BOLD response to deviant face detection informed by P300 event-related potential parameters: A simultaneous ERP–fMRI study

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Contents lists available at SciVerse ScienceDirect
NeuroImage journal homepage: www.elsevier.com/locate/ynimg

NeuroImage 71 (2013) 92–103

A B S T R A C T

Introduction: Faces are multi-dimensional stimuli conveying parallel information about identity and emotion. Although event-related potential (ERP) studies have disclosed a P300 component in oddball responses to both deviant identity and emotional target faces, it is hypothesized that partially different neural processes should subtend emotion vs. identity within the core network of face processing. In the present study, we used simultaneous ERP–fMRI recordings and ERP-informed analysis of functional magnetic resonance imaging (fMRI) data to evidence the specific neural networks underlying P300 generation in response to different deviant emotional vs. identity faces.

Method: 18 participants were scanned during a visual oddball task in which they had to detect 3 types of deviant faces representing a change in emotion—fear or happiness—or in identity, within a series of frequent neutral ones. Amplitude and latency parameters of the P300 component, recorded for each type of deviant faces, were used to constrain fMRI analyses.

Results: Analysis of fMRI data informed by single-trial parameters of the P300 component disclosed specific activation patterns for fearful, happy and identity deviant faces. For fearful faces, P300 amplitudes were associated with BOLD changes in the left fusiform gyrus whereas latencies were linked to left superior orbito-frontal and right fusiform activations. P300 amplitude modulations for happy deviant faces involved the left posterior cingulate gyrus and right parahippocampal regions whereas P300 latencies related to the right insula and left caudate regions. Finally, identity deviant faces were associated with widespread activities involving cortical and subcortical regions when P300 amplitudes were considered, and P300 latencies were associated with activity in right hippocampal/parahippocampal regions.

Discussion: Our results suggest the existence of differential cerebral functional processes involved in the responses to deviant face stimuli, depending on the quality of the deviance (fear vs. happiness vs. identity).

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Introduction

Faces are multi-dimensional stimuli, providing information about a person’s emotional state, but also conveying distinctive features about this person’s identity (Bruce and Young, 1986). In everyday life, human social interactions are shaped by our ability to recognize facial identities and emotions (e.g., Adolphs, 2001). Hence, the rapid detection of relevant changes in surrounding faces and the execution of an adequate behavioral response is an important human social skill that may, in case of potential threat, also be crucial for survival (e.g., Rolls, 2000).

The brain correlates of the rapid detection of environmental changes have been often assessed using oddball paradigms in event-related potential (ERP) studies. In oddball tasks, participants have to detect as quickly as possible among frequently occurring standard stimuli rarely occurring task-relevant targets (i.e., ‘oddballs’ or ‘deviants’ items), such as for instance simple visual flashes or auditory beeps. This procedure typically evokes the P300 response to deviant target-stimuli, i.e. a late positive parietal component (e.g., Kok, 2001; Polich, 2007 for reviews) thought to reflect general premotor decision-response-related stages, such as memory updating (Polich and Herbst, 2000), contextual integration (Halgren et al., 1998) or cognitive closure mechanism (Verleger, 1988), leading to the decision that an external stimulus matches (or not) with an internal representation of a
specific event (Kok, 2001). This P300 component is known to be followed by a late positive potential (LPP), which is seen as a long positive slow wave occurring after button press, and that is affected by the expected vs. actual action effects (e.g., Adachi et al., 2007). At a higher level of complexity, we previously adapted a “face” variant of the classical oddball design, by using neutral faces as frequent stimuli and faces depicting changes in either identity or emotion as deviant ones. Results disclosed a classical P300 component elicited upon detection of facial deviant stimuli, either due to emotional or to identity changes (Campanella et al., 2002, 2004).

Recognition of facial identity and expressions are clearly distinct tasks, and consequently, an anatomical segregation of functional processes within a face-processing network has been proposed (e.g., Vuilleumier and Pourtois, 2007). Accordingly, functional magnetic resonance imaging (fMRI) studies have highlighted the involvement of the occipital face area (OFA) in the early perception of facial features, along with the involvement of the fusiform face area (FFA) in the perception of temporally invariant aspects of faces such as identity. Moreover, a face-selective region in the posterior superior temporal sulcus (pSTS) has been implicated in the perception of dynamic aspects of faces such as emotions (e.g., Haxby et al., 2000). Hemodynamic and electrophysiological studies in humans also disclosed interactions between brain regions in this face-processing network. For instance, evidence for a functional overlap in the FFA and pSTS, both involved in identity and expression, argues against a complete independence of these processes in these regions (e.g., Fox et al., 2009). Accordingly, modulations of the P300 component are induced by both facial identities and facial emotions (e.g., Campanella et al., 2000, 2002). Therefore, since these interactions might play an important role in the normal development of face processing skills and in some neuropsychiatric disorders such as autism, their functional implications remain to be fully explored (Vuilleumier and Pourtois, 2007).

