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Electrophysiological correlates of affective blindsight

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ABSTRACT

An EEG investigation was carried out in a patient with complete cortical blindness who presented affective blindsight, i.e. who performed above chance when asked to guess the emotional expressions on a series of faces. To uncover the electrophysiological mechanisms involved in this phenomenon we combined multivariate pattern recognition (MPR) with local field potential estimates provided by electric source imaging (ELECTRA). All faces, including neutral faces, elicited distinctive oscillatory EEG patterns that were correctly identified by the MPR algorithm as belonging to the class of facial expressions actually presented. Consequently, neural responses in this patient are not restricted to emotionally laden faces. Earliest non-specific differences between faces occur from 70 ms onwards in the superior temporal polysensory area (STP). Emotion-specific responses were found after 120 ms in the right anterior areas with right amygdala activation observed only later (~200 ms). Thus, affective blindsight might be mediated by subcortical afferents to temporal areas as suggested in some studies involving non-emotional stimuli. The early activation of the STP in the patient constitutes evidence for fast activation of higher order visual areas in humans despite bilateral V1 destruction. In addition, the absence of awareness of any visual experience in this patient suggests that neither the extrastriate visual areas, nor the prefrontal cortex activation alone are sufficient for conscious perception, which might require recurrent processing within a network of several cerebral areas including V1.

Introduction

When the brain's primary visual areas are destroyed, cortical blindness normally ensues (Holmes 1918). Humans that become cortically blind normally lack conscious awareness of visual experience. Despite this deficit, some patients have been reported to be capable of guessing different characteristics of the visual stimulus (such as for example, spatial location, orientation, direction of movement, colour, etc.) at a level above chance. This phenomenon has been called "blindsight" (Poppel et al., 1973; Sanders et al., 1974; Weiskrantz et al., 1974; Weiskrantz, 1986; Stoerig and Cowey, 1989) to reflect these residual visual capacities. Subsequently, de Gelder et al., (de Gelder et al., 1999) reported a hemianopic patient (GY) whose performance was above chance when he was asked to guess facial expressions of emotion presented in his blind visual field, showing that blindsight could be extended to include affective stimuli, hence the term "affective blindsight".

Considerable effort has been dedicated to understanding the neuroanatomical pathways giving rise to this phenomenon. The prevailing view suggests that the remaining visual function is subserved by an extrageniculate retino-tectal pathway (Poppel et al., 1973; Weiskrantz et al., 1974; Rafal et al., 1990; Sahraie et al., 1997). However, another view suggests that residual function may rely on projections from retinogeniculate projections to extrastriate visual areas (Stoerig and Cowey, 1989). Indeed, direct projections from the lateral geniculate to extrastriate cortex have been observed in the macaque monkey (Yukie and Iwai, 1981; Bullier and Kennedy, 1983; Sincich et al., 2004) showing that information may still be processed to a certain extent despite destruction of V1 and could provide a basis for the non-conscious sensitivity to different visual properties (Boyer et al., 2005).

In the field of affective blindsight, Morris et al., (Morris et al., 2001) investigated the brain areas involved in the processing of fearful and fear-conditioned faces that were presented to the blind visual field of patient GY. Amygdala activation was observed for unseen stimuli. Moreover, the response was found to covary with activity in the superior colliculus and the posterior thalamus. This suggested that the colliculo-pulvino-amygdalar pathway might constitute a secondary route allowing emotional stimuli to be processed when V1 is destroyed.

More recently, another patient (TN) with bilateral (Pegna et al., 2005) damage to visual cortical areas and affective blindsight was investigated using fMRI. Right amygdala activation was observed in

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response to the visual presentation of facial expressions of emotion although the patient was unaware of the stimuli. In order to further investigate the functional anatomy underlying affective blindsight we carried out EEG recordings in this patient while pictures of faces with different emotional expressions were presented. The goal of the analysis was to detect the classes of stimuli leading to systematic neural changes in this patient and to determine the temporal flow of information across brain regions using intracerebral estimates of field potentials obtained using ELECTRA source model (Grave de Peralta Menendez et al., 2000, 2004).

Methods

Patient description and behavioural tests

The patient TN was a 52 year-old male who suffered total destruction of his left and right visual cortices due to two consecutive cerebrovascular accidents (CVAs) that occurred 36 days apart. The MRI scans that were performed at that time are shown in Fig. 1A at the level of the CVAs, showing the extent of the lesions. The first CVA damaged the left parietotemporo-occipital cerebral area including: inferior parietal region, the left inferior/medial/superior occipital areas, the calcarine sulcus and the fusiform gyrus (see Fig. 1 for corresponding Brodmann areas). This produced right hemiplegia and transcortical sensory aphasia, which receded rapidly. However, the patient was left with a persistent right hemianopia. The second CVA occurred in the right posterior areas, affecting the inferior and medial occipital areas, the calcarine sulcus and the fusiform gyrus and producing a loss of the remaining left visual half field.

A formal neuropsychological assessment performed 2 months after the second stroke showed no cognitive impairment except for slight word-finding difficulties. However, TN remained clinically blind and unable to detect movement, colours, or geometrical shapes. At that time he described his visual experience as complete darkness and was forced to grope his way around his hospital room. This was further confirmed by his inability to detect the presence of strong sunlight coming from his window on an extremely clear and bright day. The electrophysiological tests involving his visual capacities that are reported here were carried out during this same period.

