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Original Article

Frequency-specific gaze modulation of emotional face processing in the human amygdala

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Determining the social significance of emotional face expression is of major importance for adaptive behavior, and gaze direction provides critical information in this process. The amygdala is implicated in both emotion and gaze processing, but how and when it integrates expression and gaze cues remains unresolved. We tackled this question using intracranial electroencephalography in epileptic patients to assess both amygdala ($n = 12$) and orbitofrontal cortex (OFC; $n = 11$) time-frequency evoked responses to faces with different emotional expressions and different gaze directions. As predicted, self-relevant threat signals (averted fearful and directed angry faces) elicited stronger amygdala activity than self-irrelevant threat (directed fearful and averted angry faces). Fear effects started at early latencies in both amygdala and OFC (~110 and 160 ms, respectively), while gaze direction effects and their interaction with emotion occurred at later latencies. Critically, the amygdala showed differential gamma band increases to fearful averted gaze (starting ~550 ms) and to angry directed gaze (~470 ms). Moreover, when comparing the 2 self-relevant threat conditions among them, we found higher gamma amygdala activity for averted fearful faces and higher beta OFC activity for angry directed faces. Together, these results reveal for the first time frequency-specific effects of emotion and gaze on amygdala and OFC neural activity.

Key words: amygdala; emotion; gaze; iEEG; time-frequency.

Introduction

While facial expressions play a key role in social communication across primate species, eye gaze direction provides important information about their behavioral significance (Itier and Batty 2009). Moreover, although emotional expressions such as fear or anger both signal a potential threat, appraisal theories of emotion (Sander et al. 2005) predict that their self-relevance may differ depending on gaze direction. For instance, fearful expression with averted gaze may inform about a nearby threat, whereas direct gaze in an angry face informs about a threat to oneself (Stussi et al. 2015). Accordingly, behavioral studies indicate that these 2 face conditions are rated as more intense and recognized more quickly than their counterparts (directed fearful and averted angry faces;(Adams and Kleck 2005). In addition, abnormal behavioral responses to emotional face and gaze cues are frequent hallmarks of social processing deficits in clinical populations (Itier and Batty 2009), with poor discrimination of gaze direction in individuals with autism spectrum disorder (Nomi and Uddin 2015) or schizophrenia (Grove et al. 2021), and greater attentional capture by self-threatening faces in highly anxious individuals (Fox et al. 2007).

At the brain level, converging evidence from brain-damaged patients and neuroimaging studies indicates that the amygdala is critically involved in the perception of both emotional face expression (Vuilleumier 2005; Itier and Batty 2009) and gaze direction (Kawashima et al. 1999; Cristinzio et al. 2010). However, the exact influence of gaze direction on amygdala response to emotion still remains debated. In line with behavioral results indicating an enhanced arousal response to self-relevant threat, 2 functional magnetic resonance imaging (fMRI) studies found increased amygdala response to averted fearful and directed angry expressions (relative to directed fearful and averted angry faces) in human (N'Diaye et al. 2009; Sato et al. 2010). Another fMRI study with non-human primate found similar findings (Hoffman et al. 2007), suggesting that amygdala binds emotional and gaze direction in a similar fashion in primates. However, another report in humans described a different pattern of amygdala activation (Adams et al. 2003), with increased amygdala response to directed fearful and averted angry expressions (relative to averted fearful and directed angry faces). Therefore, it remains unresolved whether emotional appraisal processes in amygdala integrate expression and gaze cues in an interactive manner, and the slow temporal resolution of fMRI does not allow determining whether such cues are encoded by amygdala neurons in similar or successive time windows.

Several studies have employed time-resolved non-invasive neuroimaging techniques to investigate the temporal dynamics of social face processing, but results about gaze and emotion integration still remain inconclusive. An early electroencephalography (EEG) study found increased responses to angry faces

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(compared to neutral) starting around 140 ms, independently of gaze direction, but gaze-related effects starting around 170 ms without interaction with emotional expression (Conty et al. 2012). In contrast, another study using magnetoencephalogram (MEG) found interactive effects of gaze and emotion around 190 ms, with stronger response to directed fearful face relative to averted and neutral faces (Dumas et al. 2013). Several differences in methodological aspects might explain such discrepancies. First, the former study used angry faces and the latter fearful faces as emotional stimuli; second, stimuli in the former study presented faces with the full upper part of the body but the latter only faces. Finally, different tasks were employed, requiring either explicit social processing in the former case (to judge if the observed nonverbal behavior was directed at them), or implicit processing in the latter case (to detect a dot simultaneously shown on the screen). In any case, these studies do not allow pinpointing the exact role of amygdala sources in these differential responses to emotion and gaze. Moreover, other brain regions are responsive to social and affective signals, including areas in OFC and medial prefrontal cortex (MPFC) implicated in theory of mind (Itier and Batty 2009).

Invasive methods with intracranial electroencephalography (iEEG) are scarce but offer unique opportunities to record local neural activity with high temporal precision. Previous iEEG studies in epileptic patients have investigated amygdala response to emotional stimuli such as faces, pictures, or sounds (Guillory and Bujarski 2014), with differential effects of facial expressions starting as early as 80 ms post-onset and lasting for several hundreds of milliseconds (Méndez-Bértolo et al. 2016), predominantly in the gamma band (Oya et al. 2002; Zheng et al. 2017; Guex et al. 2020). Other iEEG studies examined the temporal dynamics of gaze processing, without any emotional dimension, but produced mixed results concerning differences between averted and directed gaze, note here also that these studies sampled different brain regions. While some studies did not find any significant effect of gaze on amygdala response (Sato et al. 2011; Mormann et al. 2015), others found gaze direction effects around 200 ms in the fusiform gyrus (Pourtois and Vuilleumier 2010), insula and superior temporal sulcus (Caruana et al. 2014). Other iEEG studies investigating both emotion and gaze direction found inconsistent evidence for an interaction between both factors, starting around 130 ms with broadband activity (Huijgen et al. 2014). Notably, however, none of these studies were able to identify differential effects of gaze direction according to specific emotional expression. Therefore, although these results point to distinct response patterns for gaze and emotion information across multiple brain region, the neural modulations and latencies of converging gaze and emotion signals in amygdala, suggested by fMRI studies and associated with self-relevant threat perception (Adams et al. 2003; N'Diaye et al. 2009), still remain unresolved.

To address these issues, we recorded iEEG from human amygdala ($n = 12$) and orbitofrontal cortex ($n = 11$), 2 regions involved in the processing of social information and gaze processing (Hadders-Algra 2022) that were simultaneously recorded in our patient population (for clinical reasons). Using iEEG during a task with dynamic face stimuli similar to previous work (N'Diaye et al. 2009), we performed for the first time a detailed analysis of spectral activity in response to both emotion expression and gaze direction during face processing. By manipulating these social cues in the same stimuli, we set out to directly test for any interaction effects related to perceived self-relevance and to determine their latencies in the amygdala and OFC. In doing so, we were able to address the shortcomings of previous studies thanks to higher spatial resolution and temporal resolution than noninvasive methods with EEG or fMRI, respectively, as well as larger patient sample than previous iEEG studies on face or gaze perception. Following on the results of behavioral, iEEG, and fMRI studies described above, we hypothesized fearful faces would elicit stronger amygdala response in the gamma range compared to happy and angry faces (Oya et al. 2002; Zheng et al. 2017; Guex et al. 2020), and moreover this effect would be enhanced when gaze is averted due to the higher self-relevance of threat signals (N'Diaye et al. 2009). Conversely, we also hypothesized that gaze direction effect would vary depending on emotional expression, with smaller amygdala activation in response to angry averted faces in comparison to directed.

