxiety Inventory (STAI-A & B, Spielberger and Gorsuch, 1983) and the Beck Depression Inventory (BDI-II, Beck et al., 1996; **Table 1**). Each participant provided written informed consent and none of them received pecuniary compensation. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Regional Ethics Committee (CPP Nord-Ouest-IV, Nb 2011-A00176-35) and was conducted at the Fontan University Psychiatric Hospital in Lille, France.

Table 1. Demographic and psychometric data of healthy controls (HC) and depressed patients (DP). Means (standard deviation) for all items. HECAEN: Laterality Test**;** STAI-A and STAI-B: State and Trait Anxiety Inventory; BDI: Beck Depression Inventory.

	Healthy Controls (HC)	Depressed Patients (DP)	*t*	*p* value
AGE [yrs]	45.93 (10.74)	47.80 (11.86)	0.45	0.65
EDUCATION LEVEL	14.13 (3.18)	13.67 (2.26)	0.46	0.65
HÉCAEN	0.92 (0.08)	0.85 (0.27)	0.94	0.35
STAI-A	44.40 (10.18)	61.07 (7.16)	5.04	< 0.001
STAI-B	39.60 (8.74)	70.20 (7.25)	10.08	< 0.001
BDI-II	3.27 (3.56)	42.00 (8.35)	11.92	< 0.001

Pharmacological treatments indicated in depression have been considered and classified using the World Health Organisation's Anatomical Therapeutic Chemical (ATC) system and codes (WHO Collaborating Centre for Drug Statistics Methodology, 2019), distinguishing selective serotonin reuptake inhibitors (N06AB), tricyclic antidepressants (N06AA), benzodiazepines (NA05BA), other antidepressants (NA06AG; NA06AX) and antipsychotics (N05AA, N05AC, N05AH, N05AN, N05AX). Out of the 15 patients, 4 were not medicated, and 9 patients had more than 2 of the 5 types of medication in their prescription.

Stimuli and Apparatus

Two sets of 175 pictures, unpleasant and neutral, were selected from the International Affective Picture System (IAPS, Lang et al., 2008). On IAPS standardised (*a priori*) ratings, the unpleasant pictures had lower valence (ps < 0.001) and greater arousal (ps < 0.001) than neutral ones. Given the recognised differences in emotional assessment by gender (Collignon et al., 2010), we made one selection for each gender. These selections included 103 specific pictures for each gender and 247 common pictures. Pictures selections for women and men were similar (evaluated by the ratio of values between the two selections) in terms of valence (U = 87.5%; N = 96.4% of similarity) and arousal (U = 94.8%; N = 94.6% of similarity). The main physical properties of pictures were extracted (ImageJ v1.50), including the greyscale, the red, green and blue layers and spatial frequencies (Delplanque et al., 2007). The selected pictures did not differ on these properties (**Table S1**); thus, pictures differed only on emotional dimensions without physical saliency influencing visual search and attention (Lucas & Vuilleumier, 2008).

Pictures of 12°x12° angular size were randomly displayed at one of the five positions (-24°, -12°, 0°, +12°, +24°; *E-Prime 2 Professional*) on three adjoining screens covering 140° of the visual field. A chin rest was placed in front of the midline of the central screen at a distance of 44 cm. A PC (Hewlett-Packard Pentium III 1000 MHz; Windows XP professional) controlled the three screens through an NVIDIA Gforce 2 graphics card and a 2GB

DualHead box. To avoid fatigue, the presentation was divided in five blocks. There were no differences between blocks on valence, arousal or physical properties for both genders ($Fs_{4,339} < 1.07$ and $ps > 0.24$).

Recordings

Behavioural responses were gathered by a response box connected to the display computer. The skin conductance (SC) and the electrocardiogram (ECG) were recorded at 200 Hz by a BIOPAC MP35 system connected to a second computer (*BIOPAC Student Pro 3.7*). SC was recorded through Ag/AgCl electrodes filled with an isotonic electrolyte paste (0.05 molar NaCl) attached to the palmar side of the middle phalanges of the index and middle fingers of the participant's non-dominant hand, with a gain of 5 µS/V and a 10 Hz low-pass filter. The ECG was recorded with a 0.5 – 66.5 Hz band-pass filter using a DI modified bypass placing the Ag/AgCl electrodes on the participant's wrists. The electroencephalogram (EEG) was collected from 128 electrodes including four electro-oculogram and two mastoid reference channels using an EEG-cap (WaveGuardElectrocap, 10-20 system; all the impedances were kept below 5 kΩ.). The EEG cap was connected to an amplifier (Advanced Neuro Technology, ANT) and to a third computer, with *ASA 4.0* for a 1024-Hz acquisition.

Procedure

The experiment took place exclusively in the morning to minimise the effects of circadian variations (Hot et al., 2005) and was divided into three steps. *First,* participants were submitted to two blocks of 70 pictures, projected for 500 ms each with an inter-stimulus interval (ISI) randomly varying from 10 to 15 s, during which behavioural, autonomic and electrocortical variables were recorded. S*econd*, they were submitted to three blocks of 70 pictures of 500-ms duration, with an ISI randomly varying for 2 to 3 s, during which only the EEG was recorded to increase the number of trials to improve the signal quality. Throughout

the experiment, they were instructed to keep their gaze on a central fixation cross presented between each picture. The task was to categorise pictures (unpleasant or neutral) thanks to a response box using the dominant hand. *Finally*, they rated (*a posteriori* ratings) the valence and arousal dimensions of a sample of the pictures projected in previous steps by using two nine-point scales adapted from the Self-Assessment Manikin (SAM, Bradley and Lang, 1994). Each picture was projected until the valence and activation assessment were given by the participants without time limit.