Electrophysiological recordings

High-density EEG recordings were carried out with TN while he sat facing the computer screen on which a series of angry, happy, fearful and neutral faces were presented in a random order (63 per category). In order to limit movement artefacts, no response was requested from the patient during the recordings. TN was not informed when the stimuli appeared on the screen and he was simply instructed to orient his direction of gaze straight ahead. The faces were static black and white pictures selected from the Pictures of Facial Affect series (P. Ekman and W. V.Friesen, Consulting Psychologists Press, Palo Alto, CA, 1975). Each stimulation trial (~1200 ms duration) started with a fixation cross that appeared for 500 ms, followed by the face image during 250 ms and then by a blank screen for 450 ms.

Research was conducted according to the guidelines for the use of human subjects at Geneva University Hospitals and written informed consent was obtained from the patient.

The electroencephalogram (EEG) was continuously monitored at 500 Hz from 125 electrodes (Electric Geodesic Inc. system) using Cz as a reference. The experiment was carried out in an isolated, electrically-shielded room. Off-line processing of the scalp data consisted of 1) re-referencing of the data to the average reference, 2) visual rejection of trials contaminated by artefacts (for VEP computation only), 3) removal of channels at the border of the EEG helmet due to their poor contact with the skin (leaving 111 electrodes for analysis), and 4) removal of noisy channels and replacement with interpolated values using spherical splines.

Analysis procedures

From a neural point of view, if a given visual stimulus is processed by the brain, then ongoing electrical brain activity should be consistently modified. However, such changes in neural activity might

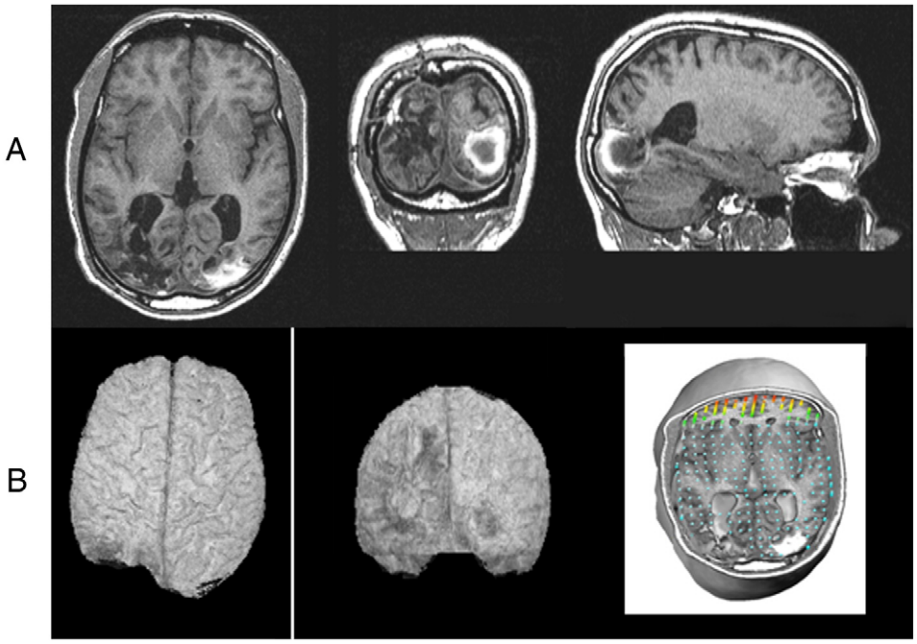

Fig. 1. (A) T_1-weighted MRI (axial, coronal and saggital views) showing the extent of bilateral striate cortex lesions. In terms of Brodmann's areas, the left hemisphere lesion encompasses BA 17, 18, 19, 37 and 39. The right hemisphere lesion encompasses BA 17, 18 and 19. (B) Leftmost plots show the three-dimensional reconstruction of patient's gray matter (top and back views). This is the inner compartment in the geometrical model used to non-invasively estimate LFP's. The rightmost plot shows the distribution of voxels used to compute LFP estimates.

not necessarily be locked to stimulus presentation such that they result in a mean event related potential. Destruction of the primary visual cortex in blindsight deprives the cortical system of its main source of input thus modifying substantially the visual evoked potential components, leading to modified or absent event related potentials (Shefrin et al., 1988; Benson et al., 1999; Rao et al., 2001; Hamm et al., 2003). We therefore opted for a single trial analysis based on the hypothesis that stable changes in neural oscillations must be produced following the presentation of faces, even when conscious awareness is lacking. We expected that such stable oscillatory patterns would constitute a sort of neural fingerprint that would be readily recognized by a multivariate pattern recognition algorithm (MPRA).

In order to explore the sequence of brain regions activated in our paradigm, we transformed the recorded scalp EEG into estimates of local field potentials (LFPs) using a distributed linear inverse solution termed ELECTRA (Grave de Peralta Menendez et al., 2000, 2004). ELECTRA selects a unique solution to the bioelectromagnetic inverse problem based on physical laws governing the propagation of field potentials in biological media. Such a model restriction leads to a formulation of the inverse problem in which the unknowns are the electrical potentials within the whole brain rather than the current density vector. Importantly, the use of ELECTRA approach has been repeatedly validated in the analysis of experimental data (Grave de Peralta Menendez et al., 2000; Morand et al., 2000; Gonzalez Andino et al., 2001, 2005) and its use on single trial data, has led to predictions (Gonzalez Andino et al., 2005) that have been confirmed through experimental recordings of local field potentials in animals (Schoffelen et al., 2005). This approach also allowed the real time decoding of perceived visual categories in healthy subjects (Gonzalez Andino et al., 2007).