A main possibility to explore these interactions is to highlight, among the core network of face processing, what are the different neural processes that should be engaged to process identity vs. emotional deviance in order to generate the deviant-facial P300 component. It would therefore be possible to differentiate the brain regions involved in fear vs. happy vs. identity deviance detection, and then tag more precisely which brain regions showed BOLD activation related to specific cognitive processes associated with different face dimensions, and triggering a common P300 component. Given that P300 is a common measure when investigating psychiatric disorders (e.g., Polich and Herbst, 2000), and that psychiatric populations often display altered recognition of facial emotions, but preserved identity processing (e.g., Phillips et al., 2003), understanding which brain regions specifically contribute to the facial P300 generation in healthy participants may potentially be useful to investigate further these clinical populations. Evidence as to generators of the P300 component had been obtained from scalp recordings in patients with brain lesions (Knight et al., 1989; Knight, 1990 for a review) and intracerebral electrical recordings in patients undergoing neurosurgery (Clarke et al., 1999; Halgren et al., 1998; Yamazaki et al., 2000), suggesting that frontal, temporo-parietal, limbic and paralimbic generators are involved in its genesis (Linden et al., 1999). But, even though providing a direct access to generators of P300 waves, this intracranial approach warrants cautious interpretation, as it requires previous damage to the brain and therefore does not necessarily display a correct picture of a normal working brain (see Lachaux et al., 2003 for a review). Alternatively, ERPs are commonly used to probe healthy brain functions but are limited in identifying the underlying sources since current distributions in the brain can give rise to a similar field distribution on the scalp (i.e., the “inverse problem”, Nunez, 1981). It is also well known that fMRI allows overviewing brain activities with good anatomical resolution. However, it was impossible to specify the generators of individual ERP components such as the P300 using fMRI alone, as, challenged by the slow hemodynamic response, the temporal resolution of fMRI is much coarser than the one provided by ERPs (e.g., Calhoun et al., 2006; Yoshiura et al., 1999). Bearing this in mind, it is clear that getting similar information noninvasively with high spatial and time resolution would be of the greatest relevance (e.g., Mulert et al., 2004).

To find the right spatial vs. time trade-off, previous studies have used simultaneous ERP and fMRI measurements during auditory and/or visual oddball tasks in healthy participants, deepening our understanding of the underlying cerebral activity subsuming the P300 generation (e.g., Mulert et al., 2008). To the best of our knowledge however, no study yet has combined ERP and fMRI during an oddball task using faces material. Consequently, we conducted simultaneous ERP and fMRI recordings during a visual target task using faces varying in identity or in emotion, with the aim to identify the neural networks underlying the P300 generation for faces and highlight differential networks subterminating the processing of faces deviant for either identity or emotion.

In the present simultaneous ERP-fMRI study, 18 healthy participants were confronted to a visual oddball task, in which they had to detect 3 types of deviant faces (representing a change in emotion—fear or happiness—or in identity) within a series of frequent neutral faces. Besides the classically observed ERP effects such as a P300 component elicited by deviant faces (e.g., Campanella et al., 2002) and fMRI findings of ventral fronto-parietal network activity associated with target detection (e.g., Corbetta and Shulman, 2002), we hypothesized that an ERP-informed analysis of fMRI data using single-trial P300 parameters will reveal specificities in the neural networks underlying fear vs. happy vs. identity deviance for faces. Indeed, it has been shown that both single-trial P300 amplitude and P300 latency are informative when included in the General Linear Model when analyzing fMRI data, while reaction time has been shown to be less informative in detecting neural activity related to decision making due to the fact that it covers a longer time window than P300 and includes some processes irrelevant to decision making (Warbrick et al., 2009). With this in mind, we used both P300 amplitude and latency parameters to constrain fMRI data, as in such an analysis, measures of ERPs’ amplitude may reflect differences in the intensity of responses whereas measures of latency may inform on processing time duration (Warbrick et al., 2009, 2012).

Methods

Subjects

Eighteen healthy subjects from an academic environment (University of Brussels, Belgium), with no history of neurological or psychiatric disorder, participated in this study approved by the local Ethics committee. Two subjects were later excluded due to technical problems (mean age of the final sample 23.8±2.8 years, n=16). All subjects were right-handed (assessed by Edinburgh scale; Oldfield, 1971; mean score 85.4±24), with normal vision and receiving no medication. As gender has been shown to modulate ERP components recorded to emotional faces in visual oddball task (Campanella et al., 2004, 2012), only female participants were selected. Similarly, as subclinical level of depression (Rossignol et al., 2008), trait-anxiety (Rossignol et al., 2005) and alexithymia (Vermeulen et al., 2008) have been shown to modulate the P300 component recorded during emotional oddball task, we checked that participants displayed normal scores to the 13-item Beck Inventory Depressive Scale (mean score 1.3±1.5; BDI, Beck and Steer, 1987; French version: Collet and Cottraux, 1986), the Spielberger Trait Anxiety Inventory (mean score 45±5.5; STAI-T, Spielberger et al., 1983; French version: Bruchon-Schweitzer and Paullhan, 1993), and the Toronto-Alexithymia Scale (mean score 39.5±10; TAS-20, Bagby et al., 1994; French version: Loas et al., 1996). All subjects signed an informed consent.
Paradigm

The face oddball ERP–fMRI paradigm was adapted from previous ERP studies performed by our group (Campanella et al., 2002, 2004, 2005, 2006, 2010, 2012; Maurage et al., 2007, 2008; Mejias et al., 2005; Rossignol et al., 2005, 2008, 2012; Vermeulen et al., 2008). Deviant faces differed from the standard faces either in emotion (same identity, happy or fearful expression), or in identity (different identity, same gender, and neutral expression) (see Fig. 1). Face categories were chosen in order to elicit specific brain activities devoted to positive emotion (happy), negative emotion (fear), and to a non-emotional facial change (identity), as these processes are well known to be mediated by different brain networks (e.g., Vuilleumier and Pourtois, 2007). Two faces (one male and one female) with neutral, happy and fearful expressions were selected from the standardized set of Ekman and Friesen pictures (1976), as well as two more faces (one male, one female) to be used as neutral deviant identity-targets. During the fMRI session, these stimuli were back projected on a translucent screen positioned 2 m away from participants visible through a mirror fixed to the MRI head coil and located in front of the subject. Images (size 4×5 cm) were displayed using Eevoke software (Eenschede, A.N.T.®). Head stabilization was achieved using head-restraining foam and MR scanner noise was attenuated using earplugs and headphones. The participants underwent 2 fMRI sessions (separated by a pause of maximum 3–4 min), each comprising 510 stimuli, i.e., 408 repeated (regular) and 102 infrequent (20% probability) stimuli (e.g., 408 neutral faces A, 34 deviant happy faces A, 34 deviant fearful faces A, and 34 neutral deviant face B within a run). Deviant faces were interspersed within frequent faces in pseudo-random order with the following conditions: a block always began by at least 3 frequent stimuli, and two deviant stimuli were separated by at least two frequent faces. Each face was presented for 500 ms, separated by a black screen randomly displayed for 500 to 1000 ms to avoid participants’ anticipation and periodic overlap between the timing of the MR-induced artifact and that of evoked responses. The order of the 2 blocks was randomized across the participants, and each block lasted around 11 min. The participants were instructed to indicate as quickly as possible the occurrence of a deviant stimulus by pressing a button with their right forefinger on a commercially available MR-compatible keypad system (fORP; Current Design INC., Philadelphia, USA). The timing of MR image acquisitions and stimuli presentations was synchronized using the clock signal of the MRI scanner; the timing and the stimuli presentations together with response time and error rate were recorded on a personal computer using the Eevoke software (Eenschede, A.N.T.®). The participants were told that speed was important but not at the cost of accuracy (Fig. 1).

