Intracerebral gamma modulations reveal interaction between emotional processing and action outcome evaluation in the human orbitofrontal cortex

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ABSTRACT

The orbitofrontal cortex (OFC) plays a key role not only in processing emotions but also in monitoring performance outcome. Although the neuroanatomical substrates underlying each of the two processes have been extensively investigated, they have predominantly been probed separately and therefore a precise knowledge of the functional overlap within the multiple OFC sub-portions involved is still lacking. Here, we explore the neural dynamics mediating performance monitoring and emotional processing using direct intracranial EEG (iEEG) recordings from multiple OFC sites of an epileptic patient. Neural activity was recorded during two experiments. The first task required processing of emotional faces and the second investigated action outcome evaluation based on a visual feedback on the subject’s performance. Task-related neural dynamics were assessed using modulations of high frequency responses in the gamma-band (50-150 Hz). Our results reveal that processing negative facial emotions as well as receiving negative feedback both elicited gamma-band responses in the lateral OFC. By contrast, the mid-OFC was selectively activated for positive feedback. Furthermore, we also found significant gamma-band deactivation in the gyrus rectus during processing of negative feedback. Our findings provide novel evidence for an intricate valence-selective interaction between the networks mediating emotion processing and performance monitoring in human OFC and support the hypothesis of a tight relationship between gamma-band activity and behavior.

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1. Introduction

As noted in a recent review (Kringelbach, 2005), the precise functions of the human orbitofrontal cortex (OFC) are still enigmatic. Most evidence to date, from lesions and neuroimaging studies and from analogies with animal studies, suggest that the OFC is crucial in emotional processing and reward-based decision-making processes (Morrison and Salzman, 2009; Rolls, 2004; Wallis, 2007). Indeed, single-unit recordings in monkeys and functional magnetic resonance imaging (fMRI) studies in humans have shown that OFC neurons are involved in the tracking of current reward values of environmental stimuli but also in monitoring the outcome of one's action (O'Doherty et al., 2003).

So far, investigations of the neural substrates underlying performance monitoring have often overlooked the emotional dimension of the observed processes. Clearly, evaluation of the outcome of one's action is a cognitive function inherently associated with variable extents of emotional reactions which ultimately also contribute to behavioral adaptation. The role of OFC in affective processing has been highlighted by numerous studies showing OFC responses to emotional faces, both in fMRI and intracranial EEG studies (Kawasaki et al., 2001; Kringelbach, 2005; Krolak-Salmon et al., 2004). In line with these observations, lesion studies have also shown that damage to the OFC causes major changes in personality, behavior, social conduct and decision-making (Rechard et al., 2000). However, direct evidence for overlapping OFC activations in response to emotional stimuli and to feedback on one's performance at the individual level is still lacking.

Generally, the wide range of deficits caused by OFC lesions suggests that its functional role is likely to be multi-faceted. This view is strengthened by the large size of the OFC which covers the entire ventral surface of the frontal lobe, and by well-known differences in anatomical connectivity patterns, phylogeny and cytoarchitectony within the OFC (Ongur and Price, 2000). Recently, a functional distinction between the lateral and medial part of the OFC has been proposed (Kringelbach and Rolls, 2004). Based on a meta-analysis of human neuroimaging studies, Kringelbach and Rolls (2004) reported convincing evidence supporting the hypothesis that
located in the posterior medial frontal cortex between the pre-anatomical MRI. According to SEEG data, the epileptogenic focus was partial cryptogenic epilepsy, and no lesion was detected on her pathology after the pre-surgical evaluation. The patient suffered from this study are connected to the present experimental protocol. All results reported in implantation was solely based on clinical considerations with no recordings and which were connected during evaluation of one's action? And does the overlap (or segregation) between the two networks depend on the valence of the stimuli (positive versus negative)?

To explore these questions we benefited from a unique opportunity to record neural activity simultaneously in both lateral and medial parts of the OFC in an epileptic patient under pre-surgical evaluation with intracerebral EEG. The fine spatio-temporal properties of OFC activity were assessed by performing direct recordings while the patient performed two types of tasks. The first paradigm was a challenging time-estimation task that included immediate positive or negative feedback about performance (action outcome evaluation and monitoring), while the second task consisted of processing positive and negative facial expressions (emotional processing). We characterized the activity recorded in multiple OFC sites in response to both positive and negative feedback on performance, and contrasted the obtained maps to those elicited by responses to positive and negative emotional stimuli recorded in the face perception condition. We found that lateral OFC displayed significant increases in high frequency activity during processing of negative facial emotions as well as negative feedback on performance. By contrast, the mid-OFC was selectively activated in response to positive feedback. Hence, the novelty of the findings presented here are two-fold; First, to our knowledge, our observations are the first to report high gamma activity patterns that reveal a clear anatomical segregation between positive and negative stimuli processing in human OFC. Second, we provide the first direct demonstration in humans that negative feedback on performance and negative emotional stimuli are both associated with high gamma responses in the same sites within lateral OFC. Finally, the valence-specific modulations of gamma activity revealed here, both for emotion processing and performance feedback, suggest a tight link between gamma and behavior.