Using this procedure we obtained the 3D distribution of estimated LFPs (eLFPs) within 4427 nodes homogeneously distributed within the inner compartment of a realistic head model derived from the patient's individual MRI. The voxels were restricted to the gray matter and formed a regular grid with 6 mm spacing. The details of the head model are shown in Fig. 1B.

The basic principle of the analysis is therefore to learn to recognize the patterns of oscillatory activity that should be specific to each facial expression presented. Consequently, the power spectral density was computed for each eLFP (i.e., each voxel) during the pre-stimulus and post-stimulus epochs, and the oscillatory pattern that differentiated maximally the conditions in the two periods were sought for (Feature selection). Since the speed of face perception might be severely compromised in this patient, we selected temporal windows of 400 ms length for spectral analysis based on the Multitaper method.

Decoding based on pattern recognition

In order to discriminate the cases of face stimuli that induced consistent changes in brain oscillatory activity, we quantified the percentage of EEG trials correctly attributed by the pattern recognition algorithm to the facial category presented to the patient. Multivariate pattern recognition has been offered as an alternative to conventional forms of analysis in neuroimaging (Haynes and Rees, 2006). The decoding-based approaches used here aim to decode a person's mental state by learning to recognize spatial patterns of brain activity associated with mental states. More specifically in our case, if a particular facial expression is processed by the patient (with or without awareness), then a consistent pattern of neural activity should appear every time the same expression is presented.

In our analysis we used a multivariate statistical pattern recognition method known as linear Support Vector machine (Hastie et al., 2001) (OSU-SVM). Statistical pattern recognition algorithms are designed to learn and later classify multivariate data points based on statistical regularities in the data set. Learning is based in selecting some patterns (features) over one part of the trials (the learning set formed by half of the trials in our case). We then give these patterns to the classifier along with a label that identifies the facial expression presented to the subject. This is usually done for only a part of the trials. The classifier learns a mapping between patterns of brain activity (the neural oscillations) and the facial expression presented. The classifier must then predict the facial expression presented on the set of yet unknown trials, based on the features computed from the initial set. The accuracy in decoding is computed in terms of the percentage of correctly predicted trials. Features selected in our study were the neural oscillations at the 150 brain sites that best differentiated the faces in the learning set. The ranking of the features was based on the Discriminative Power measure described in (Gonzalez et al., 2006). Decoding accuracy was computed using ten-fold cross-validation.

Since the number of trials in our data was limited we used a 10-fold cross-validation approach for the MPRA. This procedure allowed us to estimate the predictive accuracy of the categorization process while avoiding overly optimistic estimates. The results from the folds were averaged to produce an estimate of the classes of stimuli that, although unacknowledged and presumably unperceived, still induced systematic changes on neural activity. The features, i.e., the oscillatory activity at each brain voxel, were selected on each fold and ranked according to their relevance to discriminate between pre and post-stimulus. Ranking of the features was based on the discriminative power measure (Gonzalez et al., 2006), which is a lower bound estimator for the number of true-positives that can be obtained with a single feature while the number of false-positive is set to zero. The best 150 features were kept for use with the MPRA.

We therefore applied the pattern recognition to the features selected from the eLFP in the pre-stimulus (Pre) and post-stimulus (Post) periods for each of the categories of facial expressions. As a control condition, and to exclude significant differences in oscillations due to natural fluctuations of the subject state, we compared different pre-stimulus periods between each other, which should of course be identical. The following five conditions were compared: 1) Pre vs. Post for angry faces, 2) Pre vs. Post for happy faces, 3) Pre vs. Post for neutral faces, 4) Pre vs. Post for fearful and 5) Pre for happy and neutral faces together vs. Pre for fearful and angry faces together.

Spectral analysis

The power spectral density (PSD) was computed for all brain voxels and single trials during the selected window using a multi-taper method with seven sleepian data tapers. The multi-taper method proposed by Thomson (Thomson, 1982) provides a trade-off between minimizing the variance of the estimate and maximizing the spectro-temporal resolution. The application of tapers to the data allows an estimation of power that is robust against bias. Hence, for the T=400 ms windows used here, a bandwidth parameter of W=8 Hz and a variance reduction by a factor of 1/7 was attained by using seven sleepian data tapers. Each 400-ms time series was multiplied by each of the tapers and the Fourier components were then computed via FFT. The PSD was computed by taking the square of the modulus of these complex numbers corresponding to frequencies from 0 (DC) to 256 Hz.

Results

Behavioural test carried out prior to EEG recordings have been reported elsewhere (Pegna et al., 2005). Briefly, in a series of two alternative forced choice (2AFC) procedures, patient TN was presented with sequences of visual stimuli which fell into one of two categories that he was asked to guess. When presented with sequences of geometric shapes and asked to guess which of the 2 shapes had appeared, his performance was at chance level. Similarly, when presented with male or female faces, or faces vs. scrambled faces, he remained at chance. He also responded randomly when attempting to guess whether the stimuli presented were threatening

or non-threatening animals, or whether complex emotional scenes were positive or negative. By contrast, his performance was significantly above chance when he was presented with series of 200 images of angry/happy faces (P=0.011); sad/happy faces (P=0.001); and fearful/happy faces (P=0.024) demonstrating the presence of affective blindsight.