**EEG recording and analysis**

Electroencephalogram (EEG) was recorded simultaneously with fMRI data using a 32-channel MR-compatible amplifier (BrainAmp MR Plus, Brain Products GmbH, Gilching, Germany) and a MR-compatible EEG cap (BrainCap MR, EASYCAP GmbH, Herrsching, Germany) with 32 ring-type electrodes. The EEG cap included 30 scalp electrodes that were referenced online to Cz, as well as one electrooculogram (EOG) and one electrocardiogram (ECG) channels. By using electrode paste (Electro-Gel, Electro-Cap International Inc., Ohio, US), electrode-skin impedance was kept below 10 kΩ (including the 5-kΩ resistor built into the electrodes). EEG was digitized at 5000 Hz sampling rate with a 500-nV resolution. Data were transferred outside the scanner room through fiber-optic cables to a personal computer where the EEG system running Vision Recorder software (Brain Products GmbH, Gilching, Germany) was synchronized to the scanner clock; the EEG clock being synchronized to the MRI clock driving the MRI scanner gradient switching system (SyncBox, BrainProduct, Gilching, Germany). The EEG was monitored online with RecView software (Brain Products, Munich, Germany).

For analysis, EEG data were exported to the BrainVision Analyzer software (Brain Products GmbH, Gilching, Germany). Scanner gradient artifacts were first removed using an adaptive average subtraction method (Allen et al., 2000). EEG signals were low-pass filtered at 70 Hz and down-sampled at 500 Hz. Pulse-related artifacts were removed using an algorithm based on a constrained independent component analysis (ICA) method (Leclercq et al., 2011) implemented in the fMRI Artefact rejection and Sleep Scoring Toolbox (FASST; Cyclotron Research Centre, University of Liège, Belgium). Resulting

![Fig. 1. Illustration of the facial oddball design used in the present experiment. Subjects were confronted to neutral stimuli (for a total of 816 stimuli) and three types of rare (probability of 20%) deviant faces (Fear vs. Happy vs. Identity; 68 trials each) they have to detect as quickly as possible.](image-url)
data were then exported to the Statistical Parametric Mapping (SPM8) EEG software (Wellcome Trust Centre for Neuroimaging, London, United-Kingdom) implemented in Matlab 7.8 (Mathworks Inc., Sherbom, MA). Bandpass filtering (0.5–30 Hz) was first applied. Then, epochs corresponding to correct answers (i.e., deviant stimuli for which the subjects pressed the answer key) were extracted from −200 to 800 ms relative to stimulus onset for each deviant faces and corrected by subtracting the response associated to the previous frequent face (e.g., Campanella et al., 2002). DC offset evaluated from −200 to 0 ms was further subtracted. To avoid contamination by eye blinks, epochs with EOG amplitude exceeding 50 μV were rejected. Remaining epochs were then averaged separately for each kind of deviant faces (fear, happy, and identity).

Raster plots of the rare events at electrode Pz, reordered based on single-trial P300 latency were then obtained. Pz electrode was used to analyze P300 as it typically shows maximal response amplitude in visual oddball task (see for instance, Campanella et al., 2002). For each subject, we searched within the P300 classical time window (300–600 ms) for the point with maximum amplitude and retained its amplitude and timing of occurrence, which were considered to be estimators of the single-trial P300 amplitude and latency, respectively. We computed the distributions of these P300 features and rejected the points with an amplitude lying outside the 3 standard deviations (SDs) range from the mean, or with a latency at the edges of the time window (number of rejection range per deviant: 6–39 (mean 20.7) out of 68). Finally, in order to validate the parameters obtained on a trial-by-trial basis, we performed (using S.P.S.S. 17.02/8) paired Student t tests (across subjects) to compare the mean P900 amplitudes and latencies obtained for each deviant, and Pearson correlations of reaction times (RTs) and P300 latencies (but not amplitudes) since they are well-known to be linked (e.g., Folstein and Van Petten, 2008).

fMRI data acquisition and analysis

Data were acquired on a 3 T scanner (Achieva 3 T, Philips Healthcare, Best, the Netherlands) using a T2* sensitive gradient echo (EPI) sequence (TR = 3000 ms, TE = 35 ms, FA 90°, EPI factor 29, bandwidth in phase/ frequency encoding direction 3704Hz/79Hz SENSE acceleration factor 2.9, spectral fat suppression, acquisition voxel size 3 × 3 × 3 mm3, reconstruction size 1.8 × 1.8 × 1 mm3). Forty-two contiguous transverse slices were acquired, covering the whole brain. Two dummy scans were acquired before the actual fMRI images in order to ensure magnetization equilibrium. Anatomical images were obtained using a T1-weighted sagittal 3D TFE sequence (TR 9.9 ms, TE 4.6 ms, TI 1045 ms, flip angle 8°, 112 TFE shots each of 2042 ms applied every 3 s, FOV 238 × 200mm, 160 slices, acquisition voxel size 0.8 × 1.19 × 1 mm3, reconstruction size 0.8 × 0.8 × 1 mm3). The MR scanner was equipped with the Quasar imaging gradients (maximum amplitude and slew rate: 30 mT/m and 200 mT/ms) and an 8 channel SENSE head coil.