2. Material and methods

2.1. Experimental subject

The patient, a 48 year-old female, suffered from drug-resistant partial epilepsy and was candidate for surgery. Because the location of the epileptic focus could not be identified using noninvasive methods, the subject underwent intracerebral EEG recordings by means of stereotactically implanted multilead depth electrodes (SEEG) (for a complete description of the rationale of electrode implantation, see Isnard et al., 2000). The selection of the target sites for electrode implantation was solely based on clinical considerations with no reference to the present experimental protocol. All results reported in this study are confined to electrode sites that did not show pathological recordings and which were confirmed to be unrelated to the subject's pathology after the pre-surgical evaluation. The patient suffered from partial cryptogenic epilepsy, and no lesion was detected on her anatomical MRI. According to SEEG data, the epileptogenic focus was located in the posterior medial frontal cortex between the pre-Supplementary Area and the anterior part of the superior frontal gyrus (F1). The orbitofrontal cortex was not part of the epileptogenic focus. Subsequently, following the pre-surgical evaluation period during which these experiments were performed, the patient underwent a left frontal cortectomy with a resection including the posterior and medial part of F1. Surgery resulted in a significant decrease of seizure frequency, from 1 seizure per week to 1 seizure per month (Engel Class III). The patient presented a moderate and transient (<1 month) language deficit (slight verbal fluency decrease) after surgery. At the time of recording, the patient received a treatment combining three antiepileptic drugs: Carbamazepine 1200 mg per day, Clobazam 20 mg per day and Primidone 750 mg per day. The detection of task-related brain activations were performed by the clinical staff as part of an ensemble of procedures (alongside neuropsychological and psychiatric evaluation) which constitute standard pre-surgical clinical routine. The patient gave informed consent.

2.2. Electrode implantation and coregistration

One-dimensional arrays of electrodes were implanted orthogonal to the inter-hemispheric plane using the Talairach's stereotactic scheme. Neural activity was recorded at 5 to 15 contact sites along each electrode. The estimated spatial resolution of bipolar recordings (difference between consecutive electrodes) is approximately 3.5 mm, given by the spacing (center-to-center) between two consecutive sites (Lachaux et al., 2003). The electrode positions were reconstructed onto the subject's individual MRI through the superposition of the CT-scan images showing the electrodes, the angiography and the patient's structural MRI slices using in-house software (Activis, Lyon, France). In addition, all electrode coordinates were converted from the individual Talairach space to the normalized Talairach space (Talairach and Tournoux, 1988). Furthermore, for visualization purpose all electrode locations were converted into the Montreal Neurological Institute (MNI) standard brain space onto 3D renderings of the single-subject MNI brain. The cortical surface segmentation was performed with the BrainVisa package (CEA, France).

A total of 11 individual electrode arrays were implanted in frontal lobe structures (yielding 118 recording sites in total). Among these, one particular electrode array, with 15 distinct recording sites, targeted the orbitofrontal cortex (Fig. 1). Due to the spatial configuration of electrode implantation, this depth electrode provided recordings in various sub-portions of the OFC along the medial-lateral axis: the most medial contacts (sites e′ 1 to e′ 3) were located in the gyrus rectus, the intermediate contacts (sites e′ 8 to e′ 11) recorded the mid-OFC between the medial orbital sulcus and lateral orbital sulcus, while the lateral contacts (sites e′ 12 and e′ 14) probed the lateral OFC laterally towards the orbital sulcus. See Fig. 1 for a graphical representation of the anatomical location of this electrode array.

2.3. Experimental paradigms

The subject performed multiple tasks aimed at exploring two main types of behavior. The first one was a challenging time-estimation task involving performance monitoring (PM task). This task was associated with a control task that consisted of a simple visual oddball (VO) paradigm. Additionally, emotional face processing was also investigated using a further paradigm which consists of a visual detection (EMO) task. The details of each task are described in the following section.