Method

Participants

Nine epileptic patients (4 females) participated prior to brain surgery for pharmacologically intractable epilepsy (see Supplementary Table S1 for demographic information). All patients gave written informed consent and the procedure was approved by the ethical committee of the University Hospital of Geneva (Switzerland). The patients had normal or corrected-to-normal vision, and no history of head trauma or encephalitis (see Supplementary Table S1 for clinical details). Three patients had bilateral implants in the amygdala, 2 had in the left amygdala, and 4 in the right amygdala, resulting in a total of 12 amygdalae in final dataset. Four patients had bilateral implants in the OFC, 1 in the left OFC, and 2 in the right OFC, resulting in a total of 11 OFC in final dataset. Besides these regions included in our analysis, 3 amygdalae and 2 OFC sites were excluded due to excessive noise in the signal.

Stimuli

Face stimuli consisted of dynamic animated faces created with FaceGen Modeler 2.0 (Singular Inversion Inc. http://www.FaceGen.com; (Roesch et al. 2011) and were previously validated by behavioral and fMRI studies on the neural correlates of emotional gaze processing (N'Diaye et al. 2009; Cristinzio et al. 2010). This database was chosen over classic picture of static faces as it provided highly controlled physical attributes through computerized parameters, including specific action units, precise gaze motion cues, and comparable color and luminance aspects. Further, these dynamic stimuli resemble more to real life situations than static pictures with different direction of gaze manipulated by an abrupt sequence of directed vs. averted gaze (see for more details (Roesch et al. 2011). For the current study we selected 96 stimuli from this database, 16 for each experimental condition (half female and half male). For averted gaze trials, the face started with a central gaze that then shifted to an averted direction (half right and half left); whereas the opposite sequence was used for the directed gaze trials where the face started with a deviated gaze that then shifted to a straight (eye contact) position.

Experimental procedure

To allow comparison with fMRI work on emotional gaze integration in the human amygdala, we adapted a previously validated task (N'Diaye et al. 2009; Cristinzio et al. 2010), with fearful, angry, and happy faces presented with either directed or averted gaze. After an initial cross fixation (1,000 ms plus jitter of 0–200 ms to make target onset unpredictable), a neutral face was shown for a time-period varying from 800 to 1,200 ms (to avoid

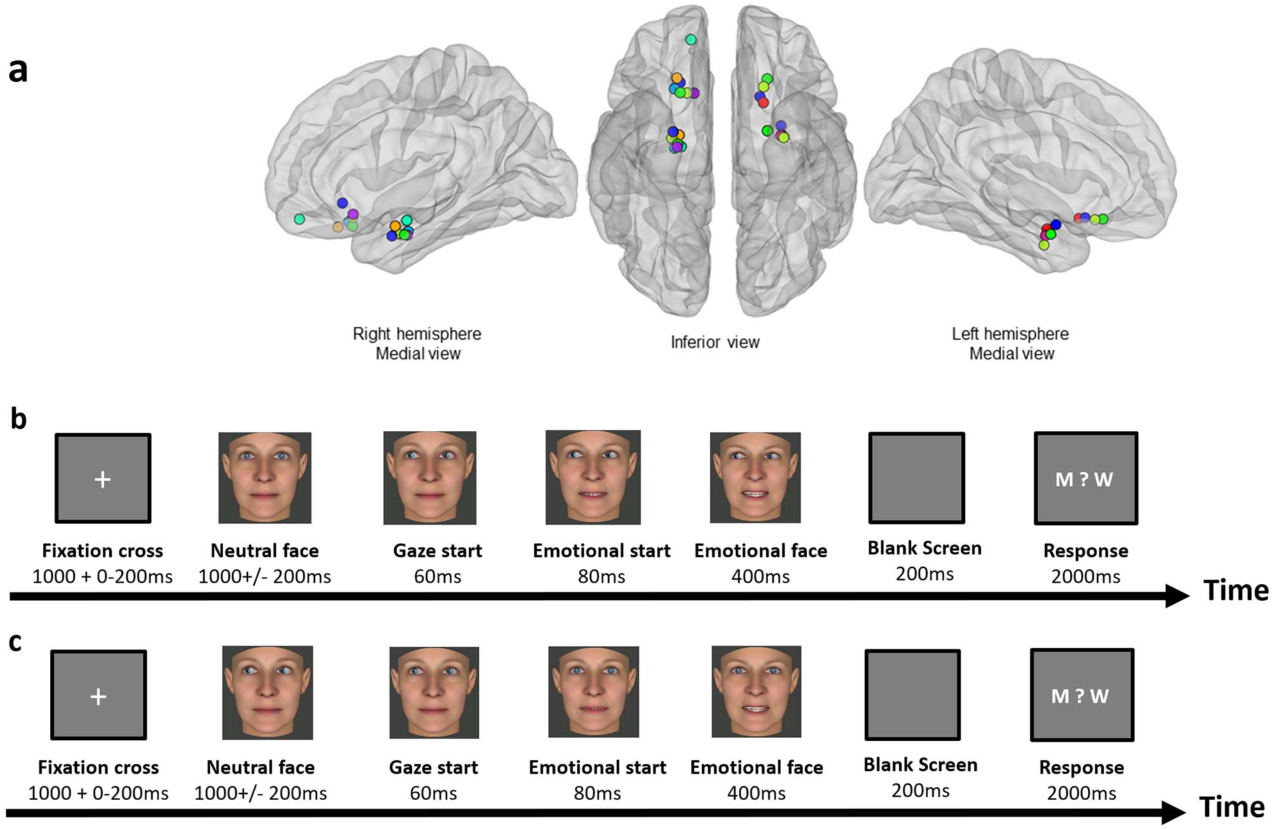

Fig. 1. Recording sites and face stimuli. a) Electrode localization is shown for amygdala and OFC contacts used in our study. All electrodes are plotted on the average brain template, color-coded by patient; left inset: right hemisphere; middle: Inferior; right inset: left hemisphere. b, c) Visual stimuli and trial structure in the gender discrimination task. b) Example of a stimulus sequence in averted anger condition. After an initial fixation cross (1,000 + 0–200 ms), a neutral face appeared (for 1,000 ± 200 ms), then gaze direction smoothly shifted during 60 ms, followed by a dynamic emotional expression unfolding during 80 ms. This final face target was displayed for 400 ms. c) Example of a trial in directed anger condition (where gaze shifted in opposite direction). All iEEG analyses focused a 1 s time-window starting from the emotional expression onset, allowing us to compare the same emotions but preceded by different gaze shifts and thus associated with different degrees of self-relevance.

anticipation of gaze movement onset), followed by a progressive change in gaze during 60 ms and then a progressive display of emotional expression during 80 ms, with the final emotional face image remaining visible for 400 ms. Next, the face was replaced by a blank screen during 200 ms and then a response screen indicating "M or F" (i.e. male or female) during 2,000 ms; see Fig. 1b and c for examples of trials with averted and directed gaze respectively. The experiment was divided into 8 block with 48 trials each, where experimental conditions were equally counter-balanced across conditions, A brief break was proposed between blocks. A total of 64 trials per condition was presented to each patient. Please note that this stimulus presentation procedure is similar to the continuous-stimulation paradigm used in previous studies (Jacques and Rossion 2006), where event related potential (ERP) to a face image are recorded following another face image rather than a blank-screen baseline, allowing a purer assessment of process-specific responses while removing non-specific visual onset effects. In our experiment, patients had to report the face gender after stimulus offset by pressing on corresponding button with their right hand, such that both emotion and gaze were task-irrelevant. response time (RT) were recorded from the onset of the response screen.