Event related potentials

Visual Event Related Potentials (VEPs) were obtained by averaging the single trial EEG responses to each category of faces. The VEPs obtained for each of the 4 facial expressions are shown in the supplementary material. The first typical visual components (N70, P100) were absent in the patient. This finding was common to all types of faces. The amplitudes of the responses were not significantly different from pre-stimulus activity and are not further discussed here.

Resolving affective blindsight in time and space

The analyses of the scalp-recorded VEPs suffered from two major limitations: 1) no information about the sequence of brain areas activated by different facial expressions was provided and 2) the absence of early visual evoked responses could be interpreted as the total absence of activation of visual areas in blindsight, or alternatively, as the lack of time locked responses within the still reactive visual areas. In the second case, changes in neural oscillations non-strictly locked to visual stimulus onset might provide a neural substrate for the implicit perception observed in blindsight.

Categories of stimuli leading to neural changes in blindsight

In order to assess whether a given pattern of neural oscillations was unambiguously linked to each facial expression, we combined spectral analysis of eLFPs with a pattern recognition algorithm (PRA). As previously described, we trained the PRA to recognize the oscillatory activity in the periods before and after stimulus presentation in half of the presented faces. We then quantified the percentage of remaining facial stimuli (not used for training) that were correctly assigned by the PRA to the face category actually presented on this trial. This percentage reflects the classes of stimuli that although unacknowledged and presumably unperceived still induced systematic changes on neural activity.

Table 1 presents the percentage of correctly decoded trials within each category and the significance of this proportion with respect to the amount of faces in the test set. While classification rates remain at the chance level (50%) for the comparison between all the pre-stimulus periods, they are significantly different from chance for all categories of faces including neutral ones.

In order to verify whether these classification rates were not due simply to changes in luminosity on the screen, we carried out the same analysis to compare the post-stimulus periods. For this purpose, we applied the MPR procedure to the 400 ms post-stimulus intervals to evaluate the oscillatory patterns across emotional expressions. Our aim was to detect the percentage of facial expressions attributed correctly to their specific category. In this case the analysis consisted in comparing each of emotional face categories with the neutral ones. Consequently, we compared 1) Post angry vs Post neutral, 2) Post happy vs Post neutral and 3) Post fearful vs. Post neutral faces.

Table 1
Percentage of correctly decoded trials (CCT) within each category and significance of the proportion (p-value)

Face type	CCT	p-value
Angry	77	5.0e-10
Joy	85	2.0e-15
Neutral	86	5.0e-16
Fear	87	4.9e-17
Pre-stimuli	46	0.289, (p>0.05)

Note that classification rates remain at the chance level (50%) for the comparison between all the pre-stimulus periods, but are significantly different from chance for the all categories of faces including neutral ones.

Classification results were highly significant (p<1.0e-06, proportion test) for all three comparisons. The percentage of trials correctly assigned to their corresponding category was: 1) Post angry vs Post neutral: 82.1%; 2) Post happy vs. Post neutral: 79.3%; and 3) Post fear vs. Post neutral faces: 85.6%.

While the pre vs. post-stimulus comparison indicates that consistent oscillatory patterns appear after stimulus presentation, the post-stimulus comparison between faces allows determination of the specificity of such oscillatory responses across emotional expressions. Thus, although not consciously perceived by this patient, face stimuli consistently modified the ongoing brain activity, allowing the face-induced oscillations to be categorised with a high level of accuracy.

Visual routes in affective blindsight

In order to investigate the possible visual pathway that might underlie affective blindsight we compared the eLFP amplitudes statistically over time for the different facial expressions, a procedure previously applied to intracranially recorded LFPs in monkeys (Kreiman et al., 2006). We thus conducted the following analysis at the voxel level from stimulus onset to 300 ms post-presentation. We performed a one-way non-parametric ANOVA (Kruskal-Wallis) on the amplitudes of the eLFP responses using facial expression as the main factor (Kreiman et al., 2006). This global analysis aimed at identifying the time periods during which emotional expressions induced different activation patterns. In these time-course analyses, LFPs were ranked by amplitude across facial expressions (e.g. amplitudes from one voxel at the first time frame from 63 angry trials, 63 fearful trials, and 63 happy trials were ranked, and so on). The ranks, categorized by expression, were entered into the non-parametric ANOVA. The result of each analysis were then corrected for multiple tests, considering that although 4427 comparisons were carried out, only the number of recording electrodes were actually independent (Grave de Peralta Menendez et al., 2004) since the LFP estimated at each voxel is a linear combination of the recording electrodes. Therefore, the probability obtained at each voxel was corrected by multiplying each value by 111 and the significance level was set at p<0.05.

Likewise, in order to account for temporal auto-correlation in the data, only temporally sustained differences over at least 5 consecutive time points (i.e. >10 ms) were retained. This procedure then tells us which voxels differ in their behaviour between expressions at what times. Wherever and whenever significant differences were found, specific post-hoc comparisons were carried out. Since non-conscious processing is reported for emotional facial expressions in general (Morris et al., 2001, Pegna et al., 2005) and fearful expressions in particular (Morris et al., 1999), we sought for differences across these two groups on our post-hoc comparisons. A voxel was considered significant in one of the specific post-hocs if (and only if) all involved pair-wise post-hocs were significant at the 0.05 level. For instance, a voxel was considered to exhibit a fear-specific effect if the responses for fearful faces were different from the responses for neutral, angry and happy faces together. In this way, the probability of spurious findings due to multiplicity of tests was reduced.