2.3.1. Performance monitoring (PM task)

The performance monitoring paradigm used here was very close to the paradigm used by Miltner (Miltner et al., 1997) in a seminal EEG study reporting feedback-related potentials. The patient performed a classic time-estimation paradigm in which the objective was to press a button twice with an interval as close as possible to one second. Each trial started with the presentation of a white fixation cross in the
center of a black screen. After 500 ms, the color of the cross switched to blue to instruct the participant to begin (GO signal). When ready, the subject would press the same button twice in an attempt to produce a one second interval. The performance for each trial was defined as the difference between the actual duration of that interval and the target duration (1000 ms). 3000 ms after the second button press, the central fixation cross was replaced with a small square (FEEDBACK signal). Depending on whether the produced duration was within or outside a tolerated margin of error, the color of the square indicated success (green square: positive feedback) or failure (red square: negative feedback) respectively. Three seconds after the feedback signal, the actual quantitative performance was displayed (e.g., −236 ms) for a duration of 1 s to allow behavioral adjustment in the next trial. Finally, the trial ended with a 1 s display of the overall score obtained by the subject. The score started at 0 at the beginning of a block and increased by steps of 1 or 2 with each successful trial, depending on performance (see details below). The challenge was to reach a total score of 14 in as few trials as possible, at which point the session was ended. In case the target score could not be reached a session was ended at latest after 20 trials. A key parameter in this task was the margin of error tolerated in each trial. Because we intended to compare neural responses to positive and negative feedbacks, we defined the experiment to balance the number of successful and unsuccessful performances. For this purpose, the margin was adjusted to the performance on a trial-to-trial basis. It was initially set to 800 ms and 1200 ms was considered a success. Next, the margin was updated as a function of the performance in all previous trials, starting with the error in trial i (difference between produced and target interval) the tolerated margin is the standard deviation of all previous errors. A performance within this margin was rewarded with +1 score increase, while a performance below 50% of the tolerated margin of error was rewarded with +2 increase in order to further increase the participant’s motivation. The duration of each trial depended on the timing of the subject’s performance and varied between 10 s and 15.3 s. A total of 16 blocks was performed, yielding 180 trials (11 were discarded because of artifacts) for a total duration of the experiment of approximately one hour.

2.3.2. Visual oddball (VO) task (control condition for PM)

To rule out the possibility that neural response modulations in the PM task could be simply related to different visual processing of the stimuli (eg. red versus green color) a visual control task was necessary. To this end we used a simple visual oddball paradigm. The subject had to press a button in response to blue squares (20% trials) while ignoring red (40%) and green (40%) squares. The stimuli were identical to those used for feedback in the PM task. Both targets and distracters were presented for 1000 ms with a random stimulus onset-asynchrony equal to 2000 ms on average (between 1800 and 2200 ms). There were a total of 80 red squares, 80 green squares and 40 blue squares, presented in random order. Note that the oddball control paradigm was performed first, followed after a short rest period by the PM paradigm. In both VO and PM tasks, the subject responded by pressing a button with his right hand. The stimuli were presented to the participant on a 17” computer screen at a 56 cm viewing distance using the stimulus software Presentation (Neurobehavioral Systems). The square stimuli yielded a horizontal and vertical angle of approximately 4°.

2.3.3. Visual detection of emotional faces (EMO task)

In the EMO paradigm, the subject performed two visual detection tasks of emotional stimuli, one implicit and the other explicit. Overall, five categories of visual stimuli were presented: the first four consisted of 4 types of emotionally expressive faces (fear, joy, disgust and neutral) taken from Ekman’s pictures of facial affect (Ekman et al., 1969) and the last category contained the target stimuli which were to be detected. The nature of the targets differed between the implicit and the explicit tasks (details below). All stimuli were black and white, brightness-adjusted and had an angular size of 4° × 5.5°.

In the first detection task (implicit EMO), the target stimulus consisted of one of the faces randomly chosen among the first 4 different categories but with a red circle superimposed on the center of the face. The processing of emotional faces in this condition was thus considered to be implicit as the subject only had to detect the red circle, irrespective of the emotional content of the face presented with it. In the second task (explicit EMO), the subject had to detect angry faces taken from Ekman’s pictures of facial affect. Here, the processing of emotional faces was considered to be explicit since successful target detection required emotional evaluation of the visual stimuli.

In both conditions, the subject was instructed to press a button when a target was detected. In both tasks, 70 stimuli for each category (50 for the target) were presented one at a time for 150 ms, separated by a central fixation cross. 23 stimuli were discarded in the explicit EMO task because of artifacts and 13 in the implicit EMO task. To ensure a comparable level of difficulty, the ISI was set to 1000 ms for the implicit task and to 1500 ms for the explicit task.

2.4. Data acquisition

Intracerebral recordings were conducted using an audio–video–EEG monitoring system (Micromed, Treviso, Italy) which allowed for simultaneous recordings of 128 depth-EEG channels sampled at
512 Hz [0.1–200 Hz bandwidth] during the experimental paradigm. Additionally, all signals were re-referenced to their nearest neighbor on the same multilead electrode array (consecutive leads are separated by 3.5 mm center-to-center). Such a bipolar montage is used to increase local sensitivity (spatial resolution) by suppressing common input from distant sources. Recording sites showing pathological activities were excluded from the analysis, and among the remaining sites, bipolar data were systematically scanned for artifacts using visual and semi-automatic inspection. Any trial showing epileptic spikes or abnormal activity in any of those traces was systematically discarded.