Data analyses

To exclude possible saccades towards visual stimuli, all trials containing eye movements during stimulus presentation were rejected upon Brainstorm's detection procedure on the VEOG/HEOG signals, followed by visual inspection: 17.8% of the trials were rejected (14.6% in HC and 20.9% in DP). The eye movements detection procedure is based on the absolute values of the bandpass filtered EOG signal from 1.5 to 15 Hz, with a threshold set at 2 times the standard deviation. This use of Brainstorm software package is documented and freely available for download online under the GNU general public licence (http://neuroimage.usc.edu/ brainstorm).

Behavioural Data

A posteriori ratings were obtained for a sample of 40 from the 350 selected pictures and ratios between this sample and the whole selection were calculated for valence and arousal. The sample was similar to the whole selection on valence (women: U = 99.2% and N = 96.5%; men: U = 98.5% and N = 99.0%) and arousal (women: U = 97.9% and N = 97.7%; men: U = 98.3% and N = 99.7%). Moreover, the Signal Detection Theory (SDT) was applied to categorisation accuracy, considering unpleasant pictures as signal and neutral ones as noise. The sensitivity (d') to unpleasant pictures was computed (Stanislaw & Todorov, 1999), a value of 0 indicating an inability to distinguish unpleasant stimuli from neutral ones. The response bias (β) was computed (Stanislaw & Todorov, 1999), a $\beta < 1$ indicating a bias toward unpleasantness.

Autonomic Data

Using *AcqKnowledge 4.1* software, the phasic waveforms of SC were extracted from the signal with an offline 0.05 Hz high-pass filter. Specific SCRs were retained using classical latency (1 to 4 s) and amplitude (> 0.01 µS) criteria. HR in beats per minute (BPM) was calculated from the R-R intervals and smoothed using a 1-s width triangular Bartlett window (*LabChart7)*. HR variations were obtained by subtracting the averaged HR over a 3-s pre-stimulus period to the 10-s post-stimulus period. For each condition and participant, the epochs (-3 to 10 s) were averaged and the initial HR deceleration and the subsequent HR acceleration were analysed by integrating the negative and positive HR variations, respectively.

Brain Data

All trials exceeding ±100 µV were excluded and a 0.032 – 30 Hz band-pass filter was set offline. Event-related potentials (ERPs) were averaged over a 800 ms period with a 100 ms baseline correction. We conducted a spatiotemporal Principal Component Analysis (PCA) on the ERPs (Spencer et al., 1999) beginning with a spatial PCA (sPCA), which identifies highly correlated electrodes and reduces them into principal "Spatial Factors" (SF, Pourtois et al., 2008). SF loadings correspond to the contribution of electrodes to the SF. The factorial scores were considered as "virtual ERPs" and submitted to a temporal PCA (tPCA). This tPCA identifies correlated time series and reduces them into principal "Temporal Factors" (TF, Pourtois et al., 2008). TF loadings correspond to the contribution of each SF time point to the TF and determine SF activity latencies (D'Hondt et al., 2013). SF and TF were selected according to the Karlis, Saporta and Spinakis rule (KSS, Karlis et al., 2003) and to the broken stick test (Frontier, 1976; Legendre & Legendre, 2012).

Separate HC and DP sPCAs were conducted using a covariance matrix with unrestricted varimax rotation (SPSS V. 20) and with 122 variables (EEG-cap electrodes) and 123,000 observations (15 participants x 10 conditions x 820 samples). Then, an sPCA combining HC and DP datasets was conducted, increasing the number of observations (246,000 observations with 30 participants) to improve the stability of the component solution

(Barry et al., 2016). Each SF selected from separate and combined sPCAs was submitted to a tPCA using a covariance matrix with unrestricted varimax rotation (SPSS V. 20) and with 820 variables (from 0 to 800 ms at 1024 Hz sample rate) and 150 observations (15 participants x 10 conditions) for separate and 300 observations (30 participants x 10 conditions) for combined sPCAs. The result of the spatiotemporal PCA procedure was a set of factor scores that were used to compare the activity of the "virtual ERPs" (SF) at particular latencies (TF) in response to each condition.

Statistical Analyses

In order to validate our pictures selection, and since we have a pictures selection by gender, *a priori* and *a posteriori* ratings of the pictures were assessed with a Group x Gender ANOVA and Spearman's coefficient. Concerning the position of stimuli, as our hypotheses only concern the CV vs. the PV, the effects of laterality were not considered here and the analyses focused on the effects of eccentricity (CV: 0°; near PV: ±12°; far PV: ±24°): either monotonic changes modelled by a quadratic contrast (C2) or changes from CV to near PV fading in far PV, modelled by a quartic contrast (C4). The effect of emotion was evaluated by contrasting the neutral and the unpleasant conditions (linear contrast = unpleasant – neutral). The use of contrasts makes it possible to test the specific hypotheses about position effects and is more accurate than omnibus tests, this accuracy going hand in hand with a higher statistical power (Brauer & McClelland, 2005). Contrasts were assessed by repeated measures ANCOVA applied to each variable with the group as between-subject factor. As participants were matched by gender, the gender was not taken into account for these analyses. We classified patients' medication using the World Health Organisation's Anatomical Therapeutic Chemical (ATC) system and codes (WHO Collaborating Centre for Drug Statistics Methodology, 2019), distinguishing selective serotonin reuptake inhibitors (N06AB), tricyclic antidepressants (N06AA), benzodiazepines (NA05BA), other antidepressants (NA06AG; NA06AX) and antipsychotics (N05AA, N05AC, N05AH, N05AN, N05AX). The prescribed daily dose to the Defined Daily Dose (DDD, WHO Collaborating

Centre for Drug Statistics Methodology, 2019) ratio was used as covariate for the five categories of medication. State (STAI-A) and trait-anxiety (STAI-B) scores were also included in the model, giving seven covariates. A sensitivity analysis with *G*Power 3.1.9.2* indicates that, for a one-way ANCOVA with the seven covariates, given a sample size N = 30, $\alpha = 0.05$ and $\beta = 0.2$, we can detect an effect of minimum size of $f = 0.536$ (i.e. $\eta^2 = 0.223$). Concerning brain measures, SF loadings were compared using Tucker's (1951) congruence coefficient (rc), evaluated using a rule of thumb, which is sensitive to similarities in the contribution of electrodes to the SF (Lorenzo-Seva & ten Berge, 2006; Barry & De Blasio, 2017).