Data acquisition

iEEG data were recorded on a Micromed System Plus (Micromed, Italy) with a sampling rate of 2,048 Hz and an online high-pass filter of 0.02 Hz. Stainless electrode arrays consisted of 8 contacts for all patients, except 1, whose amygdalae were implanted with electrodes containing 10 contacts (ADTech, electrode diameter: 3 mm, inter-contact spacing: 2 mm). Initial reference was set to Cz and data were re-referenced offline to the nearest white matter contact of the same electrode strip for further analysis to obtain a local signal; moreover, note here that iEEG signal is supposedly less sensitive to muscle artifact (Lachaux et al. 2003).

Signal preprocessing

Data preprocessing was performed with Fieldtrip (Oostenveld et al. 2011) in Matlab (Mathworks 2018). A low-pass non-causal Butterworth filter (200 Hz) and a notch filter (50, 100, 150 Hz) were first applied. Epochs from −2,000 to 2,000 ms were then segmented and baseline corrected relative to the 200 ms prior to stimulus-onset. We defined the stimulus-onset at the time when emotional expression started, allowing us to minimize non-specific (neutral) face-related responses, and analyzed the data until 1,000 ms post-stimulus onset to reduce response contamination in the signal. The signal was down-sampled to 512 Hz. Trial were visually inspected to remove epileptic spikes or excessive noise. Time-frequency data were obtained with Fieldtrip on each trials using a wavelet approach with multitapers (mtmconvol function) from 2 to 200 Hz, in steps of 2 Hz for low frequencies (3 to 30 Hz) and in steps of 10 Hz for gamma frequencies, a smoothing of 20 ms was applied. Then, to fully characterize spectral activity in both regions, this signal was divided into 5 frequency bands, from 4 to 8 Hz (theta), 8 to 12 Hz (alpha), 12 to 30 Hz (beta), 60 to 150 Hz (low gamma), 150 to 220 Hz (high gamma), as well as 60 to 220 (full gamma). Trials were averaged for each experimental condition and each electrode contact. There was no difference in the number of trials kept for analysis across conditions (see Supplementary Table S3 for details) and the very same trials were used for all contacts in one given patient. Contacts showing stimulus-driven response during visual inspection of grand averages (all conditions collapsed) were selected for further analysis (1–4 per electrode; see Supplementary Table S1 for details). Oscillatory activity in the different frequency bands were averaged across selected contacts within each region for each experimental condition.

Statistical analyses

To test for any effect of emotion or gaze direction, or interaction between both factors, we submitted the time–frequency from each time-point to statistical tests with generalized linear mix model (GLMM; Matlab function fitglme) and corrected for multiple comparisons with permutation test (1,000×) over the time-window of interest (from 0 to 1,000 ms). Please note that all analysis with the fitglme function produce a *T*-value as statistical output for all comparisons, including interaction terms. Main effects of emotion and gaze were obtained by pooling conditions. Reported *T* and *P* values correspond to the averaged value over significant clusters. Beside a classic cluster-threshold of $P < 0.05$, we also applied more conservative thresholds of 0.01 and 0.001 as reported in the main text and in the supplementary table (Supplementary Table S2). Significant clusters were defined by temporal adjacency of time-points with significant effects. Only *P* values with a minimum of 50 consecutive milliseconds under the alpha threshold of 0.05 were considered. As our permutation approach required applying a high number of statistical tests in different frequency ranges, we also corrected for multiple comparison with a local false discovery rate (Benjamini and Heller 2007) taking into account all statistical test producing a positive results (*T* values) in amygdala and OFC, in both the gamma and beta ranges (the 2 frequencies showing significant effects here). This procedure defined a *T* threshold of 1.82, meaning that all *T* values below this threshold were uncorrected and therefore not reported. We also present scatterplots depicting individual average amplitudes over significant time-windows to support our statistical results, considering the first window of significant differences when multiple were found. Behavioral data were submitted to GLMM following the same statistical analysis pipeline than the time–frequency data.

Supplementary information

Additional results on different frequency bands (theta, alpha, beta, low gamma, high gamma, and full gamma) are provided as figures (Supplementary Figs. S1–S10) and table (Supplementary Table S2) in supplementary material, with corresponding statistical tests. As only few results were observed in theta and alpha bands, with shorter and later clusters compared to results in beta and gamma bands, we report these results only in the table and describe only the beta and gamma results in the main text. Supplementary Table S3 details the amount of trial available for each experimental condition (no differences were observed across conditions, all $P > 0.05$).

Anatomical localization

The placement of iEEG electrodes was determined solely based on clinical considerations, without reference to this study. The localization and display of iEEG electrodes was performed using iELVis (Groppe et al. 2017). For each participant, a postimplantation high-resolution computed tomography (CT) scan was coregistered with a preimplantation 3D T1 3 tesla MRI scan via a rigid transformation using NiftyReg (Ourselin et al. 2006). Electrodes were localized manually on the CT scan using BioImage Suite (Joshi et al. 2011). The preimplantation 3D T1 MRI scan was processed using FreeSurfer (Fischl 2012) to segment the white matter, deep gray matter structures, and cortex; reconstruct the pial surface; approximate the leptomeningeal surface (Schaer et al. 2008); and parcellate the neocortex according to gyral anatomy (Desikan et al. 2006). For a similar approach, see (Mégevand et al. 2020).

Results—Behavior

No differences in accuracy were observed between any of our stimulus conditions during the gender categorization task, with globally high discrimination performance in all patients (mean 85 ± 11%). In contrast, response times showed an interaction between emotion and gaze factors ($P = 0.021$, $t_9 = 2.29$), as well as a main effect of gaze ($P = 0.025$, $t_9 = 2.23$) but no main effect of emotion ($P = 0.18$, $t_9 = 1.32$). Responses were faster for faces with directed than averted eye gaze (respectively: 1,182 ± 319 ms; 1,244 ± 338 ms). Comparing single conditions, between each pair of emotion or gaze direction, we found faster response for angry faces with directed gaze relative to happy faces with directed gaze ($P = 0.025$, $t_9 = 2.23$; respectively: 1,128 ± 415 ms; 1,239 ± 273), but no other significant difference (all $P > 0.05$). Please note that these effects were observed even though participants were not asked to respond as fast as possible.