Functional MRI data were pre-processed and analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London) implemented in MATLAB 7.8 (Mathworks Inc., Sherbom, MA). Pre-processing included within-session realignment and adjustment for movement related effects, co-registration of functional and anatomical data, spatial normalization into standard stereotactic MNI space and spatial smoothing using a Gaussian kernel of 8 mm full width at half maximum (FWHM).

First, a conventional analysis was conducted on fMRI data alone to assess group level changes in BOLD response associated with the processing of deviant stimulus types. Data were analyzed using a mixed-effects model aimed at showing a stereotypical effect in the population from which the subjects were drawn (Penny and Holmes, 2003). For each subject, a first-level intra-individual analysis aimed at modeling data to partition observed neurophysiological responses into components of interest, confounds and error, using a general linear model (Friston, 2003). The regressors of interest were built using stick functions separately positioned at the onset of each deviant stimulus type (fear, happy, and identity) for which subjects correctly pressed the answer key. Stimuli for which subjects incorrectly pressed the answer key were included in a separate regressor of no interest. Movement parameters derived from realignment of the functional volumes were included as regressors of no interest in the design matrix. Regressors were secondarily convolved with the canonical hemodynamic response function. High-pass filtering was implemented in the matrix design using a cut-off period of 128 s to remove low drift frequencies from the time series. The two fMRI sessions were modeled separately. Effects of interest were then tested by linear contrasts, generating statistical parametric maps [SPM(T)]. Here, the contrasts of interest searched for significant changes associated with each deviant (fear, happy or identity) in both fMRI sessions. Since no inference was made at this fixed effect level of analysis, summary statistic images were thresholded at p < 0.05 (uncorrected). Resulting images were then spatially smoothed (6 mm FWHM Gaussian kernel) and entered in a second-level factorial analysis (fear vs. happy vs. identity) in which subjects were treated as a random effect (RFX). Planned comparisons tested for changes associated with each deviant separately. Additionally, a null conjunction analysis was conducted to identify the brain network commonly activated in deviance detection at the group level. Results were considered significant at p < 0.05 corrected for multiple comparisons in the whole brain volume, unless otherwise stated. Restricted maximum likelihood estimates of variance components were used to allow possible departure from the sphericity assumptions in RFX conjunction analyses (Penny and Holmes, 2003).

Next, we performed combined ERP/fMRI analyses testing for significant changes in hemodynamic responses modulated by electrophysiological responses (i.e. P300 amplitude and P300 latency, separately). For each subject and each design matrix (i.e. P300 amplitude or latency), the first-level intra-individual design matrix comprised three regressors of interest (fear vs. happy vs. identity deviant stimuli), each modulated by the P300 amplitude or latency. Each regressor of interest consisted of stick functions positioned at the onset of each deviant stimulus type for which participants correctly pressed the answer key. Additionally, parametric modulators were defined using the P300 amplitude or latency centered values. Stimuli for which the subjects incorrectly pressed the answer key were included in a separate regressor of no interest. Movement parameters derived from realignment of the functional volumes were included as regressors of no interest. Regressors were secondarily convolved with the canonical hemodynamic response function. High-pass filtering was implemented in the matrix design using a cut-off period of 128 s to remove low drift frequencies from the time series. Serial correlations were estimated with a restricted maximum likelihood (ReML) algorithm using an intrinsic first order autoregressive model during parameter estimation. The two fMRI sessions were modeled separately. Effects of interest were then tested by linear contrasts, generating statistical parametric maps [SPM(T)]. The contrasts of interest searched, for each deviant, for significant changes associated with the modulating parameter. Since no inference was made at this fixed effect level of analysis, summary statistic images were thresholded at p < 0.05 (uncorrected), then spatially smoothed (6 mm FWHM Gaussian kernel) and entered in a second-level analysis in which subjects were treated as a RFX. Planned comparisons separately tested for significant increase in BOLD signal associated with each deviant and P300 parametric modulator (i.e. amplitude or latency). For that purpose, t-contrasts tested for significant changes that were specific to each deviant (fear vs. happy-identity; happy vs. fear-identity; identity vs. fear-happy) when modulated by P300 amplitude or latency. As the modulation is a subtle effect superimposing on the large effect of processing rare events, we did not expect effects of the same amplitude, and lower statistical thresholds (voxel-level p = 0.005 uncorrected, cluster extent ≥ 50) were used as typically done in ERP–fMRI studies (see for instance Bénar et al., 2007; Mulert et al., 2008).
Results

Behavioral data

As participants accurately reported 99.1% of the target stimuli across all conditions (range: 97–100%), only the correct response latencies were statistically analyzed. Fear (489 ms±32) and Happy (491 ms±37) deviant stimuli, which did not statistically differ (t(15) = −1.584; NS), induced faster responses than Identity ones (504 ms±44) (respectively, t(15) = 3.099; p = 0.007 and t(15) = 2.428; p = 0.028).

Conventional ERP analyses

Fig. 2A illustrates that, as commonly observed in visual oddball tasks (e.g., Campanella et al., 2002; Polich, 2007), the P300 showed its maximal amplitude on parietal site to deviant stimuli. This was assessed by an ANOVA using four electrodes (Pz, Cz, P2, and O2) as within-factors, and showing a main effect of electrode (F(3, 45) = 20.086; p<0.001) when the mean amplitudes recorded for the three types of deviants were considered.

Fig. 2B shows the raster plot for the evoked activity recorded at Pz electrode for a typical subject for all target stimuli (68 fear+68 happy+68 identity trials = 204 deviants), reordered by increasing reaction times.