Finally, series of hierarchic linear regression analyses were performed on behavioural or autonomic effects with stPCAs components as independent factors.

Results

Results focus on significant group-dependant eccentricity or emotional effects.

Behavioural data

Subjective assessment of pictures

Selected pictures were validated by comparing *a priori* and *a posteriori* ratings of valence and arousal. *A priori* and *a posteriori* ratings were correlated for both groups and both genders on valence (all ρs > 0.79 and ps < 0.001) and arousal (all ρs > 0.51 and ps < 0.001; **Fig. 1**). Moreover, *a posteriori* ratings from HC and DP were correlated on valence and arousal (all ρs > 0.45 and ps < 0.004).

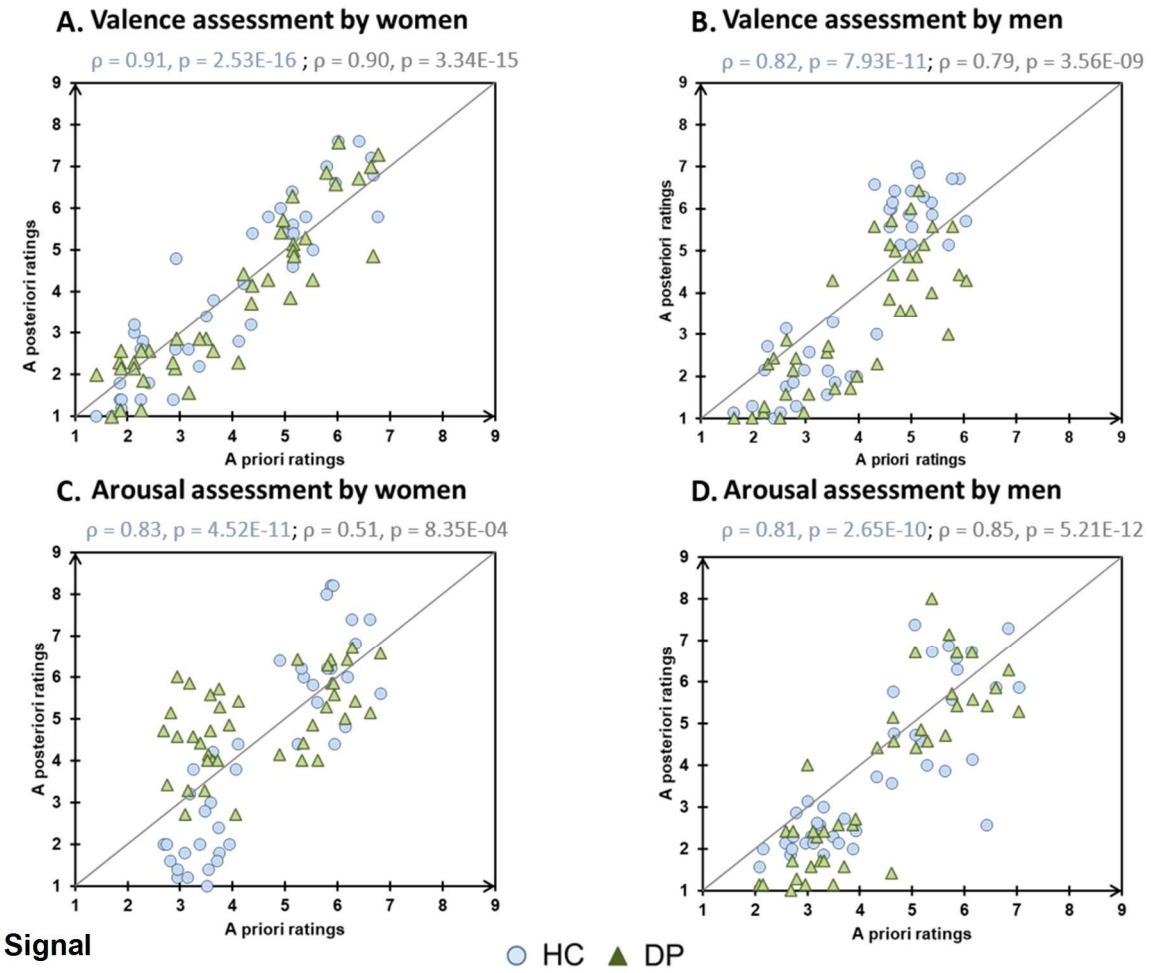

Figure 1. Validation of picture selection using correlations between standardised *(a priori)* ratings according to the International Affective Picture System (IAPS) and mean subjective *(a posteriori)* ratings of unpleasant and neutral pictures. Ratings for controls (HC) are represented in blue and ratings for patients (DP) in green. **(A)** Valence ratings for women; **(B)** valence ratings for men; **(C)** arousal ratings for women; **(D)** arousal ratings for men. *A posteriori* ratings did not depend on group or gender (All Fs < 3.11 and ps > 0.091).

Detection Theory (SDT)

No main effect of the group was observed on the sensitivity ($F_{1,21}$ = 1.16; p = 0.295; η^2 = 0.052). However, the contrast analysis revealed that the effects of eccentricity on this sensitivity were opposite between HC and DP (d', C4: $F_{1,21}$ = 4.53; p = 0.045, η^2 = 0.178; **Fig. 2A**). Compared to CV (0°), for HC, the sensitivity to unpleasant increased in near PV (12°), while for DP the sensitivity to unpleasant decreased in near PV. In large PV (24°), the sensitivity in DP was closer to that of HC compared to CV (0°) (C2: $F_{1,21}$ = 6.46; p = 0.019; η^2 = 0.235). In DP, TCA medication increased the effect of eccentricity in near PV (β-coefficient

= -87.51; p = 0.012; η^2 = 0.618) while antipsychotics reduced it (β-coefficient = 5.64; p = 0.009; η^2 = 0.642).