Results—iEEG

Gamma band in the amygdala

Separate main effects of emotion and gaze

In a full 3 (Emotion) × 2 (Gaze) analysis of variance (ANOVA) on gamma band data, we found a significant main effect of Emotion from 410 to 460 ms when discarding the Gaze factor ($P = 0.046$, $t_{11} = -2.14$). As expected, this reflected an increase of amygdala activity to negative valence stimuli, fearful and angry faces, in comparison to happy. However, different modulation patterns arose at different latencies. In accord with previous iEEG research (Oya et al. 2002; Méndez-Bértolo et al. 2016; Zheng et al. 2017; Guex et al. 2020), an early and sustained response to fearful faces was observed in comparison to happy from 110 to 160 ms ($P = 0.006$, $t_{11} = -3.34$) and from 300 to 1,000 ms ($P = 0.005$, $t_{11} = -3.29$; at cluster threshold $P < 0.01$ from 300 to 360, 440 to 510, and 550 to 930 ms; and at cluster threshold $P < 0.001$ from 510 to 550 m; Fig. 2a); while only later and transient increases were found for angry faces (compared to Happy) from 460 to 540 ms ($P = 0.017$, $t_{11} = -2.7$; Fig. 2a). In contrast, there was no main effect of gaze in the gamma band (all $P > 0.05$ uncorrected; Supplementary Fig. S1m). Overall, these data are also consistent with previous research (Sato et al. 2011; Mormann et al. 2015).

Interactive effects of emotion and gaze

We then tested for any interaction between emotion and gaze factors on gamma activity. The same 3 × 2 ANOVA revealed a significant effect from 340 to 570 ms ($P = 0.031$, $t_{11} = -2.34$;

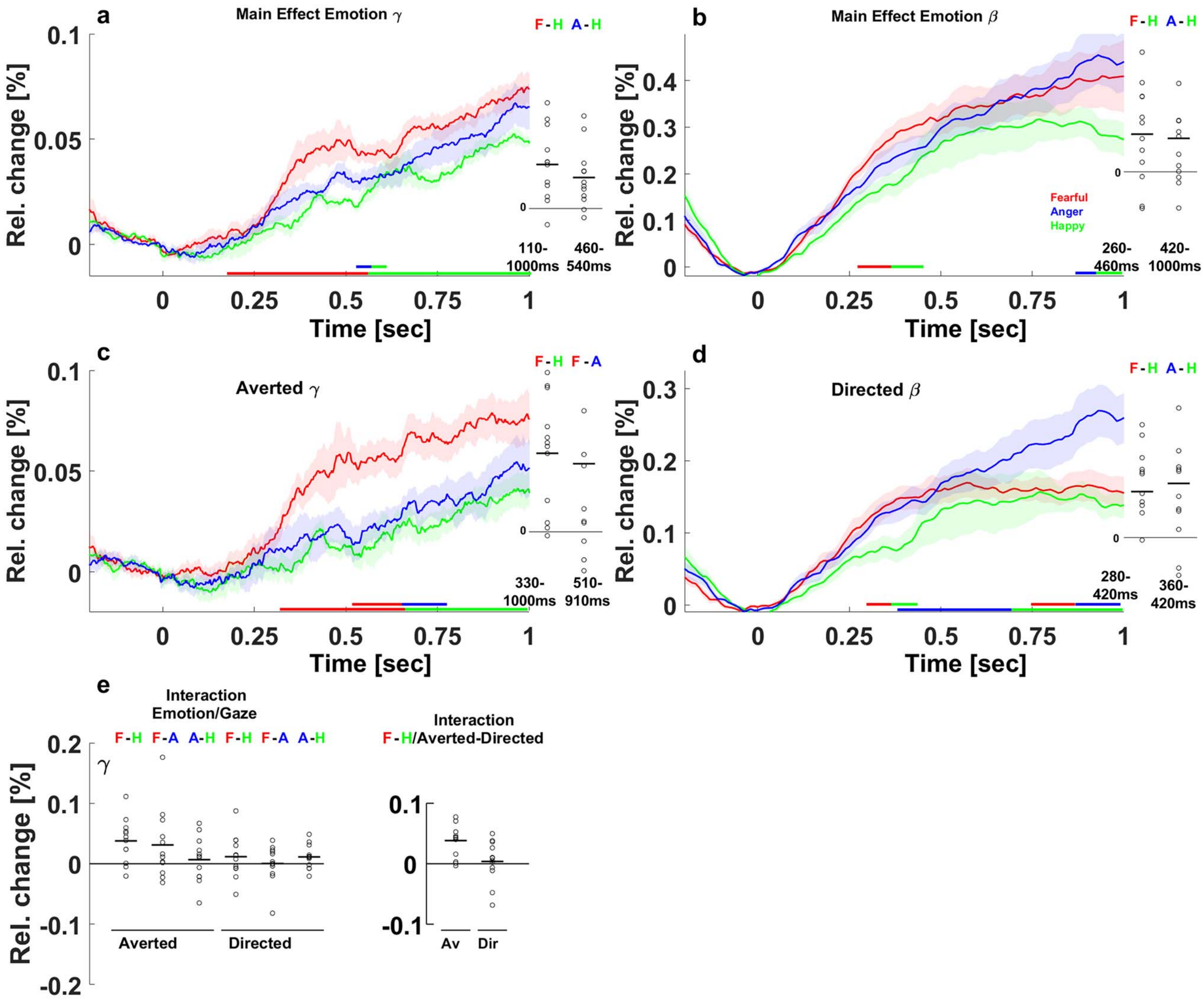

Fig. 2. Amygdala response to emotional expression and modulations by gaze direction in the gamma and beta bands. Main effect of emotion independently of gaze direction in gamma band (a), with scatterplots for individual amygdalae during time intervals exhibiting significant differences between fearful and happy (from 110 to 1,000 ms; left), and between angry and happy faces (from 460 to 540 ms; right). Emotional responses in the gamma band predominated for fearful expressions in the averted gaze condition (c), as illustrated by scatterplots of differences between fearful and happy faces (330–1,000 ms; left) and differences between fearful and angry faces (510–910 ms; right). Similar analyses are shown for the beta band (b), with scatterplots illustrating differences between fearful and happy faces (from 260 to 460 ms; left) and between angry and happy faces (from 420 to 1,000 ms; right). These emotional responses in the beta band predominated with direct gaze faces (d), as illustrated by scatterplots of differences between fearful and happy from 280 to 420 ms, and between angry and happy faces from 360 to 420 ms. e) Left inset. Interaction between gaze and emotion from 340 to 570 ms in the gamma band. Right inset. Interaction between gaze and emotion for fearful and happy faces from 310 to 1,000 ms in the gamma band. F stands for fearful, a for angry, H for happy faces, Av for averted, and Dir for directed. All waveforms are presented with standard deviation (shaded areas) and correspond to the relative percent signal change in comparison to baseline. Bi-colored lines show time-windows of significant differences between two conditions of corresponding colors. Please note that given preceding visual stimulation with a neutral face (similar across all conditions), baseline activity is non null.

Fig. 2e). However, such interaction could reflect either different responses to emotion depending on gaze orientation, or different responses to gaze direction depending on emotion expression, or both but at different points in this time window. Indeed, the latter time-dependent pattern was observed when running post hoc comparisons between pairs of condition for each factor separately.

First, post-hoc tests showed a significant effect of emotion across the whole time-window for faces with Averted gaze (1-way ANOVA with 3 emotions, 400–910 ms: $P = 0.011$, $t_{11} = -2.73$, with a peak from 500 to 570 ms at cluster threshold $P < 0.01$; Fig. 3d and Supplementary Fig. S1b–f–j for pairs of conditions). Further pairwise comparisons between emotion conditions showed more sustained activity in response to fearful than happy or angry faces with averted gaze (respectively, fearful–happy from 330 to 1,000 ms, $P = 0.003$, $t_{11} = -3.58$; at cluster threshold $P < 0.01$ from 330 to 430, 560 to 670, 840 to 1,000 ms; and at cluster threshold $P < 0.001$ from 510 to 560, 670 to 760, 780 to 840 ms; fearful–angry from 510 to 910 ms, $P = 0.012$, $t_{11} = -2.83$; and at cluster threshold $P < 0.01$ from 510 to 620 and 660 to 720 ms; Fig. 2c). There was no significant effect of emotion for any of the same comparisons for faces with directed gaze (all $P > 0.05$ uncorrected; Fig. 3d and Supplementary Fig. S1c-g-k).