The results of the general ANOVA and two examples of post-hoc comparisons are displayed in Fig. 2. Fig. 2A depicts the percentage of voxels showing significant differences (at 0.05) with respect to the total number of voxels estimated in the brain model (4227). Fig. 2B illustrates the results of the post-hoc comparison for responses to

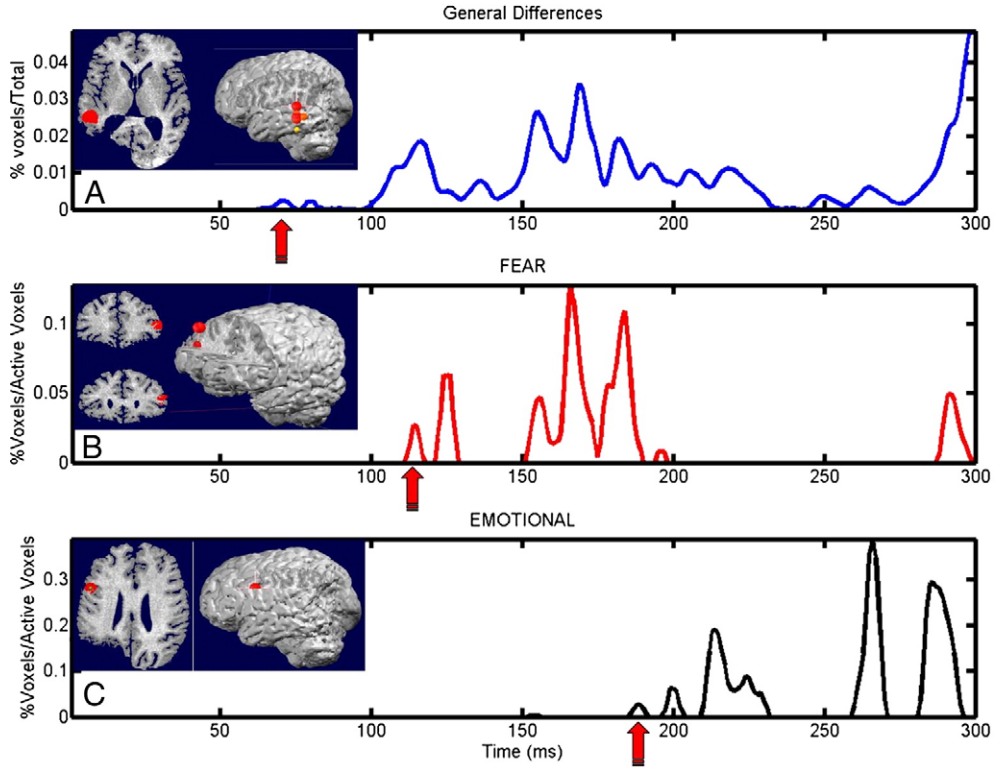

Fig. 2. Spatial localization of earliest differences between face stimuli revealed by non-parametric ANOVA. (A) ratio between the number of voxels showing significant differences between all facial expression at the 0.05 level (adjusted) and the total number of voxels (4227). (B and C) results of the post-hoc analysis for 2 comparisons: Fear (fearful faces are compared to neutral, happy, and angry faces) and Emotion (happy, angry and fearful faces are compared to neutral faces). The plots represent the percentage of pixels showing fear or emotion-specific effects. Only the first 300 ms after stimulus onset is shown.

fearful faces contrasted with those of neutral, happy, and angry faces together. Finally, Fig. 2C shows the post-hoc comparison for emotional faces (happy, angry and fearful) contrasted with the responses induced by neutral ones.

As can be seen in Fig. 2A, there is an initial period where differences were found that were not specific to fear or emotion in general. These early differences last from 70 up to 120 ms, where the first fear-specific responses started. These general differences were located around the Left Middle Temporal areas (Left Inset in Fig. 2A) with maxima at the Superior Temporal Sulcus (STS). This activation spread progressively within the temporal and the parietal lobe in the interval between 70–100 ms post-stimulus. Within this period differences appeared in the inferior temporal cortex and the more anterior part of the middle temporal lobe. At 100 ms post-stimulus presentation, differences were noted in the posterior cingulate cortex with a brief involvement of right frontal lobe (medial and dorsal walls). At around 120 ms most non-specific differences were located in the right prefrontal cortex, the medial superior frontal, the anterior cingulate cortex and the inferior frontal gyrus. During the 100–120 ms interval, the differences were also significant in the STS.

At 120 ms, the non-specific differences at two different locations in the right IFG became specific to fearful faces as revealed by the post-hoc tests. Around 10 ms later, fear-specific differences were also observed in the anterior cingulate, medial superior frontal and right orbito-frontal cortex (OFC). Further differences occurred after 150 ms with a more occipito-temporal distribution, which was bilateral and involved medial and superior temporal areas. Fear-specific differences in the right amygdala appeared in this period with peaks at 156 ms for the fear-specific post-hoc and 205 ms for the emotion-specific post-hoc. At around 150 ms we observed differences in the right IFG between angry and happy faces (see also Fig. 3 for an illustration of these time periods and locations).

