From methods to meaning in functional neuroimaging
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Detecting fearful and neutral faces:
BOLD latency differences in amygdala-hippocampal junction

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(In preparation)
Abstract

Evolutionary survival and procreation are augmented if an individual organism quickly detects environmental threats and rapidly initiates defensive behavioral reactions. Thus, facial emotions signaling a potential threat, e.g. fear or anger, should be perceived rapidly and automatically, possibly through a subcortical processing route which includes the amygdala. Using event-related functional magnetic resonance imaging (fMRI) we investigated the time-course of the response in the amygdala to neutral and fearful faces, which appear from dynamically decreasing random visual noise. We aimed to detect differences of the amygdala response between fearful and neutral faces by estimating the latency of the blood oxygenation level dependent (BOLD) response. We found that bilateral amygdala-hippocampal junction activation occurred earlier for fearful than for neutral faces. Our findings support the theory of a dual route architecture in which the subcortical thalamic-hippocampal-amygdala route serves fast preconscious threat perception.

Introduction

An essential feature for evolutionary survival is to rapidly acknowledge and respond to a potential threatening object, thereby improving the chances of procreation of an individual. Facial expressions are a particularly salient stimulus that directly conveys information about the potential harmfulness of the environment. For the perception of threatening information the brain sustains a dual route architecture consisting of a slow cortical and a fast subcortical route including the amygdala (Le Doux, 1996).

The participation of the amygdala in conscious perception of threat-related stimuli through the cortical route has been demonstrated in early functional neuroimaging (Morris et al., 1996; Breiter et al., 1996). This pathway routes information through primary visual cortex and inferior temporal cortex (IT) to the amygdala and is important in the evaluation of the emotional salience of the information (Davis and Whalen, 2001; Pessoa et al., 2002; Sander et al., 2003). These results obtained from normal subjects are accompanied by data from psychiatric (Rauch et al., 2000; Sheline et al., 2001) and brain-damaged patients (de Gelder et al., 1999; Kubota et al., 2000; Vuilleumier et al., 2002). The latter have shown that processing and recognition of negative facial emotions, especially fear, is impaired in case of damage to the human amygdala as reported in several patient studies (Adolphs et al., 1994; Calder et al., 1996; Young et al., 1996; Broks et al., 1998; Adolphs et al., 1999; Peper et al., 2001).

Using antero- and retrograde tracer techniques animal studies have laid down structures involved in the subcortical route to the amygdala (LeDoux et al., 1984;
LeDoux and Farb, 1990). This route relays visual information directly through the thalamus bypassing visual cortex (LeDoux et al., 1984; Le Doux, 1996; LeDoux, 2000), and provides the hippocampus (Liddell et al., 2004) and the amygdala with rapid and coarse inputs to allow for a rapid and subconscious assessment (Le Doux, 1996; Morris et al., 1999; Pasley et al., 2004). The amygdala can then trigger defensive behavioral reactions through amygdala-fugal projections (Davis and Lee, 1998; Lang et al., 1998).

Several techniques exist that confine the processing of visual stimuli in humans to the subconscious domain. Backward masking (Esteves and Ohman, 1993) involves the brief, e.g. 30 ms, presentation of an (emotional) target stimulus, immediately followed by a masking stimulus for a slightly longer duration, e.g., 170 ms, thus precluding the target from conscious perception. This technique has been widely employed in psychophysiological (e.g. Esteves et al., 1994; Dimberg et al., 2000), neuroimaging (Morris et al., 1998a; Whalen et al., 1998; Phillips et al., 2004) and lesion studies (e.g. Kubota et al., 2000; Gläscher and Adolphs, 2003) and the findings point toward a robust amygdala involvement during subconscious processing of emotional stimuli. Binocular rivalry has also been employed as a technique to study subconscious processing of facial stimuli in the amygdala (Pasley et al., 2004; Williams et al., 2004). A potential limitation of this technique is the difficulty to assess the level processing (subconscious or conscious) online rather than in post-experimental questionnaires (see debates in: Lovibond and Shanks, 2002; Wiens and Ohman, 2002; Manns et al., 2002; Shanks and Lovibond, 2002).