Finally, Fig. 2C illustrates that, on Pz electrode, P300 latency was longer for identity trials (494 ms) as compared to both fearful (448 ms; t(15) = −5.9; p = 0.001) and happy ones (467 ms; t(15) = −2.43; p = 0.028). This matched behavioral results, as longer RTs to identity trials were associated to later P300 latencies (as compared to fear and happy trials) in 13 participants out of 16. This was also reflected in the positive correlation between mean RTs and mean P300 latencies (Pearson correlation: r = 0.310; p = 0.033). Similar analyses conducted on amplitude values failed to disclose significant differences, suggesting that the P300 amplitude was not affected by the type of the deviance (all p>0.100). This congruency between RTs and P300 latencies, classically observed in two-stimuli oddball designs (e.g., see Folstein and van Petten, 2008 for a review), as well as the common higher amplitude displayed by P300 on Pz electrode (see for instance Polich, 2007 for a review), validates the detection of P300 waveforms, allowing the further use of single-trials values.

Conventional fMRI analyses

In line with previous findings in healthy adults (e.g., Ardekani et al., 2002; Corbetta and Shulman, 2002; Kiehl et al., 2005; Stevens et al., 2000), a null conjunction analysis (p = 0.001 uncorrected) revealed that, independently of the type of deviants, target detection involves a distributed neural network mainly encompassing bilateral fronto-parietal areas and the cerebellum (see Table 1 and Fig. 3).

fMRI analyses informed by P300 parameters

Fear vs. Happy–Identity

Table 2 and Fig. 4 illustrate the significant activations that were specific to Fear deviants when the fMRI model was informed by P300 amplitude or latency. The modulation by P300 amplitude yielded significant BOLD signal-related changes for Fear deviants compared with Happy and Identity deviants in the left fusiform gyrus, while modulation by P300 latency elicited significant activations in the right fusiform and the left superior orbito-frontal areas.

Happy vs. Fear–Identity

Table 3 and Fig. 5 illustrate activations that were specific to Happy deviants when the fMRI models were informed by P300 amplitude or latency. Significant increase in BOLD signal was observed for Happy deviants compared with Fear and Identity deviants in the left posterior cingulate cortex and the right parahippocampal region. When latency values of the P300 component were considered, specific activations were disclosed in the right insula and the left caudate nucleus.

Identity vs. Fear–Happy

Table 4 and Fig. 6 illustrate the activations that were specific to Identity deviants when the fMRI models were informed by P300 amplitude or latency. As compared to Fear and Happy deviants, Identity deviants engaged a more widespread cortical network when P300 amplitudes were considered. When the P300 latency was considered, specific activations in the left hippocampus, the left parahippocampal region and the right cerebellum were observed.

Discussion

In the present study we have found that P300 component-informed analyses of fMRI data disclose differential functional cerebral patterns in response to identity vs. emotional deviant faces. Healthy participants were subjected to a visual oddball task using faces displaying changes in emotion or in identity during a combined ERP–fMRI experiment. In line with prior reports, a conventional fMRI approach found activations involving the fronto-parietal network typically engaged in target detection (e.g., Corbetta and Shulman, 2002 for review), and, even inside the scanner, single-trials ERP analyses evidenced the “oddball” commonly observed P300 component (e.g., Polich, 2007). Single-trial parameters of the P300 component suggested that identity trials were less salient than emotional deviants (longer P300 latency as compared with fear and happy deviants), while no difference in amplitude emerged between targets. We expected that, even if the observed scalp recorded P300 component

![Fig. 2](image-url) Part A: Grand-averaged waveforms (mean across the 16 participants and 3 types of deviants) representing the higher amplitude of the P300 component on Pz electrode (red line). Part B: Raster plot observed in a typical subject at Pz electrode illustrating the evoked activity related to each deviant trial (total of 204; 68 by deviants’ types) for the P300 component while black points represented for each trial the associated response time. Part C: Grand-averaged waveforms (mean across the 16 participants) representing the classical P300 component observable for each deviant faces.
is topographically similar across deviants, a specific neural network may be devoted to the specific processing of fear vs. happy vs. identity deviance. With this in mind, P300 parameters were used to constrain fMRI analyses, with the idea that the variability of P300 amplitudes recorded to single trials will reflect differences in the intensity of responses in brain regions specifically devoted to fear or happy or identity deviance, while P300 latency variability will be more related to differences in regions devoted to processing time duration (Warbrick et al., 2009, 2012).

**Detecting a facial change expressing “Fear”**

Several brain imaging studies have shown that when participants are confronted with fearful faces (as compared to positive or neutral ones), distinct temporal neural sequences take place. On the one hand, early modulations of EEG components, such as the visual P1 component (recorded at occipital sites around 100 ms, e.g., Pourtois et al., 2004), as well as greater activation in face-selective areas in the fusiform gyrus (e.g., Vuilleumier et al., 2004) and in limbic regions such as the amygdala (e.g., Morris et al., 1998) and the orbito-frontal cortex (e.g., Kawasaki et al., 2001) have been shown, indicating the existence of a “rapid route” allowing the visual system to prioritize the processing of “threatening stimuli” by capturing attention in order to furnish rapid and adapted responses (see Vuilleumier and Pourtois, 2007 for a review). On the other hand, increased responses to fearful vs. neutral faces have also been observed for later ERP components, such as the P300 (e.g., Campanella et al., 2002). Such sustained responses indicate that fusiform and orbito-frontal regions may be components of a pathway subserving later conscious identification (e.g., Kesler/West et al., 2001). In other words, the existence of both early and late effects related to fearful faces processing have been shown in separate ERP studies, suggesting that fearful face processing may unfold over a large temporal window following the stimulus presentation, even though the neural sources of these different temporal manifestations are still uncertain (Vuilleumier and Pourtois, 2007).