2.5. Data analysis

i) PM task: Analyses were conducted in the time-frequency domain to measure the effect of feedback stimuli on each frequency band separately. For each stimulus category, data were segmented into epochs ranging from 3000 ms before to 3000 ms after stimulus onset. Then individual data segments were transformed into time-frequency power representations as follows: for each single trial, the data from bipolar derivations (computed between adjacent electrode contacts) were transformed into a time-frequency (TF) representation by convolution with complex Gaussian Morlet’s wavelet (Tallon-Baudry et al., 1997). The result of this procedure is a TF map for each recording site and for each epoch presenting the signal power as a function of time (from −3000 ms to 3000 ms relative to stimulus onset) and frequency (from 1 Hz to 150 Hz). The task-related oscillatory power modulations can then be evaluated by statistical comparison between pre and post-stimulus power values at each frequency. This comparison was performed using Wilcoxon non-parametric tests that compared across epochs, the total power in a given time-frequency tile, with that of a tile of similar frequency extent, but computed over a prestimulus baseline period (from −500 to 0 ms). For each recording site, we performed 2280 Wilcoxon tests to cover a set of [100 ms × 4 Hz] time-frequency tiles across a [−3000:3000 ms] × [1:150 Hz] TF domain. We set the statistical threshold to p<0.05, corrected for multiple comparisons across tiles and recording sites with the False Discovery Rate method (Genovese et al., 2002). This procedure was first used to identify sites with significant feedback-related power changes in the PM task.

A complementary analysis was performed to investigate responses across a range of standard frequency bands (theta 3–7 Hz, alpha 8–12 Hz, beta 16–24 Hz and gamma 50–150 Hz). The amplitude in the theta, alpha and beta-band was computed using a band-pass filter followed by a Hilbert transform (which estimates instantaneous phase and amplitude). The amplitude time series was then expressed in percentage of the mean amplitude computed over the duration of the whole recording session for each channel (divided by the mean and multiplied by 100). To compute the broadband 50–150 Hz gamma-band amplitude while correcting for the 1/f power decrease of the signal (simply band-pass filtering the signal in the 50–150 Hz band would yield a signal dominated by frequency components close to 50 Hz), we applied the same procedure to compute ten amplitude time series (also expressed in% of their global mean) measured for ten consecutive frequency bands (from [50–60 Hz] to [140–150 Hz]). The broadband 50–150 Hz gamma-band amplitude was the average of those ten normalized time series. The same procedure was applied for theta, alpha and beta activity (but with a single frequency band for each). Note that, by construction, the mean value of each amplitude time series across the recording session is equal to 100. Note that including two approaches for estimation of task-related spectral modulations (one based on Wavelet analysis and the other on the Hilbert transform) provides a way to assess the robustness of our result and rule out any bias caused by the specificities of the method used.

We then compared the TF power maps obtained in these sites for positive and negative feedback on performance. The comparison between conditions was done via a Kruskal–Wallis non-parametric analysis applied on the raw time-frequency power values, on a set of 480 time-frequency tiles [100 ms × 10 Hz] covering a [−200:3000 ms] × [10:150 Hz] domain (one test per tile comparing the values obtained for all the trials in the two conditions). Bonferroni correction was applied to all Kruskal–Wallis tests taking into account the number of recording sites and time-frequency tiles. The significance threshold was thus set at a corrected p-value of 0.01 for all such comparisons.

ii) VO task: the procedures used to detect OFC sites generating oscillatory responses to all categories of visual stimuli (targets, red and green squares) were the same as in the PM task except that the data were segmented into epochs extending from 1000 ms before stimulus onset to 1000 ms after. The same complementary analysis evaluating the envelope (i.e. amplitude) of activity in different frequency bands (theta, alpha, beta and gamma) as in the PM task was also applied to data obtained during the VO task.

The comparison between the responses induced by the different stimuli was also performed with the identical procedure as in the PM task (Kruskal–Wallis non-parametric test) except that a set of 180 time-frequency tiles [100 ms × 10 Hz] covering a [−200:1000 ms] × [10:150 Hz] domain was used.

iii) EMO task: the procedures used to detect OFC sites generating oscillatory responses to all categories of visual stimuli (targets and non-targets) were the same as in the PM task except that the data were split into segments extending from −1500 ms before stimulus onset to 1500 ms after stimulus onset. The same complementary analysis evaluating the envelope of activity in different frequency bands (theta, alpha, beta and gamma) as in the PM task was applied in the EMO task.

The comparison between the responses induced by the different stimuli was also performed with the exact same procedure as in the PM task (Kruskal–Wallis non-parametric test) except that a set of 255 time-frequency tiles [100 ms × 10 Hz] covering a [−200:1500 ms] × [10:150 Hz] domain was used.

All intracranial EEG signal pre-processing and TF analysis were carried out with the software package for electrophysiological analysis (ELAN-Pack) developed in the INSERM U821 laboratory and custom MATLAB (The Mathworks, inc., Sherborn, MA) scripts.

3. Results

3.1. Behavioral results

3.1.1. Performance monitoring (PM task and control condition VO)

On average the intervals produced in the PM task differed from the 1-second target duration by 132±131 ms (standard deviation). The subject performed a total of 74 successful and 95 unsuccessful trials (Note that a trial is considered successful if the performance is within the accepted margin of error). The online adjustment of error tolerance did indeed lead to a reasonably balanced number of positive and negative feedbacks. In the visual oddball control task (condition VO), the subject successfully detected the targets almost invariably (92% correct detection) and with a mean reaction time of 223±66 ms.