Conversely, in a later time window, the emotion x gaze interaction was manifested through different responses to gaze shifts across emotions (460–570 ms: $P = 0.02$, $t_{11} = 2.42$; Fig. 4 and

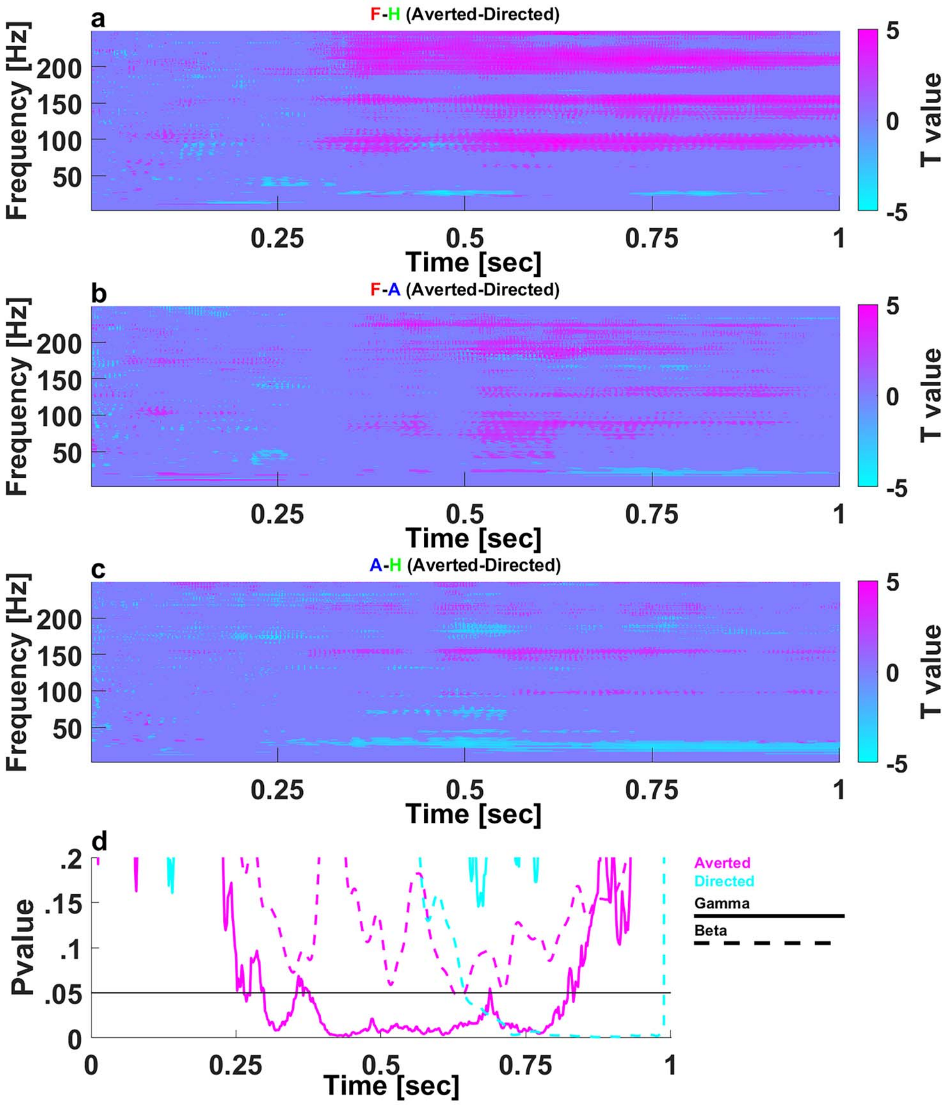

Fig. 3. Dissociation of amygdala response to emotional expression in the gamma band for averted gaze and in the beta bands for directed gaze. *T*-value (−5 to −2 and 2 to 5) maps across frequencies bands for the comparison fearful vs happy (a), fearful vs angry (b), and angry vs happy (c) in averted minus directed gaze conditions. d) *P*-value of 1-way ANOVA between emotions for averted and directed gaze, in the gamma and beta bands.

Supplementary Fig. S11). Indeed, when now comparing gaze effects in each emotion condition separately, we found not only stronger gamma responses to averted than direct gaze for fearful faces from 550 to 700 ms ($P = 0.034$, $t_{11} = 2.59$; Fig. 4a), but also the opposite pattern (stronger responses to directed than averted gaze) for angry faces from 470 to 570 ms ($P = 0.035$, $t_{11} = -2.48$), 590 to 650 ms ($P = 0.039$, $t_{11} = -2.49$), and 740 to 830 ms ($P = 0.041$, $t_{11} = -2.58$; Fig. 4b), as well as for happy faces from 460 to 510 ms ($P = 0.31$, $t_{11} = -2.42$; Fig. 4c). Interestingly, these gaze effects appeared stronger in high gamma for fearful faces (150–250 Hz; Supplementary Fig. S2d) and stronger in low gamma for angry faces (60–150 Hz; Supplementary Fig. S3d; Supplementary Table S2). Other gaze effects were seen in the beta band, but at later latencies (see below).

Finally, the emotion × gaze interaction was also confirmed by breaking down this effect into pairs of conditions, with a robust 2 × 2 interaction between fearful–happy expressions and averted-directed gaze conditions from 310 to 360 ms (at cluster threshold $P < 0.01$, $P = 0.009$, $t_{11} = -2.8$), and then from 450 to 560 ms ($P = 0.018$, $t_{11} = -2.47$), 700 to 830 ms ($P = 0.024$, $t_{11} = -2.35$), and 910 to 1,000 ms ($P = 0.027$, $t_{11} = -2.24$; Fig. 2e).

Taken together, these data highlight distinct patterns of gamma activity elicited by emotion expression and gaze direction in the amygdala, with the strongest and earliest effects observed for 2 self-relevant threat conditions, supporting an integration of expression and gaze information rather than purely parallel processing of these 2 facial signals.