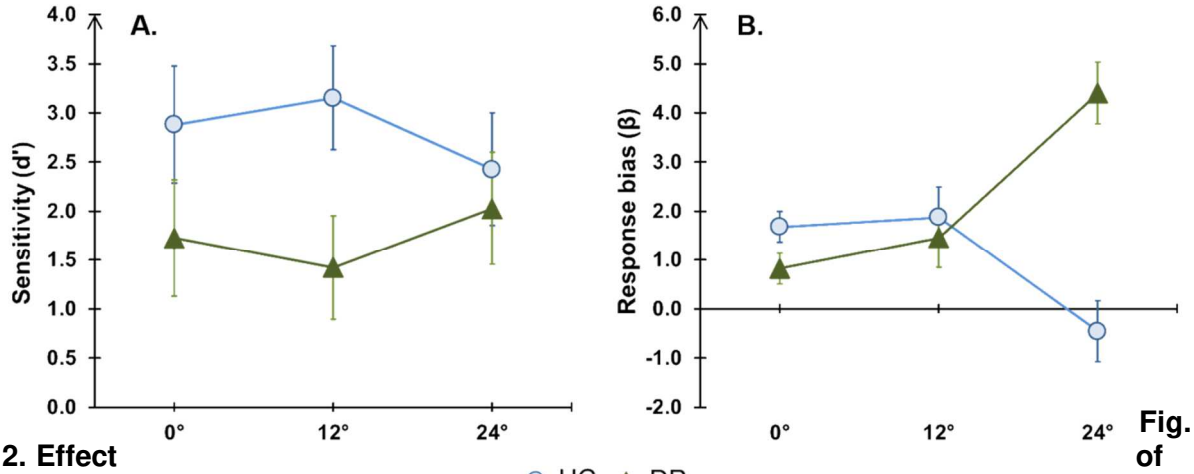

Fig. 2. Effect of eccentricity on detection of unpleasant pictures from neutral ones. Data are estimated marginal means of sensitivity (d', panel A) and response bias (β, B) parameters of SDT with standard errors according to position of stimuli (central: 0°; near periphery: 12° and far periphery: 24°), for Healthy Controls (HC, blue line) and Depressed Patients (DP, green).

The effects of eccentricity were also opposite between HC and DP for response bias (β, C2: $F_{1,21}$ = 20.49; p = 0.002; η^2 = 0.494; **Fig. 2B**). For HC, the β parameter decreased with eccentricity with a response bias toward unpleasantness in PV, while for DP, the β parameter increased with eccentricity with a response bias toward unpleasantness in CV. Interestingly, this effect of eccentricity vanished in DP as anxiety increased (STAI-B: β-coefficient = -0.88; t = -3.00; p = 0.020; η^2 = 0.563). The quartic contrast was not significant ($F_{1,21}$ = 0.71; p = 0.411; η^2 = 0.494). In brief, the SDT showed that DP were more able to distinguish unpleasant pictures from neutral ones with a response bias toward unpleasant pictures in CV, whereas HC presented a similar bias in PV.

Autonomic data

The contrast analysis revealed eccentricity effects depending on the group on autonomic data. The effects of eccentricity, were opposite in HC and DP for SCR amplitude (C2: $F_{1,21}$ = 8.33; p = 0.009; η^2 = 0.284; **Fig. 3A**), cardiac deceleration (C4: $F_{1,21}$ = 9.99; p = 0.005; η^2 = 0.322; **Fig. 3C**) and cardiac acceleration (C4: $F_{1,21}$ = 11.31; p = 0.003; η^2 = 0.350;

Fig. 3D). For HC, greater SCRs and cardiac deceleration, and lower cardiac acceleration, were observed in PV, while for DP this pattern was observed in CV. The effect of eccentricity on the SCR was not modulated by any covariable in DP (all ps > 0.14) nor in HC (all ps > 0.31).

In HC, the effect of eccentricity on cardiac variations was not modulated by state or trait-anxiety (STAI-A: p = 0.64; STAI-B: p = 0.96), while in DP greater anxiety decreased the effect of eccentricity on deceleration (STAI-B: β-coefficient = -6.13; t = -2.74; p = 0.029; η^2 = 0.518) and increased it on acceleration (STAI-B: β-coefficient = -6.96; t = -3.27; p = 0.014; η^2 = 0.604).