In the present study, by combining ERP and fMRI, we showed that the fusiform gyrus was specifically activated when P300 parameters constrained the fMRI analysis for “fear-deviant” stimuli. More precisely, the left fusiform gyrus seems to be specifically related to the variability in the amplitude of the single-trial P300, while its right counterpart seems to be involved in speed of processing. The role of the fusiform gyrus in face identification is well-known (e.g., Kanwisher et al., 1997), so that later modulations of the P300 component induced by

![Brain areas activated for each deviant faces (Red: Fear deviants, Green: Happy deviants, Blue: Identity deviants, white: brain areas activated by all deviants).](image)

![Brain areas commonly activated during infrequent target detection (null conjunction analysis).](image)

<table>
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<tr>
<th>MNI coordinates</th>
<th>Anatomical area</th>
<th>K (cluster extent)</th>
<th>Peak Z score</th>
<th>Significance</th>
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</table>

**Table 1**

Brain areas activated during target detection (null conjunction analysis). Coordinates x, y, and z (mm) are given in Montreal Neurological Institute (MNI) standard stereotactic space. All results are significant at the voxel level p < 0.001 uncorrected, cluster extent ≥ 50 voxels.
the processing of fearful faces may be explained through the maintenance of a sustained activity in the face fusiform region in order to keep an enhanced level of attention (probably triggered through the amygdala) towards this stimuli and to prioritize their processing. The distinct pattern of activation between the right and left fusiform gyri, as highlighted by P300 amplitude and latency parameters, potentially suggests the existence of a functional specialization difference between right and left fusiform gyri: the left part being more involved in the intensity of processing, and the right part, being more related to the speed of processing.

Moreover, we also found a specific activation of the left superior orbitofrontal cortex (OFC) when modulation by P300 latency parameters was considered. This is consistent with studies showing an increased activation in OFC during negative emotional stimulations, while positive stimulations led to decreased activity in this region (e.g., Northoff et al., 2000). Its main role seems to be related to a “basic valuation mechanism”, as encoding the value of a stimulus as it is perceived may help to select or avoid high-reward value vs. low-aversive ones for the future (O’Doherty, 2007). Accordingly, orbitofrontal activity has been implicated both in the processing of facial expressions and the regulation of experimentally induced physiological responses (e.g., Critchley, 2009), as the recognition of emotion has been proposed to include (even if unconsciously) the retrieval of pertinent past states of the organism’s body (e.g., Adolphs et al., 1996).

Table 2
Brain areas specifically devoted to the detection of Fear deviant faces. Latency and amplitude values of the P3b component were respectively used as regressors. Coordinates x, y, and z (mm) are given in Montreal Neurological Institute (MNI) standard stereotactic space. All results are significant at the voxel level p<0.005 uncorrected, for a least a cluster of 50 voxels.

<table>
<thead>
<tr>
<th>Amplitudes P3b Fear vs. Happy-Identity</th>
<th>Anatomical area</th>
<th>K (cluster extent)</th>
<th>Peak Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 − 48 − 18</td>
<td>Left fusiform</td>
<td>62</td>
<td>2.99</td>
</tr>
<tr>
<td>− 26 − 48 − 18</td>
<td>Left posterior cingulate</td>
<td>89</td>
<td>3.60</td>
</tr>
<tr>
<td>Latencies P3b Fear vs. Happy-Identity</td>
<td>Anatomical area</td>
<td>K (cluster extent)</td>
<td>Peak Z score</td>
</tr>
<tr>
<td>Activations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− 10 − 26 − 18</td>
<td>Left sup orbito-frontal</td>
<td>265</td>
<td>3.40</td>
</tr>
<tr>
<td>− 18 − 26 − 2</td>
<td>Left caudate</td>
<td>60</td>
<td>3.14</td>
</tr>
</tbody>
</table>

Fig. 4. The left superior orbito-frontal cortex and the left fusiform area were specifically activated for the Fear deviant stimuli, when latency and amplitude values of P300 were respectively considered.

Table 3
Brain areas specifically devoted to the detection of Happy deviant faces. Latency and amplitude values of P3b component were respectively used as regressors. Coordinates x, y, and z (mm) are given in Montreal Neurological Institute (MNI) standard stereotactic space. All results are significant at the voxel level p<0.005 uncorrected, for a least a cluster of 50 voxels.

<table>
<thead>
<tr>
<th>Amplitudes P3b Happy vs. Fear-Identity</th>
<th>Anatomical area</th>
<th>K (cluster extent)</th>
<th>Peak Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− 10 − 46 − 8</td>
<td>Left posterior cingulate</td>
<td>89</td>
<td>3.60</td>
</tr>
<tr>
<td>− 32 − 16 − 26</td>
<td>Right parahippocampal</td>
<td>54</td>
<td>2.97</td>
</tr>
<tr>
<td>Latencies P3b Happy vs. Fear-Identity</td>
<td>Anatomical area</td>
<td>K (cluster extent)</td>
<td>Peak Z score</td>
</tr>
<tr>
<td>Activations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− 36 − 16 − 26</td>
<td>Right insula</td>
<td>85</td>
<td>3.60</td>
</tr>
<tr>
<td>− 18 − 26 − 2</td>
<td>Left caudate</td>
<td>60</td>
<td>3.14</td>
</tr>
</tbody>
</table>

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Detecting a facial change expressing “Happiness”

Compared to the study of negative emotions such as fear, the neurobiology of positive emotional processes has only recently received more scientific attention (Burgdorf and Panksepp, 2006). The main reason for this recent interest is probably that, along with being happier, people who experience high subjective well-being seem to have better health outcomes and longevity (Fredrickson, 2004). Therefore, several studies have tried to define the brain regions specifically involved in the processing of happy faces as compared to other types of facial emotions (e.g., Winston et al., 2003). It is well known that happiness perception on faces involve partially distinct system subsets of cortical and subcortical regions (e.g., Adolphs et al., 1996), as there are now convergent evidences to suggest that various regions of the limbic system, including especially ventral striatal dopamine systems, are implemented in anticipatory positive affective state (e.g., Burgdorf and Panksepp, 2006 for a review). Besides, a mood-relevant effect was observed with a reduced P300 amplitude for control (but not depressed) participants for previously viewed happy faces and words (collapsed together), interpreted as a positivity bias in controls that is not present in depressed participants (Deldin et al., 2001). The present study links the modulation of neuronal activity by P300 component (evoked when healthy participants had to detect deviant happy faces from a train of neutral ones) to the activation of a specific neural network.