Beta band in the amygdala

Effects of emotion

Applying the same statistical approach as above to the beta band, we found no interaction between gaze and emotion, and no main effect of emotion or gaze in a full 3 × 2 ANOVA. However, given our hypotheses and planned comparisons between trial types, we also compared pairs of emotion conditions (regardless of gaze) as done above for the gamma band. This revealed significant effects of emotion on beta band responses to the 2 negative stimuli (fear

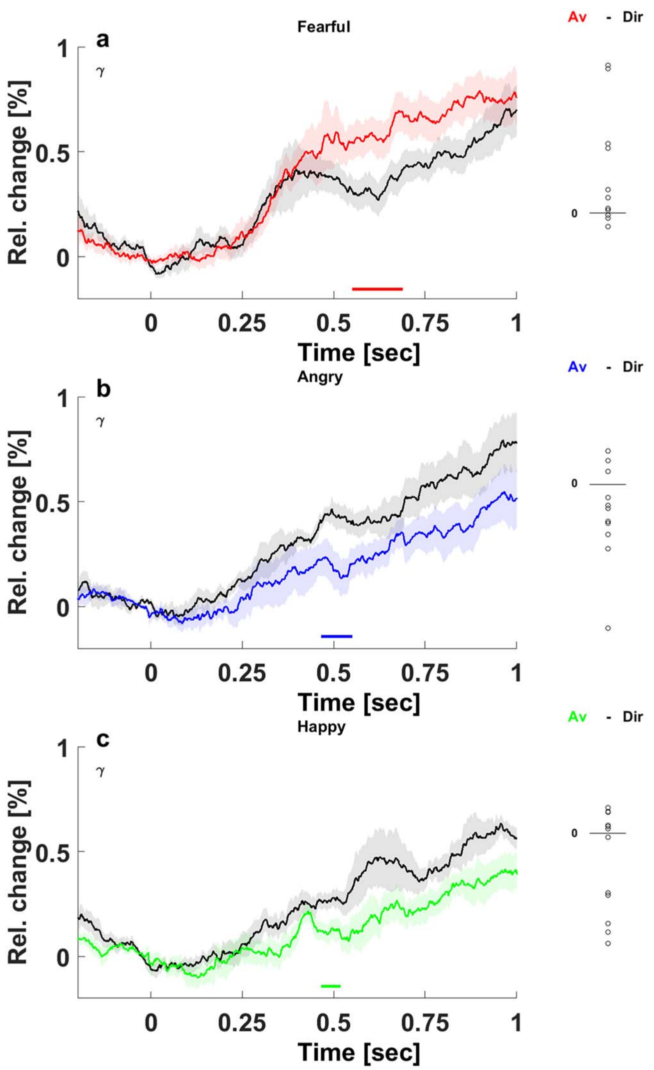

Fig. 4. Differential gaze effect depending on emotion expression in the gamma band. a) Stimulus-evoked activity to fearful face expressions with averted and directed gaze, with scatterplots of average responses from individual amygdalae in the time interval showing significant differences (550–700 ms). b) Same comparison for angry face expression, with scatterplots from individual amygdalae (470–570 ms), and c) for happy face expression, with scatterplots from individual amygdalae (460–510 ms). Same color code as Fig. 2.

and anger vs happy), but at different latencies. Specifically, there were significant increases for fearful vs happy faces from 260 to 460 ms (at cluster threshold $P < 0.01$, $P = 0.008$, $t_{11} = -3.51$) and for angry vs happy faces from 840 to 1,000 ms (at cluster threshold $P < 0.01$, $P = 0.001$, $t_{11} = -3.37$; Fig. 2b).

Effects of gaze on emotion responses

We then performed a 1-way ANOVA on emotion expression for each gaze direction separately which revealed that the main effect of emotion arose only in the direct gaze condition (from 830 to 1,000 ms, at cluster threshold $P < 0.01$, $P = 0.0096$, $t_{11} = 3.02$; Fig. 3d), while there was no emotion effect with Averted gaze in the beta band (all $P > 0.05$ uncorrected; Fig. 3d and Supplementary Fig. S4b–f–j). This emotion effect was driven by greater activation to angry faces with directed gaze, compared to happy faces with directed gaze (from 360 to 420 and 670 to 1,000 ms, $P = 0.013$, $t_{11} = -2.83$; at cluster threshold $P < 0.01$ from 360 to 420 ms; and at cluster threshold $P < 0.001$ from 920 to 1,000 ms), and compared to fearful faces with directed gaze (from 750 to 1,000 ms, $P = 0.009$, $t_{11} = 3.11$; at cluster threshold $P < 0.01$ from 830 to 1,000 ms; Figs. 2d and 3b, c). Fearful compared to happy faces with directed gaze produced only transient increases in beta activity in the initial response phase, from 280 to 420 ms ($P = 0.0174$, $t_{11} = -2.78$; at cluster threshold $P < 0.01$ from 350 to 420 ms; Fig. 2d).

Conversely, comparing the 2 gaze direction conditions (directed vs averted) showed a significant difference in the beta band only for angry faces, but at later latencies from 710 to 1,000 ms ($P = 0.014$, $t_{11} = -2.63$; at cluster threshold $P < 0.01$ from 880 to 1,000 ms; see Supplementary Table S2 and Supplementary Fig. S4h for this specific finding).

In sum, beta band activity was distinctively modulated by both negative expression and gaze direction, with the most prominent increases observed for angry faces with directed gaze.

Emotion and gaze effects in orbitofrontal cortex

We applied the same statistical approach to iEEG data from the OFC, as this region had electrode contacts in most patients and could thus serve as a control site. Unlike the amygdala, however, most effects in OFC arose in the beta band, with no (or limited) modulation of gamma activity.

The full 3 × 2 ANOVA on the beta band revealed no main effect of emotion or gaze, nor interaction, but specific comparisons between conditions of interest indicated consistent responses to emotion expression that were reliably modulated by gaze direction. Specifically, we observed a greater response to fearful than happy faces (pooling across gaze conditions) in the beta band, from 160 to 280 ms (at cluster threshold $P < 0.01$, $P = 0.009$, $t_{10} = -3.03$; Fig. 5a). However, this emotion effect was mainly driven by faces with averted gaze (Fig. 5c) and differed across latencies, with an early increase to fearful in comparison to happy expression from 110 to 490 ms ($P = 0.0089$, $t_{10} = -3.01$; at cluster threshold $P < 0.01$ from 110 to 250 ms), while the inverse pattern arose at later time points from 510 to 590 ms ($P = 0.015$, $t_{10} = 2.88$; Fig. 5c). Similar effects were found for Angry compared to happy faces with averted gaze, with differential activity from 150 to 400 ms ($P = 0.019$, $t_{10} = -2.64$), and then the reverse from 420 to 520 ms (at cluster threshold $P < 0.01$, $P = 0.007$, $t_{10} = 3.14$; Fig. 5c). There were also increases for fearful compared to angry faces in the averted gaze condition over several time points (from 180 to 280 ms, 310 to 350 ms, and 400 to 450 ms; $P = 0.034$, $t_{10} = -2.38$; Fig. 5c).

In the directed gaze condition, these emotion differences were not significant, except for a relatively sustained increase to angry compared to happy faces from 260 to 510 ms ($P = 0.01$, $t_{10} = -3.04$) and from 750 to 800 ms ($P = 0.045$, $t_{10} = -2.14$; Fig. 5e).

On the other hand, when evaluating directly the effect of Gaze for each emotion condition in the beta band, we found an increase of beta activity with directed compared to averted gaze for angry expression from 940 to 1,000 ms ($P = 0.028$, $t_{10} = -2.37$; Fig. 5d), and the opposite pattern for happy expression from 500 to 570 ms (at cluster threshold $P < 0.01$, $P = 0.0087$, $t_{10} = 2.94$; Fig. 5f). This opposite pattern of emotion by gaze effects was supported by a significant interaction from 440 to 510 ms ($P = 0.039$, $t_{10} = -2.13$).

For the gamma band, no significant modulation whatsoever was observed in OFC (Supplementary Table S1 and Supplementary Figs. S6–S8), except for an increase to the (most threat-relevant) fearful faces with averted gaze compared to directed gaze from 410 to 460 ms (at cluster threshold $P < 0.01$, $P = 0.009$, $t_{10} = 3.5$; Fig. 5b).