Degradation of visual stimuli provides another viable way of studying subconscious processing by the amygdala. This technique is especially suitable in the context of a subcortical route to the amygdala because only coarse stimulus representations are conveyed through this route (Le Doux, 1996). Furthermore, different degrees of stimulus degradation allow accurate assessment of the perceptual threshold for conscious perception (Gold et al., 1999; James et al., 2000; Kleinschmidt et al., 2002). Recently, functional magnetic resonance imaging (fMRI) studies reported preferential amygdala (Vuilleumier et al., 2003) and fusiform gyrus activation (Winston et al., 2003) to degraded pictures of facial expressions which only exhibit a low spatial frequency range, lending support for the hypothesis.

In the previous chapter the neural correlates of robust perception under degraded stimulus conditions were assessed by fMRI. Processing of emotionally salient information was found to suffer less from a coarse visual representation, i.e. is more robust, than non-emotional salient information when appearing from dynamically decreasing random visual noise. More specifically, the behavioral data showed that fearful faces were perceived earlier than neutral faces, suggesting that biologically salient, e.g. threat-related, stimuli exhibit a perceptual advantage. In addition, the fMRI data revealed that the amygdala exhibited a significant
perception related response for faces, as compared to houses that was further enhanced for fearful faces, as compared to neutral faces.

The goal of the present study was to explore the neurobiological basis for this perceptual advantage. We hypothesized that, when a stimulus is appearing from dynamically decreasing random visual noise, activation in the amygdala is (i) present before conscious pop-out, and (ii) occurs earlier for fearful visual information, i.e. fearful faces, than for neutral visual information, i.e. neutral faces. Therefore we investigated the temporal dynamics of fear perception by exploring the latency of the event-related blood oxygenation level dependent (BOLD) response (Henson et al., 2002) in the amygdala for fearful faces as compared to neutral faces.

**Methods**

**Subjects**

Seventeen normal subjects participated in the study (approved by the local ethics committee), after they gave their written informed consent. One subject was excluded due to medication use and one subject was excluded due to excessive movement during the scanning sessions. The data of the remaining 15 subjects (seven male, eight female) with a mean age of 25.8 years (range 18-36 years) were analyzed.

**Stimuli and procedure**

Neutral face and fearful face images were drawn from the Ekman series of facial affect (Ekman and Friesen, 1976; Ekman, 1982). House pictures were taken from standard north European houses of light color and were adjusted to remove additional distracting information, like trees or fences. All pictures were grayscale pictures. The images were cropped so that house height and width was approximately the same as face height and width.

We used Fourier methods (Rainer et al., 2001) to generate a sequence of 80 pictures with increasing image information. This frequency domain method ensures that all stimuli for all conditions were matched for luminance, contrast, brightness and spatial frequency information. For decreasing noise levels, we linearly interpolated between the noise image and the original image information. Images of the three conditions (neutral faces, fearful faces and houses) had dimensions of 640 by 480 pixels and were presented within the visual focus of 5 degrees. One run of pictures, from noise to the original image, consisted of 80 pictures. These were dynamically presented, for 490 ms each, to obtain a gradual smooth rebuilding, i.e., the image appeared gradually from dynamically decreasing random visual noise.
Methods

The stimuli initially contained only noise, but gradually a neutral face, a fearful face or a house picture emerged from the noise. During the presentation of the picture sequence a dot at the center of the screen, serving as point of fixation, infrequently changed its color, which had to be acknowledged by the volunteer by a button press. This additional task was introduced to keep attention and motor cortex activation at a constant level throughout each run. At a certain point in the stimulus sequence (approximately after two-thirds of the sequence on average) the subjects became aware of a house or a face appearing 'out of the noise', which they had to indicate with an additional button press indicating the perceptual pop-out (see for more detail chapter 7 and its accompanying supplementary material on page 115).

Image acquisition

The neural correlates of the perceptual pop-out were investigated using blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI). Magnetic resonance scanning was performed on a 1.5 Tesla magnetic resonance imaging (MRI) system (Siemens vision, Erlangen, Germany). Six sessions were obtained with a total of 271 (one subject 270) fMRI scans (25 axial slices, 3 mm thick slices each, 1 mm gap). A gradient echo, i.e. echo-planar imaging (EPI), T2* sensitive sequence was used to acquire these scans (TR 2.1 s, echo-time 40 ms, flip angle 90 degrees, matrix 64 x 64), in descending order. The head was positioned to include the amygdala in a standard head coil using foam pads. To minimize motion artifacts, the head of the subject was fixated by vacuum cushions. The first five volumes in each session were discarded to allow for T1 equilibration effects.