Fig. 3 shows the temporal flow of differences in processing for the four facial expressions presented to the subject. For the display, we selected six voxels showing the earliest differences in the temporal lobe (which were not specific for fear or emotion — Fig. 3A, B), and the earliest fear-specific responses at the frontal and orbito-frontal sites (Fig. 3C, D). Fig. 3F illustrates the emotion-specific differences at occipital sites occurring later in time. Finally, a voxel in the right amygdala showing sustained fear-specific differences (from ~150 ms) is also displayed in Fig. 3E. For compatibility with the statistical test performed, the traces illustrated in this figure reflect the mean of the ranks computed over all single trials with yellow boxes indicating periods where the differences between facial expressions reached statistical significance (Kruskal–Wallis, $p<0.05$, corrected). It is worth noting that the ranks were individually scaled between the maximum and minimum for each plot to better expose the temporal spreading of differences from left temporal to right frontal and then to right amygdala and occipital areas. Thus, the absolute size of the differences among plots is not comparable.

The results from this and the previous section depend on the accuracy of the LFP provided by an inverse solution which is far from perfect. However, confidence in the estimates and their spatial resolution can be quantified a posteriori by using the concept of resolution kernels (Grave de Peralta-Menendez and Gonzalez-Andino, 1998). Details and plots of the resolution kernels (RK) for the voxels with significant differences between facial expressions are shown in the *supplementary material*. The RK plots suggest that the inverse solution temporal estimates are correct for all interesting cortical voxels. The RK for the amygdala show that activity arising from the right middle temporal cortex might contaminate the estimates in case of simultaneous activity at both sites. Since no significant differences over the period of interest were observed for these voxels, it is very likely that amygdala estimates are reliable (except for their amplitude). This is guaranteed by the impulse responses of the amygdala

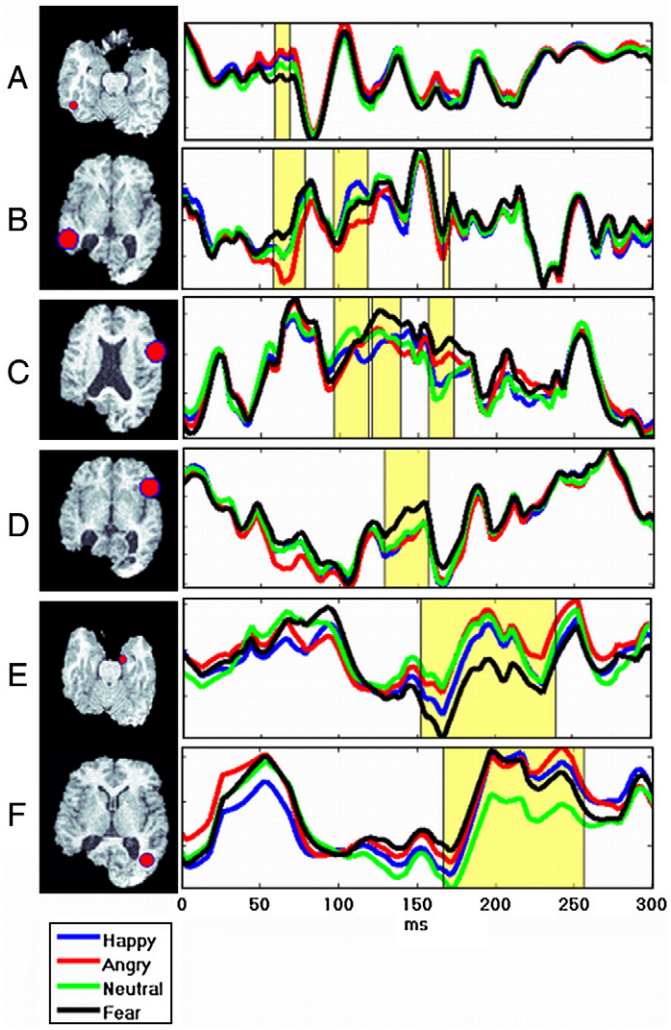

Fig. 3. Temporal evolution of the differences in facial expression processing. Plots of the mean of the ranks computed over all single trials (the statistics for the Kruskall–Wallis) for six selected voxels (red points in leftmost insets). Insets A and B show the earliest non-specific differences at the temporal lobe. Insets C and D show examples of earliest fear-specific responses at the frontal and orbito-frontal areas. Inset F is an example of later emotion-specific differences at occipital areas. A voxel in the right amygdala showing sustained fear-specific differences (E). Yellow boxes signal the intervals where the differences between facial expressions were significant (Kruskal–Wallis, $p<0.05$, corrected). Note that values are normalized to full rank on each subplot to better illustrate the spreading of differences.

voxel that are correctly centered on the target with no influence from voxels outside the right amygdala.

Discussion

Surface EEG activity was measured in a cortically blind patient with affective blindsight while angry, happy, fearful and neutral faces were presented to him. ELECTRA method was applied to these recordings to estimate the electrical activity within the brain. The oscillatory activity resulting from stimulus presentation was further submitted to a multivariate pattern recognition algorithm to identify the face stimuli that consistently modified neural responses.

Consistent changes in oscillatory patterns were found to be induced after presentation of all facial expressions. Changes in spectral amplitudes allowed the MPRA to accurately differentiate the neural activity linked to the presentation of the different categories of faces from ongoing spontaneous activity as well as the activity between categories.