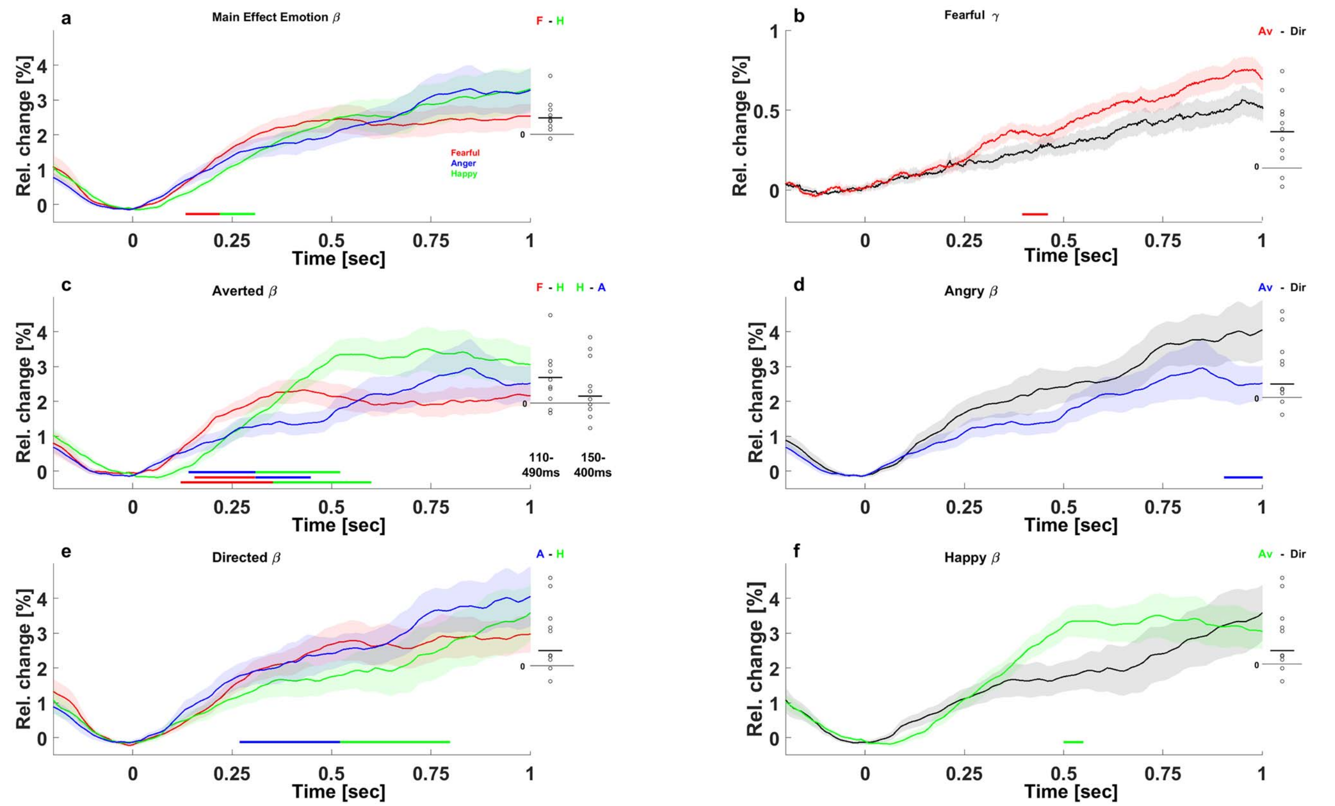

Fig. 5. Orbitofrontal cortex responses to emotion and gaze direction. Main effect of emotion independently of gaze direction in beta band (a), with scatterplots for individual amygdalae during time intervals exhibiting significant differences between fearful and happy (160–280 ms). Emotional responses in the beta band in the averted gaze condition (c), with scatterplots for individual amygdalae for differences between fearful and happy faces (110–490 ms), and between angry and happy faces (150–400 ms). Emotional responses in the beta band in the directed gaze condition (e), with scatterplots for individual amygdalae for differences between angry and happy faces (410–460 ms). b) Stimulus-evoked activity to fearful face expressions with averted and directed gaze in the gamma band (60–250 Hz), with scatterplots of average response from individual amygdalae in significant time intervals (940–1,000 ms). d) Same comparison for angry face expression in the beta band, with scatterplots from individual amygdalae (460–840 ms), and f) for happy face expression in beta band, with scatterplots from individual amygdalae (500–570 ms). Same color code as Fig. 2.

Differential self-relevant threat effects

Finally, we directly compared the 2 self-relevant threat stimuli among them (fearful faces with averted gaze vs angry faces with directed gaze). This revealed a significantly larger increase in high gamma band activity in the amygdala for the former relative to the latter, from 400 to 740 ms ($P = 0.015$, $t_{11} = -2.73$; Fig. 6a), and the opposite pattern in OFC in the beta band from 710 to 1,000 ms ($P = 0.021$, $t_{10} = 2.55$; Fig. 6b).

Discussion

To the best of our knowledge, we report for the first time amygdala ($n = 12$) and OFC ($n = 11$) time-frequency evoked responses to emotional gaze information in the human brain. Our study uncovers specific time–frequency channels and distinct latencies in both amygdala and OFC responses to emotional expression in faces depending on their gaze direction. Most importantly, our results demonstrate an integration of expression and gaze processing in these regions rather than purely parallel processing of these two socially relevant cues.

In agreement with previous findings of amygdala gamma band activity evoked by emotionally negative visual stimuli (Oya et al. 2002; Zheng et al. 2017; Guex et al. 2020), we found early amygdala responses to threatening faces starting around ∼110 ms, independently of gaze direction (Figs. 2 and 3). Most notably, for fearful faces with averted gaze, this amygdala response was further sustained in the gamma band (from ∼330 ms until 1,000 ms), compared to angry and happy faces (Figs. 2 and 3), whereas faces with directed gaze, either fearful or angry, elicited different and delayed responses in the beta band (260–460 and 420–1,000 ms, respectively) compared to happy faces (Figs. 2 and 3). In comparison, emotional effects in the OFC mainly occurred in the beta band, with an early increase of activity in response to fearful and angry faces relative to happy faces, and conversely a later increase to happy faces relative to fearful and angry faces (Fig. 5). However, these emotional responses in OFC were also modulated by gaze direction, but unlike in the amygdala.

Critically, in agreement with previous research where no effect of gaze direction was reported (Sato et al. 2011; Mormann et al. 2015), we did not find a main effect of gaze independently of the concomitant emotional expression, neither in amygdala nor in OFC. However, importantly, we found clear and novel evidence that the human amygdala integrates emotional face signals depending on their gaze direction, starting around 300 ms in the gamma band (Figs. 2 and 3). This pattern may suggest that an initial emotional response in this brain region might be independent from gaze direction (at least to fear, around 110 ms) but rapidly followed by the integration of gaze-related information. Specifically, the early time-interval exhibiting this significant gaze x emotion interaction (starting around 330 ms) was primarily driven by the fact that only fearful averted faces, and not fearful directed faces, elicited a differential gamma response compared to both angry and happy faces (Fig. 2), while the later time-interval of this interaction (starting around 460 ms) manifested through