3.1.2. Processing emotional faces (emotional faces paradigm EMO)

In the explicit detection task, 86% of the targets (angry faces) were detected with a mean reaction time of 765±187 ms but 70% of the disgusted faces were also detected by the subject as being targets. On the
contrary, fear, neutral expression and joy were easily discriminated. In the implicit detection task, the patient always detected the targets (red circle superimposed on each face) with a mean reaction time of 540 ± 82 ms.

3.2. Time-frequency analysis

We used time-frequency (TF) analysis to identify significant task-related changes in spectral power recorded in the OFC in response to feedback stimuli (PM task) and to emotional faces (EMO task). The TF representations revealed task-related oscillatory responses in a wide range of frequencies including lower alpha and beta-bands (8–30 Hz) and in the gamma-band (>40 Hz). A complementary analysis evaluating the modulations of envelope amplitudes in more detail across multiple predefined frequency bands (theta 3–7 Hz, alpha 8–12 Hz, beta 12–24 Hz and high gamma 50–150 Hz) was performed (see methods section). Globally, both approaches (i.e. the TF and envelope amplitudes analyses) revealed that gamma-band modulations displayed more spatially focal patterns and more clear-cut differences between conditions, compared to lower frequencies modulations. This is in line with a growing body of evidence from intracranial recordings suggesting that high frequency activity is more spatially specific and provides a more precise marker for task-related neural activation than power modulations in the alpha and beta bands for instance (Brovelli et al., 2005; Crone et al., 1998a,b). Therefore, for the purpose of this study we focus the discussion on gamma-band modulations. However, supplementary figs. 1 to 3 also illustrate the responses obtained in the theta, alpha and beta bands for the recording sites that show significant gamma-band responses.

3.3. Gamma-band responses to feedback stimuli during performance monitoring

During the PM task, feedback stimuli induced significant gamma-band responses (GBRs) in the OFC (Fig. 2). GBRs were spatially focal and found in only 2 sites: in the mid-OFC (site e′ 8) between the medial orbital sulcus and the lateral orbital sulcus, and in the lateral orbital gyrus (site e′ 12). There was a strong and opposite effect of feedback valence in the two regions: while the mid-OFC site (e′ 8) showed gamma power enhancement only in response to positive feedback (following a successful trial), the lateral OFC site (e′ 12) responded only to negative feedback (following an unsuccessful trial). Statistical analysis confirmed that gamma-band energy in the mid-OFC was stronger for positive than negative feedback and the reverse was found in the lateral OFC (p<0.05 Mann–Whitney U test). Note that the mid-OFC gamma response lasted approx. 1500 ms and was more sustained than the lateral OFC response (less than 1000 ms).

In order to test if the OFC differential responses truly reflected specific processing of positive and negative feedback stimuli rather than being simply different visual responses to squares of different colors, we checked whether the same stimuli (red and green squares) triggered GBRs when presented as distracters in the visual oddball task (VO). Indeed, no sign of differential gamma power increases were found when the green and red squares were presented as distracters, in other words, without any feedback value on action outcome. Interestingly, we found that in the oddball task (control task), target stimuli (blue squares that were to be detected) triggered a GBR in the mid-OFC (e′ 8), with a sharp power increase around 300 ms (Fig. 2).

Alongside the gamma-range power increases, we also found that negative feedback elicited a strong reduction of gamma-band power in the most medial OFC site (e′ 2). Interestingly, this gamma-band power suppression (GBS) was located in the gyrus rectus (Fig. 2) and had a temporal profile that consisted of a sharp drop in amplitude in the first 500 ms followed by a gradual return to baseline level within 1000 to 1500 ms after stimulus onset. For comparison purposes with a “neutral state” away from the feedback stimuli, the amplitude of the gamma-band activity was compared with its amplitude during the between trial period (4 s following the score display that ends each trial). We found that the level of gamma activity following negative feedback dropped below its level during this neutral state (see supplementary fig. 4 for an illustration of the feedback-induced decrease of gamma-band activity as compared to the neutral state for the gurus rectus (site e′ 2) and supplementary fig. 5 showing that this phenomenon is not observed in mid-OFC (site e′ 8).