An initial changes in pattern of activity occurred at around 70 ms in the STS/MT region which did not differentiate fearful from other emotions or emotional expressions in general from neutral ones. Differences became specific to fearful faces from approximately 120 ms onwards in the right IFG, followed by the anterior cingulate, right OFC and medial superior frontal gyrus. Beyond 150 ms, a bilateral medial and superior temporal activity was observed along with changes in the right amygdala. Overall differences between emotional and neutral faces occurred at around 205 ms.

Thus, the first responses were found in lateral temporal areas at quite an early time period with amygdala activation taking place at a later stage. Activation of extrastriate areas has previously been noted in two patients with blindsight (Goebel et al., 2001). As mentioned above, two pathways could plausibly mediate blindsight. One possibility is that the temporal region receives its information via the geniculo-extrastriate route. For example, area MT is known to receive a direct geniculate input that bypasses V1 (Sincich et al., 2004) that could be involved in the detection of moving stimuli when V1 is destroyed (Barbur et al., 1993; Rodman et al., 2001). Alternatively, information could reach STS/MT through colliculo-pulvinar projections. In favour of this hypothesis, it has been shown that the persisting visual activity in areas MT and STP after removal of V1 input is eliminated by subsequent destruction of the superior colliculus (Rodman et al., 1990). Similarly, the recovery of detection and localisation behaviour after lesions of V1 is eliminated by lesions of the superior colliculus (Weiskrantz, 1993), at least when the lesions are sustained in adulthood. The limitations of our procedure do not allow us to determine which of the geniculo-extrastriate or colliculo-pulvino-extrastriate pathways lead to STS/MT activation in this patient. Nevertheless, our observation does show an involvement of the extrastriate cortex in the initial processing of face stimuli in patient TN, with amygdala activation kicking in at a slightly later stage.

Activation of the lateral temporal cortex for faces is not novel. In monkeys and humans, the STS is activated by movements of the eyes, mouth, hands and body, suggesting that this area is involved in the analysis of biological motion. STS is also activated by static images of faces (Puce et al., 1996; Chao et al., 1999) and has been suggested more generally to be involved in the processing of dynamic aspects of faces as well as stimuli that signal the actions of other individuals (Allison et al., 2000; Adolphs, 2002). Thus, the initial processing that occurred following the presentation of all facial expressions appears highly plausible.

In line with the first fMRI study of patient TN (Pegna et al., 2005), right amygdala activation was observed for emotional faces. However, this occurred slightly later than the differences seen in orbito-frontal and medial frontal structures. Indeed, the earliest emotion-specific differences were due to fearful faces producing right anterior activation. The right frontal lobe is known to be involved in attention, thus our finding of right frontal activity in response to fearful faces is compatible with the idea that emotional stimuli, while requiring attention, have a competitive advantage over neutral ones in gaining access to processing resources so that they are prioritized (Pessoa et al., 2006). The quick spreading of fear-specific activity into frontal and then into temporal and middle temporal structures including the amygdala, appears to reflect top-down modulation of fearful emotional expressions induced by attention. Interestingly, the time course of amygdala activation is closer to that obtained from intracranial recordings in epileptic patients. Krolak-Salmon et al., (2004) observed responses to fearful faces in the amygdala that began at 200 ms. Although these authors also observed STS/MT and OFC activity, this was apparent after amygdala activity, in disagreement with our findings. On the other hand, another intracranial study investigating OFC activity for emotional faces and scenes (Kawasaki et al., 2001) found neuronal activity 120–160 ms after presentation of negative stimuli, showing that early activation can be expected in anterior brain regions. Consequently, the cerebral regions involved as well as their

times of activation appear plausible, although this particular sequence of events has not been evidenced until now.

The findings reported in this study should be interpreted in the light of the limitations of the technique used to estimate LFP. First the spatial resolution of the estimates cannot be compared with the fine resolution obtained with deep electrode recordings in animals. Second, there is an uncertainty factor in the estimation of the LFP amplitudes. Similar to what happens with the bold response (Logethetis, 1998), it is impossible to obtain accurate estimates of the absolute magnitude of the potentials. Therefore, we are only capable of estimating the sites where differences arise between experimental conditions rather than the strict neural route that is followed during the processing of each stimulus.

The eLFP activity found in the amygdala may be challenged since the amygdala is commonly thought to behave as a closed nucleus. From the physical point of view, the existence of a closed field is only possible under a perfect geometrical arrangement of the simultaneously active sources. This is not the case in the amygdala where the different nuclei play different functional roles and are not likely to be simultaneously active. Surface EEG followed by subsequent intracranial recordings in epileptic patients show that spikes generated in the amygdala can be measured at the surface of the scalp and be retrieved by source localization algorithms (Homma et al., 2001). This implies that activity generated in the amygdala can be volume conducted to distant sites, which is the necessary condition to record such activity at the scalp surface. The *a posteriori* evaluation of the inverse model using resolution kernels (described in more detail in the supplementary material) indicates that the amygdala estimates can be distorted if some voxels at the right temporal cortex are simultaneously active. Since no significant differences between conditions were seen at right temporal areas at times during which amygdala differences were observed, it is reasonable to assume that differences between facial expressions were generated by the amygdala itself.