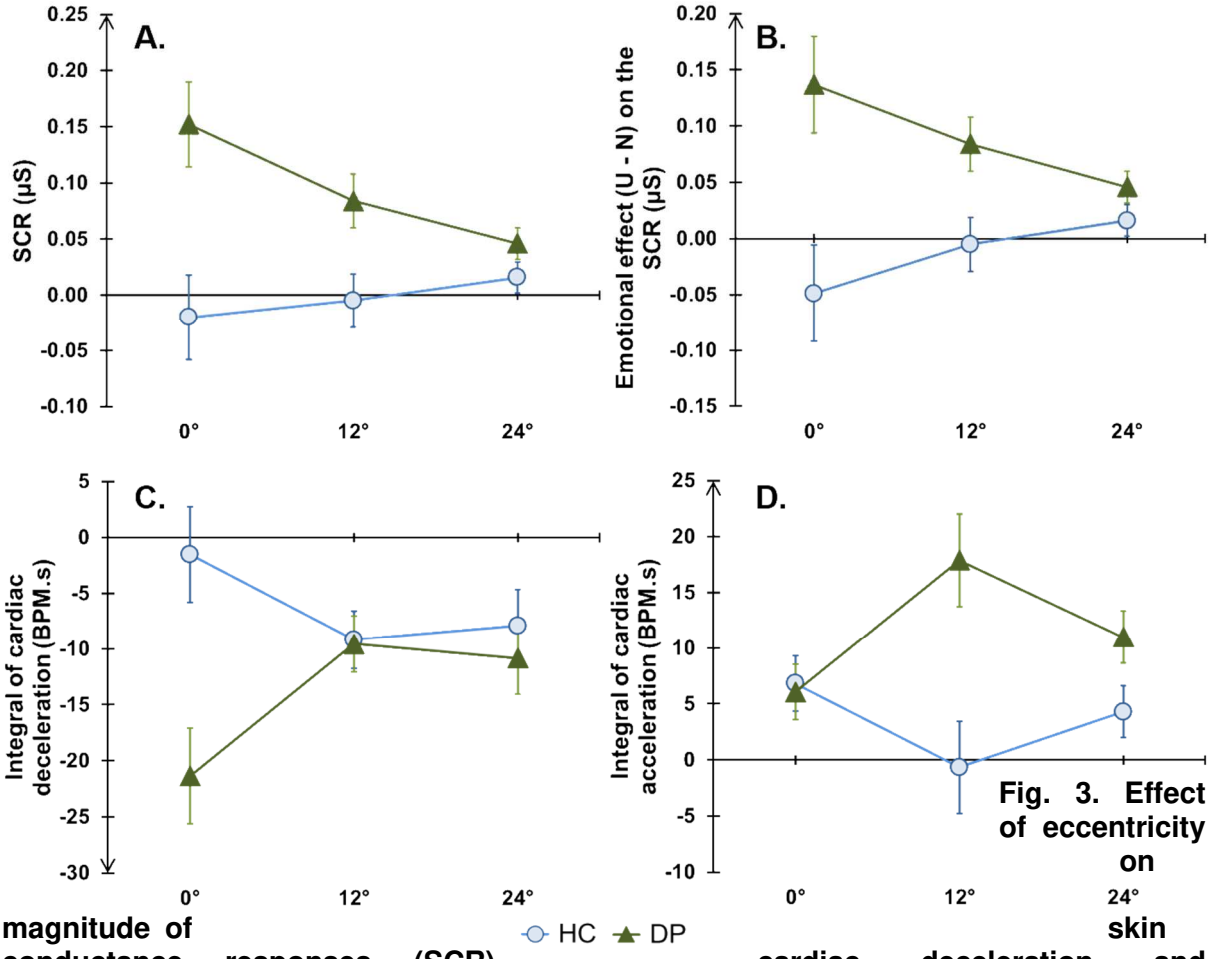

Fig. 3. Effect of eccentricity on magnitude of skin conductance responses (SCR), cardiac deceleration and cardiac acceleration. Data are estimated marginal means of magnitude of SCR (µS, panel A), effect of emotion (U - N) on magnitude of SCR (µS, B), integral of cardiac deceleration (BPM.s, C) and integral of cardiac acceleration (BPM.s, D) with standard errors, according to position of stimuli (central: 0°; near periphery: 12° and far periphery: 24°), for Healthy Controls (HC, blue lines) and Depressed Patients (DP, green).

For SCRs, the effect of emotion dependent on eccentricity was opposite in HC and DP (C4: $F_{1,21}$ = 6.19; p = 0.021; η^2 = 0.228; **Fig. 3B**). DP showed greater SCRs for unpleasant pictures than for neutral ones in CV and this difference tended to diminish in PV (p = 0.089; η^2 = 0.366). HC displayed an opposite pattern but the evolution with eccentricity was not significant (p = 0.825; η^2 = 0.004). Interestingly, the more anxious DP were, the more the SCRs to unpleasant pictures differed between CV and PV presentation (CV > PV, STAI-B: β-coefficient = 0.065; p = 0.002; η^2 = 0.751).

In summary, autonomic responses again showed an opposite pattern between HC and DP. Unlike HC, DP showed greater SCRs and cardiac deceleration in CV and greater cardiac acceleration in near PV. Interestingly, for unpleasant pictures, DP showed greater SCRs in CV. Finally, trait-anxiety modulated SCRs and both cardiac deceleration and acceleration in DP.

Brain Data

Separate sPCA yielded 9 SFs that described 66.2% of the spatial variance with the HC data set and 8 SFs that described 65.2% of the spatial variance with the DP data. Only one SF (SF1) resulting from both separate sPCA was common to HC and DP (rc = 0.88). The combined sPCA yielded 9 SFs that described 62.3% of the spatial variance (**Fig. 4A**) and the temporal PCA applied to SF1 yielded 4 TFs that described 71.2% of the SF1 temporal variance (**Fig. 4B**).