fMRI data pre-processing

Statistical parametric mapping (SPM99) was used for spatial transformation (re-alignment, normalization and smoothing) of the data (Friston et al., 1995b). FMRI time series were realigned to the mean, to correct for intra-subject's head movement. Following, using 7x8x7 non-linear basis functions and heavy regularization during the normalization procedure, all the scans were transformed into the standard stereotaxic Montreal neurological institute (MNI) space (Evans et al., 1993; Friston et al., 1995a). Subsequently, the data were spatially smoothed using an isotropic Gaussian kernel of 11 mm FWHM (Full width at half maximum) to compensate for residual variability in anatomical localization between subjects and to allow for the application of Gaussian random field theory to address corrected statistical inference (Worsley, 1994). The final voxel size was 3x3x3 mm. A high-pass frequency filter (cut-off 120s) and corrections for auto-correlation between scans was applied to the time-series.
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Figure 8.1: Stimuli examples around the moment of pop-out. The moment of pop-out as indicated with a button-press by the subjects, who perceive the stimulus sequence of 80 pictures in a movie-like manner. At the top of the figure four stimulus examples are given. For two faces the pictures of the scrambled neutral and fearful expressions, around the moment of pop-out (on average 49.12 (± 0.64 s.e.m.) and 48.59 (± 0.76 s.e.m.), respectively), are displayed. Additionally, the fully scrambled picture (picture 1) and the non-scrambled version are shown (picture 80).

Statistical analysis

In the sequence of 80 pictures the picture number at the moment of pop-out button press was obtained for neutral faces and fearful faces (see figure 8.1). These behavioral data were statistically tested for significant differences in picture perception between neutral and fearful face using a one-sided t test.

The subject specific general linear model (GLM) (Friston et al., 1995b) included ten regressors (see also chapter 7). To explain variance which is induced by visual stimulation or button presses, to color changes of the fixation dot, a block regressor (convolved with an HRF and starting at the first picture and ending at the last picture) was included. Furthermore, the fMRI data was analyzed with respect to the pop-out, i.e., the data analysis was time-locked to the pop-out. We included three block regressors (of variable duration) resembling the full perception of a neutral face, fearful face and a house, from time of pop-out until the end of the trial. Furthermore, we convolved the onset of conscious perception for each individual stimulus, i.e. the perceptual pop-out, as determined by the subject and trial specific button presses, with a canonical hemodynamic response function (HRF) (Friston et al., 1998) and entered it as a regressor in the design matrix. Additionally, the temporal derivative (TD) was included to calculate latency differences (Henson et al., 2002, see below). The stimulus and pop-out dependent HRF and TD incorporate six regressors in total in the design matrix. Because we tailored the design
Methods

matrix to the perceptual pop-out for each stimulus and subject separately, we are able to compare latency differences regardless of the appearance of the pop-out within the trial.

Latency estimation

In addition, SPM2 (www.fil.ion.ucl.ac.uk/spm/spm2.html) was used for the group analysis (random effects model) to allow for an appropriate non-sphericity correction (Glaser et al., 2002). Parameter estimate (beta) images were obtained for full perception, pop-out, and time-derivative for all three conditions (collapsing across sessions, within subjects) and used at the second level analysis and latency estimation. To explore early amygdala activation, latency effects were calculated on the basis of the method as presented by Henson and colleagues (Henson et al., 2002) for both neutral and fearful faces. In this framework, the assessment of latency differences from derivative parameters is dependent on the canonical HRF parameter estimates, in both sign and magnitude. We used the (approximately) sigmoidal logistic function $2C/(1 + \exp(D(\beta_2\beta_1))) - C$ (where $C = 1.78$, $D = 3.10$) to obtain the latency of the BOLD response in seconds at each voxel. $\beta_1$ is the parameter estimate for the HRF, $\beta_2$ is the parameter estimate for the TD. Positive values of $\beta_2$ indicate an earlier hemodynamic response and negative $\beta_2$ a later hemodynamic response (for more details, see Henson et al., 2002). Using this equation, timing values are not contaminated by amplitude differences of the BOLD response. By modeling the condition dependent moment of conscious perception, i.e. pop-out, with the HRF and its TD, we were able to assess the latency of the pop-out BOLD response relative to the pop-out, i.e. independent of when the pop-out appeared for each subject within each trial.