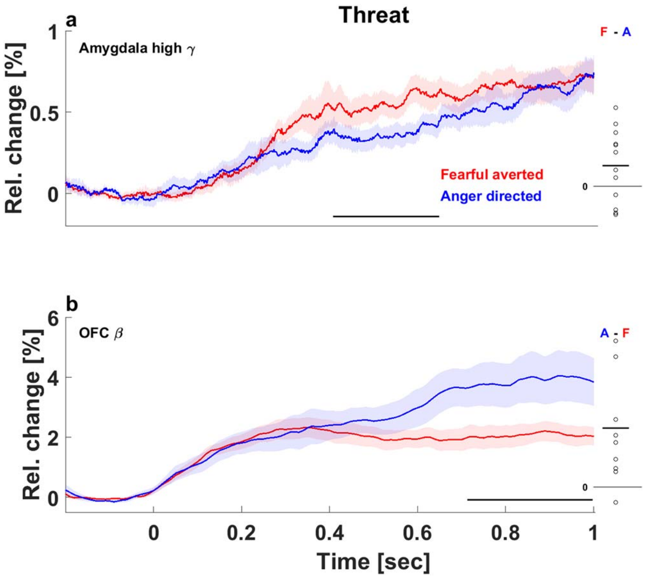

Fig. 6. Responses to threat-relevant faces in the amygdala and OFC. Differential activity between fearful averted and angry directed conditions in the amygdala in the high gamma band (a), with scatterplots for individual amygdalae during time intervals with significant differences between both conditions (400–740 ms). b) Differential activity between fearful averted and angry directed conditions in the OFC in the beta band, with scatterplots for individual amygdalae during time intervals with significant differences (710–1,000 ms). Same color code as Fig. 2.

divergent gaze effects depending on emotional expression (Fig. 4 and Supplementary Fig. S11) with increases to directed gaze for angry and happy faces and the opposite for fearful faces.

These results add to previous iEEG research (Pourtois and Vuilleumier 2010; Sato et al. 2011; Caruana et al. 2014) where the influence of gaze direction on amygdala and OFC activity was reported to occur at later latencies than emotional effects, although gaze and emotion signals were studied separately in these studies. In addition, our finding that gaze direction impacted emotional appraisal at different latencies according to emotional content and self-directed threat aligns with previous research showing that modulatory effects of task relevance on amygdala activity may arise at later latencies for negative in comparison to neutral stimuli (Guex et al. 2020), suggesting again that the initial inputs of visual emotional stimuli may be less subject to task manipulation or cognitive appraisal regulation than more delayed, possibly re-entrant, top–down inputs in the amygdala (and perhaps OFC as well).

On the other hand, our iEEG results contrast with non-invasive recordings were neural responses to faces and estimated sources in the amygdala found no reliable modulations by gaze direction for angry faces (Conty et al. 2012) or no stronger ERPs to directed than averted fearful faces (Dumas et al. 2013). However, some caution is warranted in these comparisons given that few studies have so far proved the feasibility to observe subcortical activity through noninvasive EEG recording (Seeber et al. 2019), with different tasks and procedures than those investigating emotional gaze processing. Our results also differ from a previous iEEG study reporting an early effect of Gaze direction, around 120 ms post stimuli onset (Huijgen et al. 2014). We note however that the latter study used not only a different stimulus set and a different task design, with a spatial attention cueing factor that is known to modulate eye gaze processing (Burra et al. 2018) and amygdala selectivity to peripheral stimuli (Mosher et al. 2014), but also employed a different analysis based on raw EEG signal, which might be more sensitive to low frequency activity (Buzsáki et al. 2012). Moreover, Huijgen et al. used a baseline correction corresponding to the onset of an initially neutral face, appearing several hundred ms before the emotional expression and/or gaze direction change. Moreover, recordings were restricted to the right amygdala over a relatively small sample ($n = 4$); although here we found no evidence for lateralization. Further research is therefore still needed to fully clarify how these differences in methodology, stimuli, or population, may explain discrepancies between studies.

In any case, by taking full advantage of high spatiotemporal resolution of iEEG over a range of both low- and high-frequency activity, we were able to robustly dissect emotion and gaze related effects across different frequency channels and different latencies. Higher gamma band amygdala activity was observed in response to fearful averted faces, a signal that has been proposed to reflect highly synchronized bottom-up sensory activity (Fries 2015) and related to local intra-regional processing (Lachaux et al. 2003, 2012; Buzsáki et al. 2012; Dubey and Ray 2019). In contrast, when gaze were directed, amygdala activity to threatening faces increased in the beta band, a signal known to sustain motor control in cortical areas and subcortical thalamic nuclei (Khanna and Carmena 2015), and also thought to mediate top–down influence across distant brain regions (Bressler and Richter 2015; Fries 2015; Zheng and Colgin 2015) or task-relevant signals in the prefrontal cortex (Antzoulatos and Miller 2016). This differential pattern could possibly reflect that the human amygdala contributes to parallel emotional appraisal stages in face processing through different frequency channels determined by gaze direction. We should also underscore here that no other frequency bands appeared to be involved in these processes in our study (see Methods, Supplementary Figs. S5, S10 and Supplementary Table S2).

Finally, our findings add novel support to appraisal theories of emotion predicting a key role for perceived self-relevance in eliciting affective responses and driving amygdala activity (Sander et al. 2005). Accordingly, a distinctive pattern of responses to fearful faces with averted gaze and angry faces with directed gaze converge with previous fMRI (N'Diaye et al. 2009) and neuropsychological (Cristinzio et al. 2010) work suggesting these conditions have higher threat relevance and stronger impact on amygdala activity than the reverse expression-gaze combinations. In addition, here we also directly compared these 2 self-relevant threat conditions (i.e. fearful averted vs. angry directed faces(N'Diaye et al. 2009; Cristinzio et al. 2010; Stussi et al. 2015) and found differential brain responses with greater amygdala activity in the high gamma band for fearful averted gaze from 400 to 740 ms, and greater OFC activity in the beta band for angry directed gaze from 710 to 1,000 ms (Fig. 6a and b). No differences were observed between the non-threat faces in any frequency bands. These results contrast with a prior study using surface EEG (El Zein et al. 2015) where self-relevant threat effects were observed independently of emotional face expression (for both averted fearful and directed angry faces), and suggest that different brain region involved in emotional appraisal might monitor different threat cues through different frequency bands (see Supplementary Figs. S1–S10 and Supplementary Table S2). However, our data appear consistent with different functional roles of amygdala and OFC, operating at different processing stages with more rapid responses to self-relevant fear through gamma activity in the amygdala, and slower integration of more complex social information with anger cues though beta activity in OFC.

Altogether, our novel results do not only confirm an important functional link between emotional gaze processing and amygdala activity, but they also go beyond previous work by finely unraveling specific spectral activity domains associated with emotion and gaze signals. The amygdala and the OFC both respond early on after stimulus onset, ~110 ms, with a predominant selectivity to the emotional content of faces, and regardless of gaze cues. In addition, later response components show dissociable effects on amygdala activity across frequency bands depending on gaze direction, while OFC activity is modulated by emotional gaze mainly in the beta band. Here, by showing for the first time that the human amygdala integrate specific emotional content and gaze direction over different time latencies, mainly through gamma band activity, these results provide important new insights for current models of face processing and refine classic theoretical accounts of the functional role of the human amygdala in affective and social functions.

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Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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Conflict of interest statement: The authors declare no competing interests.

Data availability

The dataset analyzed in the current study is available from the corresponding author on reasonable request.

Authors' contributions

RG, EM, and PV designed the study, MS administered clinical evaluation, RG and JDB recorded the data, RG and EM performed the analyses, PM performed the anatomical localisation, RG and PV wrote the report.

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