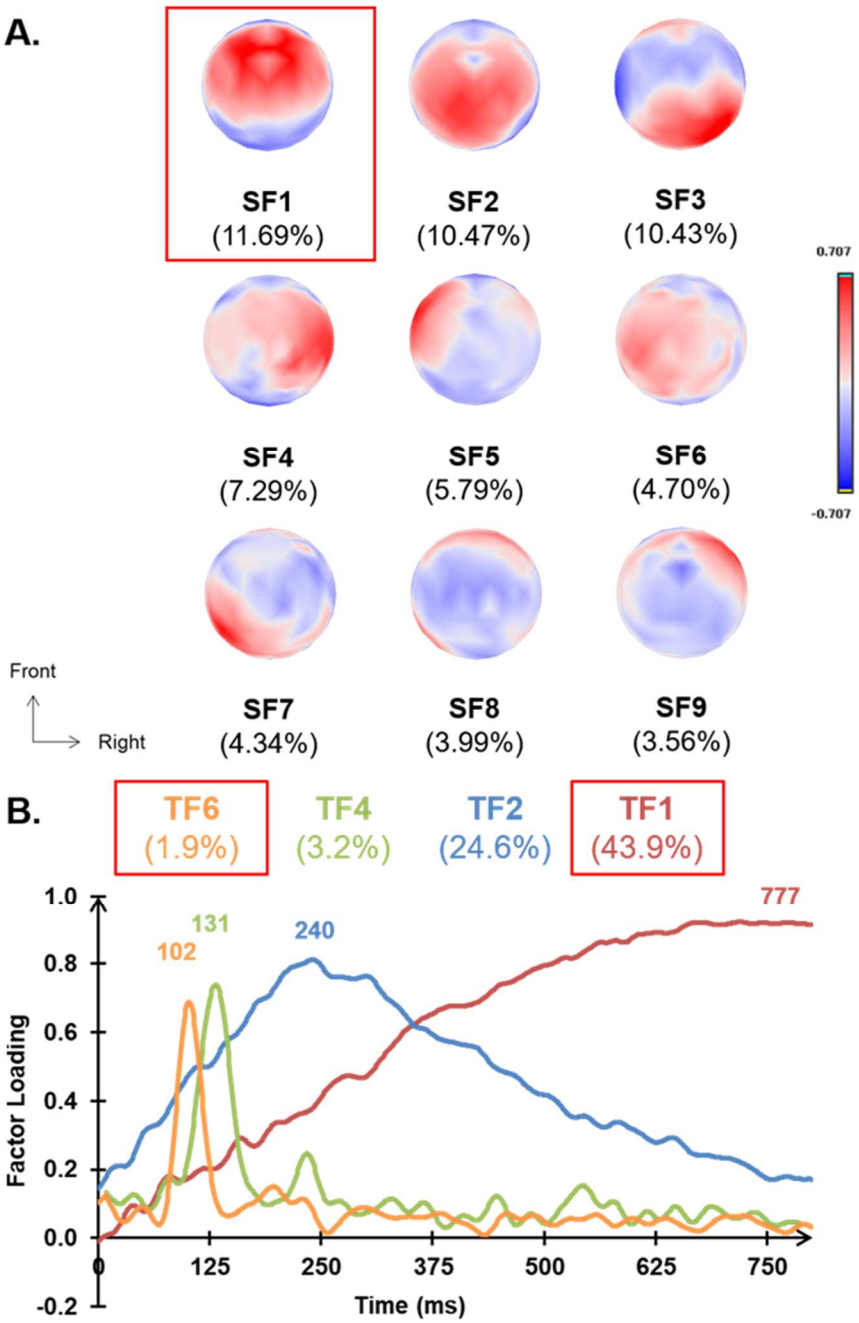

Fig. 4. Topographic map of factor loading for selected spatial factors (SF) from combined spatial principal component analysis (sPCA) and temporal principal component analysis (tPCA) solution for SF1 component. (A) Superior view of topographic map of factor loading for selected SF with percentage of variance accounted for by each SF. **(B)** Time at peak and percentage of variance accounted for by each temporal factor for SF1 component.

For the sake of clarity, we present only SFxTF combinations with significant group effects dependent on emotion or eccentricity, or which predicted the observed effects at behavioural and autonomic levels.

Centro-frontal component at 102 ms

Emotion-dependent eccentricity effects in HC and DP were opposite on SF1xTF6 component (C2: $F_{1,21}$ = 4.72; p = 0.041; η^2 = 0.184; **Fig. 5A**). For unpleasant but not neutral pictures, DP but not HC showed greater SF1xTF6 activity for CV than for PV (C2: p = 0.004; η^2 = 0.707). For unpleasant pictures, the more anxious DP were, the greater was the difference in SF1xTF6 activity between CV and PV stimulation (STAI-B: β-coefficient = 0.13; p = 0.002; η^2 = 0.782). In addition, this eccentricity effect on unpleasant pictures was reduced by TCA (β-coefficient = -19.77; p = 0.005; η^2 = 0.706) and increased by antipsychotic medication (β-coefficient = 1.08; p = 0.008; η^2 = 0.657). Interestingly, in response to CV presentation, greater 102-ms centro-frontal activity predicted a lower sensibility to distinguish unpleasant from neutral pictures (R^2 = 0.14; β-coefficient = -3.92; t = -2.10; p = 0.041).

Centro-frontal component at 777 ms

In the same centro-frontal sites at 777-ms (SF1xTF1 component), the contrast analysis revealed an eccentricity effect depending on the emotion and the group (C2: $F_{1,21}$ = 5.51; p = 0.029; η^2 = 0.208; **Fig. 5B**). Compared to CV (0°), for HC, the reactivity on the 777-ms component (SF1xTF1) was lower to unpleasant than neutral in near PV (12°), while for DP the reactivity to unpleasant was larger than neutral in near PV. In large PV (24°), the 777-ms centro-frontal reactivity in DP was closer to that of HC compared to CV (0°) (C2: $F_{1,21}$ = 1.25; p = 0.276; η^2 = 0.056).

In DP, the eccentricity effect depending on emotion was observed only with high trait-anxiety scores (STAI-B: β-coefficient = -0.108; p = 0.038; η^2 = 0.482). In response to PV stimulation, greater 777-ms centro-frontal activity predicted a greater cardiac acceleration (R^2 = 0.38; β-coefficient = 19.18; t = 4.18; p < 0.001).