While our study cannot rule out the existence of the colliculo-pulvino-amygdala pathway, it appears to favour the hypothesis of a geniculo-extrastriate route to explain affective blindsight. This is important since the anatomical and physiological evidence for a pulvino-collicular pathway are tenuous. Indeed, despite considerable research in primates showing a rich connectivity pattern for the amygdala (uni/bidirectional connections with 118 areas) (McDonald, 1998; Ghashghaei and Barbas, 2002; Lisa Stefanacci, 2002), no evidence has been found so far for a direct superior colliculus-amygdala connection. While indirect connections probably exist since direct connections between pulvinar and amygdala have been reported (Jones and Burton, 1976), the existence and (more critically) the functional efficacy of the whole pathway have not been described yet. Further doubts regarding the validity of the pulvino-collicular route are raised by direct electrophysiological recordings in the primate amygdala during passive viewing of monkey faces portraying different emotional expressions (Gothard et al., 2007). Gothard et al., showed that the neuronal firing rates obtained for threatening faces exceed the firing rates elicited by neutral or appeasing facial expressions, but only over a limited period, ranging between 200 and 300 ms after stimulus presentation. Conventional ERP analyses of intracranial LFP recordings in monkeys′ amygdaloid complex reveal two major, early ERP peaks at 70 and 100 ms respectively (Gonzalez et al., in preparation). However, in this latter study, no significant differences were observed during this early period between facial expressions with the earliest significant differences appearing at nearly 170 ms. In line with these observations, intracranial recordings in humans have also suggested that the earliest fear-specific differences in the amygdala occurred from 200 ms onwards (Krolak-Salmon et al., 2004). Hence, neither anatomical nor electrophysiological evidence directly support thus far the hypothesis of a fast, fear-specific sub-cortical route. Finally, the proposal of the pulvino-colliculo-amygdala route based on the observation of co-variations of bold responses between these three structures (Morris et al., 1999) could be subject to an alternate interpretation. Co-variations or correlations in functional responses do not necessarily indicate direct anatomical connectivity amongst the implicated regions. Co-variations in activity might be due to common inputs from another area which do not even need to be simultaneous considering the low temporal resolution of fMRI. Thus, existing evidence in favour of the subcortical pathway is debatable and alternative pathways may explain the phenomenon of blindsight, as also suggested by the present results.

Our results have implications for current models of conscious perception (Tong, 2003). In particular, they argue against a purely hierarchical model of visual awareness where only high-level extrastriate areas are involved in visual awareness. According to the hierarchical model, damage to V1 disrupts the flow of information to high-level areas preventing conscious perception of the stimuli (Zeki and Bartels, 1999). Our results show that information regarding faces reaches higher level areas such as IT or the STS despite V1 destruction. However, this information is insufficient to produce any conscious experience of a visual percept. Thus, information processing within temporal structures alone does not necessarily lead to visual awareness. Our observation of frontal lobe activation for emotional faces also shows that frontal lobe involvement by itself may be insufficient to produce any conscious visual experience.

Conscious visual experience might therefore not rely on any single brain area but could necessitate cooperative interaction between brain regions, including V1, through activation of top-down and bottom-up loops (Lamme, 2001) that were lacking in this patient, consequently leading to the absence of visual awareness. Evidence for recursive processing has been put forward in a study using transcranial magnetic stimulation or TMS (Pascual-Leone and Walsh, 2001). The authors demonstrated that conscious perception of visual motion caused by MT/V5 TMS activation can be abolished when V1 is inactivated within a certain time window. This period is consistent with the time required for recursive activity from MT/V5 to project back to V1 (Pascual-Leone and Walsh, 2001). Similarly, in macaque monkeys, a second volley of activation of neurons in V1 follows the initial afferent response by some 100 ms, but only when the animals respond to the presence of a salient texture (Super et al., 2001).

In agreement with our findings of frontal lobe activation, a number of other studies have evidenced the participation of anterior areas in healthy controls using for example binocular rivalry (Lumer et al., 1998) or masking procedures (Dehaene et al., 2001). Where emotional faces are concerned in healthy participants, awareness is also thought to necessitate the frontal lobes. For example, in a recent fMRI study, Williams et al., (Williams et al., 2006) presented fearful and neutral faces above and below the threshold of awareness. Both conscious and non-conscious presentations of fearful faces produced amygdala and extrastriate activation. Interestingly, conscious perception of the fearful stimuli was characterised by activation of the medial prefrontal cortex (dorsally) and the anterior cingulate cortex, as well as the striate cortex.

Others have emphasized a role for the prefrontal cortex and anterior cingulate in consciousness, pointing to its role in top-down processing. One influential model, that of the global neuronal workspace (Dehaene et al., 1998); see also (Baars, 1997) suggests that for consciousness to appear, the multiple cortical areas processing a stimulus must be simultaneously activated. According to this view, visual awareness would require that information processed in visual sensory areas gain access to a unique global workspace composed of distributed and heavily interconnected neurons including long-range axons which are particularly dense in dorsolateral prefrontal and anterior cingulate areas. Thus, the prefrontal cortex and anterior cingulate would play an essential role by allowing the activation of

multiple regions through top-down activation, thereby giving rise to a "neuronal workspace" which would subsequently give rise to stimulus awareness.

Our findings thus suggest that in this patient, visual awareness failed to occur due to the inefficiency of top-down processing in the absence of striate cortex, although emotional expressions activated frontal regions, extrastriate cortex and amygdala. Interestingly, the pathway giving rise to this activity appears to have transited first through extrastriate cortex, then through anterior areas before activating the amygdala, questioning the existence of a direct colliculo-pulvino-amygdalar route.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2008.09.002.

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