The observation that the lateral OFC (site e′ 12) responds more strongly to negative feedback suggests that this region might use performance feedback to adjust behavior. In such a case, one might expect that trials with strong GBR in e′ 12 would be followed by a better performance in the following trial. To test this hypothesis, we defined a measure of behavioral adjustment between trial n and trial n+1 as the ratio R = e(n) / e(n+1), where e(n) is the error measured in trial n: TR (n) = 1000 (TR being the time period between the first and second button press). R is above 1 if and only if the patient fails to correct her poor performance between trial n and n + 1. Conversely, any value of R less than 1 means that the patient tried to adjust her behavior between trials n and trial n+1, either successfully when R is between −1 and 1, or unsuccessfully when R is less than −1 (overcorrection). Our prediction is that failed trials with a strong GBR to the negative feedback (i.e. a GBR significantly stronger than for positive feedback) should be followed by a behavioral adjustment: i.e. R should be less than 1. For each negative feedback occurring at trial n, if e′ 12 reacts with a strong GBR (significantly stronger than for positive trials), then R at trial n + 1 should be less than 1 (behavioral adjustment). To test this hypothesis, we divided failed trials into two groups (G1 and G2) based on the strength of the GBR. The strength was defined for each individual trial as the average amplitude of the single trial gamma-band (50–150 Hz) response between 500 ms and 1000 ms after feedback. G1 included trials where GBR for negative feedback was significantly stronger than for positive feedback, while remaining trials were assigned to the group G2. The significance criterion was inferred from the GBR measures after positive feedback: we measured that 94% of those GBR had a strength below T = 18 (T is the mean envelope amplitude increase of gamma activity expressed in percentage). This means that any GBR above T is unlikely to correspond to a successful trial (p<0.06). This was our best estimate of a test indicating from the GBR amplitude that the trial was failed, with 95% confidence. G1 included 28% of the failed trials.

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Fig. 2. Anatomical locations of the neural responses in the orbitofrontal cortex (OFC) and time course of the responses in the PM and EMO tasks.

- The 3D brain plot displays the entry point of the electrode implanted in the OFC of the left hemisphere on a reconstruction of the lateral cortical surface. Notice that only 3 sites responded during the task, represented by black symbols (star, square and circle).
- One site was located in the gyrus rectus (e′ 2 Normalized Talairach Coordinates in mm [−7 40 −6]), one site was located in the mid-OFC between the medial orbital sulcus and lateral orbital sulcus (e′ 8 [−18 40 −6]) and the last one was located in the lateral OFC, in the lateral orbital gyrus (e′ 12 [−43 40 −6]).
- Coronal slices of the patient’s MRI (panel C, D and E) show a reconstruction of the localization of the 3 responding sites (marked at the intersect of the crossing lines).
- The curves (panel F, G and H) represent the envelope of gamma-band (50–150 Hz) responses (with standard-error of the mean) averaged across trials expressed as a percentage increase relative to the mean for the 3 responding sites (left column: e′ 2, middle column: e′ 8 and right column: e′ 12) in the different tasks and conditions.
- On the top (panel A and B), two examples of TF maps showing gamma-band responses to negative feedback during the PM task (B) and the gamma-band suppression to negative feedback of the PM task (A) are shown. Those TF maps represent the gamma-band energy increase relative to the baseline [−1000 0 ms] preceding stimuli expressed as Z score (Wilcoxon test). Notice that GBR consisted of broadband energy increase between 50 and 150 Hz.
with a GBR above T (the lateral OFC actually responded more vigorously than to positive feedback), and G2 included the remaining 72% failed trials. Simple calculation of R for G1 and G2 trials revealed that 95% of all G1 trials were followed by behavioral adjustment ($R < 1$), while 25% of all G2 trials were followed by behavioral adjustment. This result strongly suggests that the subject adjusted his behavior more consistently after negative feedback when the GBR response in lateral OFC (site e′12) was stronger than to positive feedbacks. In other words, strong increases in gamma power in lateral OFC is more likely to be associated with behavioral corrections in the following trial.
3.4. Gamma-band responses during processing of emotional stimuli (EMO task)

3.4.1. Explicit EMO task

During the explicit EMO task, we observed that pictures of emotional faces also triggered GBRs in the OFC (Fig. 2). These responses were detected in the exact same sites as in the performance evaluation task (e’ 8 and e’ 12). In the lateral OFC (e’ 12), GBRs were observed only for pictures of negative facial expressions (anger, fear and disgust) and were virtually absent for positive (joy) or neutral facial expressions (comparison of GBR after anger, fear and disgust versus GBR after neutral or joy; p < 0.05 Mann–Whitney U test). The temporal profile of the neural response after negative stimuli resembled that of the response to negative feedback in the PM task, with an increase of energy in the 300 ms, a peak near 600 ms and a duration of approximately 1000 ms. In the mid-OFC (e’ 8), GBRs were observed for the target (anger) and for the disgusted faces which were also predominantly identified by the subject as targets (see behavioral data). Note that the time course of these gamma-range responses was similar to that observed in the successful condition in the PM task.

3.4.2. Implicit EMO task

Most importantly, in the implicit condition which was designed to distract attention away from the target faces’ emotional content, we observed no lateral OFC response to any of the stimuli. The only response we found in this condition was a GBR in the mid-OFC (e’ 8) in response to target stimuli. The time course of this response in this site was very similar to the one observed for target stimuli in the explicit EMO task and the successful condition of the PM task.