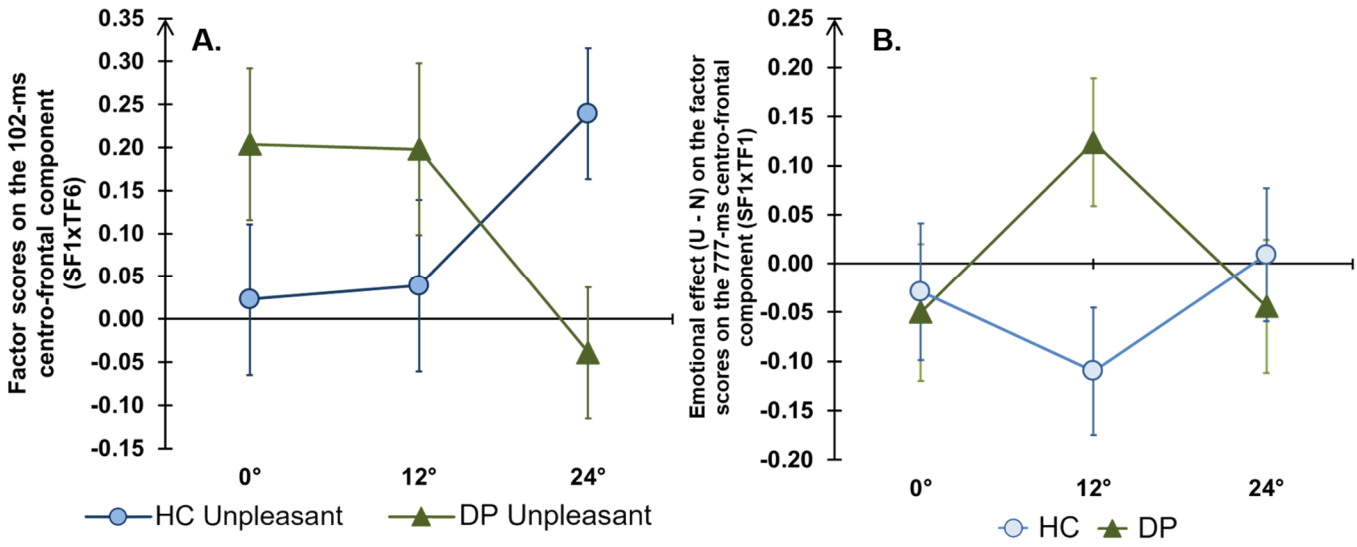

Fig. 5. Eccentricity effect on 102 ms centro-frontal component (SF1xTF6) and for 777 ms centro-frontal component (SF1xTF1). (A) Data are estimated marginal means of 102 ms centro-frontal (SF1xTF6) factor scores for unpleasant pictures and **(B)** emotional effect (U – N) on 777 ms centro-frontal (SF1xTF1) factor scores with standard errors, according to position of stimuli (central: 0°; near periphery: 12° and far periphery: 24°), for healthy controls (HC, blue lines) and depressed patients (DP, green).

Discussion

This study is the first to determine the reactivity of MDD patients to emotional scenes presented at several positions of the visual space. To this end, we used an integrated approach combining behavioural, autonomic and brain analyses. In support of our hypotheses, we found consistently opposite patterns of reactivity in HC and DP. At the behavioural level, HC manifested a response bias toward unpleasant pictures in PV, whereas DP presented similar bias in CV. At the autonomic level, greater SCRs and cardiac deceleration were observed in PV for HC and in CV for DP. At the cerebral level, DP showed an early centro-frontal reactivity to unpleasant which was larger for CV presentation, followed by a late centro-frontal reactivity to unpleasant which was larger for PV presentation. In addition, the larger was the early component, the lower was the sensibility to distinguish unpleasant from neutral pictures for CV presentation. Otherwise, the larger late centro-frontal reactivity observed in DP predicted a greater cardiac acceleration for near PV

presentation. Finally, this multilevel reactivity appeared to be modulated by trait-anxiety. Overall, these results provide evidence that depression tends to focus attentional resources on CV, especially to process unpleasant information.

Integrated Reactivity in Depression

HC and DP showed opposite patterns of reactivity. At the behavioural level, the greater sensitivity with a bias toward unpleasantness in PV observed in HC suggests that PV is used as an alert system for detecting relevant information. In DP, such a system does not seem to be used since patients showed greater sensitivity with a bias toward unpleasantness in CV. At the autonomic level, greater SCRs and cardiac deceleration were observed in DP only in CV, which suggests that orientation and focalisation responses were limited to CV information. Furthermore, DP showed greater cardiac acceleration in response to PV stimulation, which could indicate that they reject such information (Bradley et al., 2001; Bradley, 2009). In addition, while SCRs did not differ with emotion in HC, they were larger for unpleasant pictures than for neutral ones in DP. These data support our hypothesis that DP are more focused and aroused by CV information, especially unpleasant information. In the literature comparing MDD patients and controls, some authors did not observe any difference (Jin et al., 2015), while others observed lower reactivity in patients (Mardaga & Hansenne, 2009). There is also some evidence of greater reactivity (Schneider et al., 2012). Our data provide support for the negative potentiation hypothesis (i.e., greater responses to unpleasant information, Wenzler et al., 2017) by showing its relevance for CV but not for PV.

When investigating event-related brain activity, we found that HC and DP showed an opposite pattern of early (102 ms) and late (777 ms) centro-frontal reactivity. Unlike HC, DP showed high early centro-frontal activity in response to unpleasant pictures presented in CV. In response to near PV stimulation, the late component was greater to unpleasant pictures in DP and to neutral pictures in HC. Moreover, the early centro-frontal activity predicted the ability to distinguish unpleasant pictures. An enhanced P200 to positive stimuli over centro-frontal regions about 160 ms after stimulus onset in MDD patients has already been

interpreted as impaired attention toward positive stimuli (Yang et al., 2011). Furthermore, a frontal P200 has been associated with early attention to sad but not happy expressions in dysphoric individuals (Buodo et al., 2015). The literature seems to show that depression modulates the perception of negative stimuli or bias towards interpreting neutral stimuli as unpleasant (Gollan et al., 2008). However, our contribution brings for the first time a new insight in such conception by distinguishing the way the unpleasant information is processed in CV and PV.

Concerning the late centro-frontal component, its larger reactivity to unpleasant for near PV was associated with a greater cardiac acceleration for these stimuli. As a hypothesis, we cannot exclude that the cardiac acceleration to unpleasant pictures presented in PV may indexes a sensory rejection of this information (Bradley, 2009; Graham & Clifton, 1966; J. I. Lacey & Lacey, 1974; P. R. D. Lacey, 1967). Such rejection would manifest itself by a late avoidance of such stimuli, involving the modulation of the late stages' reactivity at centro-frontal sites. It would therefore be interesting to develop protocols aimed at characterising the avoidance of such information occurring in PV. In this frame, it has been suggested (Shapiro & Lim, 1989) that the advantage of enhanced peripheral detection mechanisms (e.g. peripheral vision) is to optimise the detection of a potential threat and to be prepared to react. This alert system, making it possible to capture information potentially relevant for the well-being and preservation of the individual, would be deficient in depression.