Specific P300-related activations evoked by deviant happy faces were found in the right insula and the left cingulate cortex when latency and amplitude values of P300 were respectively considered.

Fig. 5. The right insula and the left posterior cingulate cortex were specifically activated for the Happy deviant stimuli, when latency and amplitude values of P300 were respectively considered.

### Table 4

Brain areas specifically devoted to the detection of Identity deviant faces. Latency and amplitude values of P3b components were respectively used as regressors. Coordinates x, y, and z (mm) are given in Montreal Neurological Institute (MNI) standard stereotactic space. All results are significant at the voxel level p<0.005 uncorrected, for a least a cluster of 50 voxels.

<table>
<thead>
<tr>
<th>Amplitudes P3b Identity vs. Fear-Happy</th>
<th>Anatomical area</th>
<th>K (cluster extent)</th>
<th>Peak Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNI coordinates</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>16 - 26 - 18</td>
<td>Left sup orbito-frontal</td>
<td>213</td>
<td>3.88</td>
</tr>
<tr>
<td>- 40 - 24</td>
<td>Left sup temporal pole</td>
<td>524</td>
<td>3.78</td>
</tr>
<tr>
<td>- 50 22 30</td>
<td>Left inf frontal</td>
<td>170</td>
<td>3.76</td>
</tr>
<tr>
<td>58 - 48 - 26</td>
<td>Right inf temporal</td>
<td>90</td>
<td>3.74</td>
</tr>
<tr>
<td>- 28 22 12</td>
<td>Left insula</td>
<td>203</td>
<td>3.62</td>
</tr>
<tr>
<td>34 - 2 14</td>
<td>Right insula</td>
<td>88</td>
<td>3.59</td>
</tr>
<tr>
<td>36 58 - 14</td>
<td>Right mid orbito-frontal</td>
<td>228</td>
<td>3.50</td>
</tr>
<tr>
<td>- 28 2 46</td>
<td>Left precentral</td>
<td>153</td>
<td>3.46</td>
</tr>
<tr>
<td>50 - 38 42</td>
<td>Right supramarginal</td>
<td>421</td>
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<tr>
<td>26 - 96 - 8</td>
<td>Right inf occipital</td>
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<td>3.20</td>
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<tr>
<td>36 - 50 58</td>
<td>Right sup parietal</td>
<td>81</td>
<td>3.11</td>
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<tr>
<td>54 - 56 10</td>
<td>Right inf temporal</td>
<td>111</td>
<td>3.08</td>
</tr>
<tr>
<td>20 - 2 42</td>
<td>Right mid cingulum</td>
<td>87</td>
<td>3.08</td>
</tr>
<tr>
<td>32 - 4 64</td>
<td>Right sup frontal</td>
<td>91</td>
<td>2.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Latencies P3b Identity vs. Fear-Happy</th>
<th>Anatomical area</th>
<th>K (cluster extent)</th>
<th>Peak Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNI Coordinates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 - 28 - 12</td>
<td>Right hippocampus</td>
<td>54</td>
<td>3.59</td>
</tr>
<tr>
<td>6 - 18 - 30</td>
<td>Right parahippocampal</td>
<td>141</td>
<td>3.55</td>
</tr>
</tbody>
</table>
to be related to the intensity of deviant faces’ processing. Moreover, besides these “memory-circuitry” modulations, P300 parameters related to the speed of processing also evoked specific activations, involving the right insula and the left caudate nucleus. The insula is known to be involved in the monitoring of the ongoing internal mental state in order to reach a “conscious” representation of interoceptive information (e.g., Chen et al., 2009). In other words, insula is known to constitute an important neural basis for subjective evaluation of one’s own condition (“how you feel”; e.g., Chen et al., 2009), as well as for empathy to emotional other state (e.g., Bird et al., 2010) and subjective emotional experience on the basis of somatic manifestations (e.g., Ortigue et al., 2007). In this view, it is suggested that the appraisal of a happy emotion in somebody else’s face seems to invoke a “mirror-like” introspective evaluation. This mechanism, participating to the emotion recognition process, may explain how participants observing happy faces may feel mildly happy, through an experiential aspect of internally generated emotion (Phan et al., 2002 for a review). Therefore, it would be interesting in further combined ERP–fMRI studies using emotional faces to ask participants for subjective ratings about own feelings when confronted with specific emotional faces, in order to investigate whether activation of insula is correlated with subjective feelings of the participants. Such subjective ratings were not obtained in this study. Finally, an activation of the left caudate nucleus was also evidenced when modulations by P300 latencies were considered. In a recent paper of Hassel et al. (2009), it was shown that bipolar patients displayed significantly decreased caudate activity in response to intense and mild happy faces relative to neutral ones. In agreement with the idea that the caudate nucleus appears to be sensitive to the evaluation (positive vs. negative) of an action (Tricomi et al., 2004), the authors suggested that bipolar patients saw “positive faces” as less rewarding than controls did (Hassel et al., 2009). We suggest here that the left caudate activation refers to a positive evaluation of the observed happy faces (as compared to fearful and identity deviant trials).