4. Discussion

This study provides the first direct evidence using high-resolution intracranial recordings that processing of emotional faces and monitoring of one’s action activate partially overlapping subregions in the human OFC. Our results indicate that the lateral OFC is preferentially activated by negative emotional stimuli and negative performance feedback. Slightly more medial OFC responses were stronger for stimuli with positive valence and for stimuli that match expectation during target detection tasks. In sharp contrast, the most medial portion of OFC, in the gyrus rectus, was characterized either by a lack of reactivity to such stimuli, or even by a transient suppression of activity, visible as power drops in the gamma-band compared to baseline level. Taken together, these findings contribute to an emerging understanding of the role of OFC subregions in emotional processes and decision-making (Kringelbach, 2005; Wallis, 2007).

The functional dissociation between the different OFC substructures probed in the present study was achieved by comparing task-specific modulations of high frequency (gamma-range) components of the neural responses. The high task-sensitivity of gamma activity found here is in line with a growing body of evidence that neural populations code high-level properties such as the reward value of sensory events, rather than their lower-level physical properties. Indeed, iEEG gamma modulations have revealed cerebral networks underlying a wide range of sensory, cognitive and motor functions, including language, memory, auditory and visual processing (Jung et al., 2006, 2010, 2008; Lachaux et al., 2003; Luo et al., 2010; Mainy et al., 2008; Mainy et al., 2007). Furthermore, gamma-band responses have been repeatedly found to correlate with task-induced fluctuations of the BOLD signal in functional MRI studies (Lachaux et al., 2007; Mukamel et al., 2005). Given the breadth of the fMRI literature investigating human OFC, the putative correlation between the spatial distribution of gamma modulations and that of the BOLD signal provides a further incentive to specifically investigate gamma activity in human OFC. Moreover, our results support previous reports that link gamma-band activity with behavior by providing the first evidence for a significant association between the strength of gamma responses in lateral OFC and subsequent behavioral adjustments. Indeed, the likelihood of adapting behavior was higher when stronger lateral OFC gamma responses were produced at the time of feedback on a previous performance.

4.1. Interaction between emotional processing and performance monitoring in human OFC

It is well established that human OFC is activated in situations triggering emotional reactions (O’Doherty, 2007; Rolls, 2004). Indeed, a large body of studies have shown that human OFC is involved not only during basic processing of emotional stimuli, such as emotional faces, but also during decision-making or behavioral adaptation based on rewards or punishments (Chua et al., 2009; Coricelli et al., 2005; Kringelbach, 2005; Murray and Izquierdo, 2007). This leads to the question of whether (and if so how) the different views on the role of the OFC that arise from such diverse studies can be reconciled into a consistent multi-functional representation of the role of the OFC? Recently, Wallis posited that the human OFC integrates multiple sources of information regarding the reward outcome to derive a value signal (Wallis, 2007). A value signal may thus be attributed both to explicit emotional stimuli (such as an angry or scared face) but also to a reward or punishment predicting stimuli. According to this theory, it may be speculated that the OFC would be active during action outcome evaluation informed by feedback stimuli, given that this situation inherently requires the establishment of a value signal for feedback stimuli. Indeed, several recent fMRI and intracranial EEG studies have shown that the OFC is activated during action outcome evaluation (Brazdil et al., 2002; Walton et al., 2004). Our finding that identical sites in lateral OFC respond both to emotional faces and feedback stimuli may thus be considered as direct evidence supporting the hypothesis put forward by Wallis (2007).

4.2. Lateral OFC is activated by negative stimuli during face processing and action outcome evaluation

Gamma-band responses in the lateral OFC were highly concordant across tasks, and consistent with a specific role in processing negative stimuli. In the performance monitoring task, responses were only observed when the participant received negative feedback on his performance (‘failed’). During processing of emotional faces, statistically significant responses were found for negative facial expressions (fear, disgust and anger) but not for neutral or positive expressions. This result is in line with previous neuroimaging studies in which the lateral orbitofrontal cortex was found to be activated by fearful expressions (Blair et al., 1999; Paradiso et al., 1999) or by more abstract negative stimuli, such as monetary losses (O’Doherty et al., 2003). Moreover, our data recorded during the performance monitoring task not only indicates that the lateral OFC is preferentially involved in processing negative feedback but also suggests that trials with stronger gamma activations in this structure following negative feedback are more likely to be followed by a change of behavior in the following trial. This confirms previous studies postulating that the lateral OFC activity is related to the evaluation of punishers, which can lead to a change in ongoing behavior (Kringelbach, 2005).

Interestingly, lateral OFC peak responses across multiple tasks in the present study were only reached after 700 ms following stimulus onset. This observation is in line with the view that certain lateral OFC neural populations code high-level properties such as the reward value of sensory events, rather than their lower-level physical attributes or semantic category (Rolls and Grabenhorst, 2008).

In addition, according to our results the generation of gamma-range activity in the lateral OFC did not occur systematically after stimulus presentation, but it was conditioned by attention to the emotional content of the stimulus. This observation follows from the
comparison between the neural responses obtained in the implicit versus explicit EMO tasks. While both visual detection tasks were based on the presentation of emotionally expressive faces, only the implicit task required attention to the emotional aspect of the face while the explicit task required the subjects to detect the presence of a superposed red circle, irrespective of emotional expression. In the latter condition, the response to negative facial expressions, which was present in the explicit task, disappeared. This effect is in agreement with a previous intracranial EEG study showing that event-related potentials recorded in the OFC in response to fearful faces were dependant on attention (Krolak-Salmon et al., 2004). Our data can be taken to suggest that the response triggered by negative images in the lateral OFC can be strongly amplified by attention.