Influence of Anxiety

The comorbidity between depression and anxiety (Zbozinek et al., 2012) makes it difficult to disentangle the influence of each of them on emotional reactivity. In this study, anxious trait (STAI-B) but not state (STAI-A) often potentiated the eccentricity effects observed in depressed patients. With CV stimulation, the more anxious the patients were, the greater were their SCRs and their early centro-frontal reactivity to unpleasant pictures, and the lower was their cardiac acceleration. The emotion-dependent eccentricity effect on

late centro-frontal activity was observed only when trait-anxiety was taken into account: the more anxious the patients were, the weaker was the eccentricity effect on the response bias and the lower was the difference in cardiac deceleration between CV and PV stimulation. According to the tripartite model, hyperarousal due to negative affects is common to both depressive and anxiety disorders, while hyperarousal due to positive affect is considered to be specific to anxiety (Clark & Watson, 1991). Our results seem to confirm the former hypothesis, with a greater arousal in response to unpleasant pictures in MDD patients potentiated by trait-anxiety. However, this was observed only in CV, which seems to indicate an attention narrowing toward unpleasant cues and pleads in favour of the Easterbrook effect in anxiety. Indeed, Easterbrook (1959) suggests that the emotion component of a task reduces the range of cue utilisation by excluding irrelevant ones in order to improve task performance. It has been proposed that, according to this hypothesis, the Easterbrook effect would be expressed in anxiety by a restriction of visual fields in anxiety (Granger, 1953), In this context, Dien (1999) showed, at behavioural level, that medium and high fearfulness participants, according to Fear Survey Schedule (FSS, Braun & Reynolds, 1969) were slower to peripheral stimuli than low fearfulness participants when judging whether a moving number is either odd/even or moving upwards/downwards which has been interpreted as an Easterbrook effect. However, in this study, the stimuli used had no emotional content and the depressed state of the participants was not measured.

Nevertheless, the Easterbrook's hypothesis is not consistent with the weaker eccentricity effect observed on the response bias parameter and cardiac deceleration as anxiety increases. The low skin conductance and the early centro-frontal reactivity in peripheral vision compared to central vision could rather be due to depressive symptoms. Indeed, the processes requiring the involvement of significant cognitive resources, notably attentional and executive resources are deficient in depression (Thomas et al., 1998). Depression is also characterized by general exhaustion accompanied by significant psychomotor retardation (Lemelin & Baruch, 1998). This symptom combination influences the performance of patients in complex tasks (Fossati et al., 2002) and, when several

positions in the visual field are involved, can be expressed by less visual exploration, as it has already been shown in patients with depressive disorder who showed fewer saccades and longer mean fixation than controls (Li et al., 2016). The fact that the advantage of central vision for the responses bias and the orienting response disappear with anxiety can be explained by the hypervigilance which characterises this disorder (Heller et al., 1997; MacLeod & Mathews, 2012) and has been associated with an increase of the attentional capture toward peripheral information that is not obviously threatening (Mathews, 1990; Shapiro & Lim, 1989) or even toward irrelevant threat and non-threat stimuli (Gerdes et al., 2008; Wieser et al., 2009). This is consistent with the chronic arousal observed in generalised anxiety and the excessive propensity to control external stimuli in anxiety disorders (Pruneti et al., 2016). Indeed, it has been suggested (Shapiro & Lim, 1989) that the advantage of enhanced peripheral detection mechanisms (e.g. peripheral vision) is to optimise the detection of a potential threat and to be prepared to react. This hypothesis is supported by Beck and Emery (1985) who proposed that anxiety leads to a state of hypervigilance in which the individual constantly analyses his environment looking for signs of a danger, or visual information that could evoke a threat. This hypervigilance could lead to misinterpret ambiguous situations or information (Beck et al., 2005) which would impact the response bias during a categorisation task. Visual attention expansion and attention narrowing are however not contradictory. An initial expansion of the visual space monitored would allow to detect the arousal cue, then, the element which is felt as arousing would benefit attentional selection after this element is perceived, excluding the irrelevant cues. In this context, it has been shown that emotional stimuli occurring in PV are capable of interfering with the processing of information appearing in CV (D'Hondt et al., 2013); interestingly, this effect is increased with state anxiety (D'Hondt et al., 2014; Richards et al., 2014).

Finally, the eccentricity effects on sensitivity and on SCRs were not modulated by state or trait-anxiety in DP. This suggests that the greater arousal and attentional focus on

negative affect and the greater ability to distinguish unpleasant from neutral information in CV are specific to depressive patients.

Limitations and Conclusion

Besides the strict matching of participants, this study has several strengths: a rigorous selection of emotional stimuli and the systematic consideration of medication and state and trait-anxiety as covariates. Nevertheless, it has some limitations. First, the absence of pleasant stimuli precludes any conclusion about positive attenuation or, to a lesser extent, the emotional context insensitivity hypotheses, often proposed to explain depression. However, this allowed us to study a larger portion of the visual field without tiring patients by subjecting them to a long experimental session. Second, we cannot rule out the influence of other factors such as alexithymia, which is related to anxiety and depression (Berthoz et al., 1999) and has been shown to modulate autonomic reactivity (Martínez-Velázquez et al., 2017).

In conclusion, we used an integrated approach to study a psychiatric disorder that manifest itself at multiple levels. We found that, unlike HC, DP are more oriented and aroused by information presented in CV than in PV, especially unpleasant information. Thus, the data support the negative potentiation hypothesis, as far as the visual event occurs in CV. Consequently, attention and eye movement training could be used to enlarge the attentional span of depressed patients. This would improve their exploration of the environment and promote their ability to cope with negative events and their well-being.

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Declaration of interest

None.