Detecting a facial change in “Identity”

The recognition of facial identity and expression are clearly distinct tasks, so that an anatomic segregation of processing within a face-processing network has been proposed (e.g., Haxby et al., 2000). Accordingly, specific activations for identity-trials (as compared to happy and fearful ones) were displayed when modulations by P300 parameters were used to inform fMRI analyses. Specific P300 latencies-related activations in the right parahippocampal/hippocampus areas are consistent with the role of these regions in episodic memory, i.e. in the encoding of a new item (a new unfamiliar neutral face) and its context of appearance. By associating item and context information, these medial temporal lobe regions support familiarity and recollection processes (Diana et al., 2007 for a review; Joassin et al., 2011). Besides, P300 amplitude values recorded to identity trials yielded a specific sustained activity in inferior occipital and extended temporal regions, which may be interpreted as reflecting a sustained visual configural analysis of the deviant-identity face (e.g., Fox et al., 2009), serving as a support for above mentioned mnemonic processes. Moreover, right supramarginal and superior parietal activations were also displayed. A recent study has linked their activations to the greater attention to perceptual evidence that is required to perform a task (Vallesi et al., 2011). This may be consistent with the fact that in the present study identity-trials are more difficult (less salient) to detect than happy and fearful deviant stimuli, as participants implied longer processing time (higher RTs) to reach an accurate performance. Finally, besides precentral activations clearly linked to motor response (e.g., Bénar et al., 2007), widespread areas in the frontal pole as well as bilateral insula and mid-cingulate motor zones seem to modulate the P300 component when amplitude values are considered. The insular cortex has important connections to the frontal, the parietal, the temporal and the cingulate gyri (Augustine, 1996; Mesulam and Mufson, 1982). If insula has been associated with interoception (see the
Experimental limitations

We have presented here the first simultaneous EEG–fMRI study on face identity and emotions processing. Besides the need for an independent replication of these results, possible limitations should also be considered. First, we focused here on ERP modulations for faces, representing a subtle effect superimposing on the larger effect of processing rare events. Consequently and in line with prior studies, we used uncorrected statistical thresholds values (p = 0.005 uncorrected) which combined with a relatively small sample (n = 16) may question the generalizability of our results. This concern might be avoided in further experiments by increasing the number of stimuli in experimental conditions (although this will increase the duration of the experiment, which is not advisable in experimental or clinical settings) or by increasing sample size. Second, we compared in the present study face deviance concerning emotions (happy, fear) and identity. This has two main implications for the present results: (1) the observed cortical differences may result from an emotional vs. neutral comparison as well as from an emotional vs. recognition task: further studies should disentangle between these respective contributions; and (2) as suggested by reaction times and P300 latencies, the processing of emotional stimuli is facilitated as compared to identity trials: in this view, the specific activations we reported may be related to this “complexity or saliency effect”, and be therefore independent of emotional vs. identity deviance. Third, we choose to focus in the present study on the P300 component. Other components modulated by facial dimensions may have been envisaged, such as the visual P1 apparently highly sensitive to threatening content (e.g., Pourtois et al., 2005), the occipitotemporal N170 particularly sensitive to structural face encoding (e.g., Bentin and Deouell, 2000), the visual mismatch negativity (MMN) which indexed the automatic processing of minor changes in the physical features of stimuli (e.g., Clery et al., 2012), or the bipolar orienting complex “N2b/P3a” specifically involved in novelty detection (e.g., Crottaz-Herbette and Menon, 2006). Further simultaneous ERP–fMRI studies using faces should use an experimental set-up allowing these components and variables of interest to be investigated. Such approach should allow relating specific neural networks to specific ERP components along the information processing stream (for instance, from general visual perception (P100) to specific face structural encoding (N170) to facial-task-related decision (P300)), and then, inferring the timing of brain activations related to the studied face processing. Also, it would be useful to include a higher range of facial expressions in order to disentangle arousal effect (high vs. low) from valence effect (positive vs. negative), as these dimensions have been shown to affect specific ERP components (early components for valence vs. later ones for arousal: see Olofsson et al., 2008 for a review). Finally, gender has been shown to modulate P300 component in emotional oddball tasks (Campanella et al., 2004, 2012), eventually leading us to include only female participants in our sample. Consequently, it is unknown whether our results would apply in a male population. Further ERP–fMRI experiments should test this emotional gender effect.

Conclusions and perspectives

The use of simultaneous EEG–fMRI can be seen as a bridge between the well-established field of evoked cognitive potentials and the fast-growing field of fMRI (Bénar et al., 2007). To the best of our knowledge, we used for the first time in a visual oddball task faces differing in emotion or identity, and linked fluctuations of the well-known P300 component parameters with regional variations in the fMRI signal. Our results showed both specific and widespread activations associated with P300 parameters generated by specific facial changes (in identity or in emotion—fear vs. happy—). In other words, we showed that, even if facial deviance in emotion or in identity evoked a similar P300 in ERP recordings (e.g., Campanella et al., 2002), informing fMRI analysis with P300 ERP components (amplitude and latency) demonstrate that specific brain regions are responsive to amplitude or latency variations of this P300 component by showing specific modulation of BOLD activity. In particular, fear engaged some nodes of face and limbic networks; happiness some nodes of memory recollection and limbic networks; and identity widespread activities including cortical and subcortical regions, with a specific network devoted to episodic memory.

Even if preliminary, our data indicate that the elucidation of brain mechanisms underlying deviance detection for faces is possible through a combined ERP/fMRI approach. We believe that further clinical application of this simultaneous experimental set-up may be appropriate, notably in psychiatric populations often displaying deficits in facial emotion recognition (e.g., Phillips et al., 2003).

Acknowledgments

Salvatore Campanella is a Research Associate at the Fund of Scientific Research (FRS-FNRS, Belgium). Mathieu Bourguignon benefits of a research grant from the FRIA (FRS-FNRS, Belgium). Xavier De Tiège is “Clinicien Chercheur Spécialiste” at the Fund of Scientific Research (FRS-FNRS, Belgium). This study was also financially supported by the Fund of Scientific Research (Research Grant CC-1.5041.11, FRS-FNRS, Belgium).

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nion, San Antonio.