4.3. Mid-OFC responses during emotional processing

We found evidence that the mid-OFC was activated by target stimuli in the implicit and explicit EMO task and the VO task. Emotional faces did not elicit responses alone if they did not represent a target in the experimental context. This means that the mid-OFC site of our patient was not directly involved in the processing of emotional faces per se.

Previous neuroimaging studies have suggested that, by contrast to lateral OFC structures, medial OFC is preferentially involved in processing pleasant stimuli, such as pleasant tastes, smells (de Araujo et al., 2003; Rolls et al., 2003) or monetary gains (Elliott et al., 2003; O’Doherty et al., 2001). This preference is in line with results from our performance monitoring task during which mid-OFC (belonging both to the medial OFC and lateral OFC functional clusters of the Kringelbach meta-analysis (Kringelbach and Rolls, 2004) according to its Talairach coordinates) gamma responses were only present following rewarding feedback (indicating performance success). However, in the visual detection tasks, pleasant faces did not elicit such responses. Therefore, our data contradict a simple association between pleasantness of a stimulus and mid-OFC activity. However, we found significant mid-OFC responses to occur systematically following presentation of target stimuli. This was the case for both implicit and explicit visual detection tasks, as well as in the simple visual oddball paradigm. Mid-OFC thus displayed gamma activity for each target stimulus, irrespective of its nature (which was markedly different across tasks) and even when the target was a negative (fearful) facial expression. One possible interpretation is that the appearance of a target stimulus is associated with an upcoming correct detection and thus a successfully carried out trial. This could indicate that the mid-OFC is not preferentially activated by stimuli that are positive per se (e.g., joyful faces), but rather by a positive stimulus-context relationship. It is also possible that the rare occurrence of the target stimuli actively expected by the participant might trigger a positive emotion, irrespective of stimulus properties. This could imply that valence-related mid-OFC responses are not as stimulus dependent, as much as they are context dependent. Indeed, this hypothesis would explain why even aversive stimuli, such as fearful faces, can trigger a response in mid-OFC if, in the context of the experiment, they become targets that the subject is waiting for in order to provide a response.

4.4. Transient neural deactivations in the gyrus rectus during emotional processing

The most medial part of the OFC areas probed in this study, was the gyrus rectus (electrode e’ 2, Fig. 2A). Unlike the lateral and mid-OFC areas discussed above, the task-sensitivity of the gyrus rectus was radically different. Presentation of emotional stimuli did not trigger increases in gamma-band responses in this structure. In most instances, the stimuli did not elicit any response, with one notable exception: a transient task-related decrease in gamma-band power was observed after negative feedback in the performance monitoring task. Such gamma-band suppressions (GBS) have already been reported, but their exact physiological meaning is still unclear. Gamma-band suppressions were for instance found in the ventral lateral prefrontal cortex (VLPFC) during a reading task and were modulated by attention (Lachaux et al., 2008). Since gamma-band activity may correspond to local synchronization mechanisms underlying neural communication, GBS could reflect a disruption in local communication, and a withdrawal of a neural population from the task at hand. The idea that cognitive tasks require not only the participation of selective brain areas, but also the disengagement of regions that would interfere with the task is not new. It is in fact at the core of a growing body of neuroimaging studies that have identified a reproducible large-scale network, the so-called “default-mode network”, that is generally assumed to be more active during rest than during active tasks (Raichle and Snyder, 2007). Considering recent evidence that gamma-band activity and BOLD signals might be tightly linked, one might predict that gamma-band responses in the default-mode network would also decrease during task-performance. Our report of GBS in the gyrus rectus is therefore in line with neuroimaging evidence that the most medial OFC structure is part of that network (Gusnard et al., 2001). Further studies are underway to fully investigate this putative relationship between Gamma-band suppressions and BOLD deactivation patterns in various cerebral structures of the default-mode network during attention-demanding tasks (Jerbi et al., 2010; Ossandon et al., 2009).

In conclusion, direct neural recordings in human OFC confirm and extend our knowledge about its topographic functional segregation. Our findings provide the first evidence for an intricate valence-selective overlap between the networks mediating emotional processing and performance monitoring in OFC. The valence-specificity of gamma-band activity, shown here both for visual emotion processing and for performance feedback, provides further support for the functional role of high frequency power modulations in OFC through its tight link to behavior. Finally, our results indicate that assessing task-specific spatio-temporal patterns of high gamma activity with depth recordings may be critical in order to achieve a better understanding of the relationship between neuroimaging and electrophysiological studies that investigate the role of OFC sub-structures in humans.

Disclosure/conflict-of-interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

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References