Latency maps, with respect to the moment of pop-out, were calculated for both neutral and fearful faces, for each subject separately, and smoothed with an 11-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel. In SPM, these latency maps were entered into a paired $t$ test to test for significant latency differences between fearful versus neutral face stimuli across subjects. We restricted this comparison to the relevant voxels by masking the $t$ test with the result of a second level differential contrast, which compared the pop-out effects of all faces versus houses. Considering that latency analyses are limited to the face stimuli and bilateral amygdala activations, due to our specific a priori hypotheses, we used an uncorrected threshold of $p < 0.001$ during the creation of the mask. This provides us with amygdala regions in which the canonical HRF explained a significant amount of variance due to face stimuli (note that latency calculations are dependent on the existence of the BOLD response). In the latency SPMs, correction for multiple comparisons was performed for the amygdala volume (using a sphere, centered at the peak activation voxel, with a volume of 3054 mm$^3$ (Filipek et al., 1994)).
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Table 8.1: Statistical results of the behavioral data for the moment of pop-out in picture-number.

<table>
<thead>
<tr>
<th>Data</th>
<th>mean (pic)</th>
<th>s.e.m. (pic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral face</td>
<td>49.12</td>
<td>0.64</td>
</tr>
<tr>
<td>Fearful face</td>
<td>48.59</td>
<td>0.76</td>
</tr>
<tr>
<td>(t) tests</td>
<td>(t_{14})</td>
<td>(p)</td>
</tr>
<tr>
<td>Fearful face &lt; neutral face</td>
<td>2.07</td>
<td>0.03</td>
</tr>
</tbody>
</table>

s.e.m. = standard error of the mean
pic = picture number

After statistical testing, mean estimated latency maps were calculated for neutral and fearful faces, respectively. From these mean estimated latency maps (in seconds) we extracted the latency in the most significant latency peak voxels for neutral and fearful face respectively. Subsequently, latency differences were calculated by subtracting the mean neutral latency shift from the mean fearful latency shift in the most significant latency peak voxels.

Results

Behavioral data

The average picture number at the moment of pop-out for fearful faces was 48.59 (± 0.76 s.e.m.). The average picture number at the moment of pop-out for neutral faces was 49.12 (± 0.64 s.e.m.). Statistical testing of picture number pop-out revealed that the fearful face is perceived significantly earlier than the neutral face (\(t(14) = 2.07, p < 0.05\)). The pop-out related picture number statistics are given in table 8.1.

Latency responses

The right amygdala-hippocampal junction ((x,y,z) = 27,-15,-6) showed a significantly earlier response for fearful faces as compared to neutral faces. A trend was found in the left amygdala-hippocampal junction ((x,y,z) = -27,-12,-9), which showed a comparable response (see table 8.2). The bilateral significant latency shift of fearful versus neutral faces, are shown in figure 8.2. The accompanying onset differences in the BOLD responses are also depicted in figure 8.2 (left and right
Table 8.2: Statistical results of latency of the BOLD response in the functional imaging data. Latency calculations of the BOLD response were performed with respect to the moment of conscious awareness of the stimulus category, i.e., a house of a face. Amygdala activation prior to the conscious pop-out button press, as revealed by the latency analysis, was defined as preconscious amygdala activation. Coordinates are presented in MNI space. \( T \) values of the amygdala-hippocampal junction are presented with 51.75 degrees of freedom, i.e. the number of degrees of freedom in the second level analyses, and \( p \) values are corrected for multiple comparisons in the amygdala region. Latency differences in seconds in the amygdala regions were obtained by subtracting the mean estimated neutral latency from the mean estimated fearful latency.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>L/R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>( t_{51.75} )</th>
<th>( p_{corr} )</th>
<th>Latency difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyg-Hi</td>
<td>R</td>
<td>27</td>
<td>-15</td>
<td>-6</td>
<td>3.18</td>
<td>0.043</td>
<td>-765 ms</td>
</tr>
<tr>
<td>Amyg-Hi</td>
<td>L</td>
<td>-27</td>
<td>-12</td>
<td>-9</td>
<td>2.49</td>
<td>0.110*</td>
<td>-532 ms</td>
</tr>
</tbody>
</table>

\( *p \) = not significant after multiple comparisons correction, reported because of contralateral significant activation.

L/R = left or right hemisphere; \((x,y,z)\) = MNI coordinates in mm

Amyg-Hi = amygdala-hippocampal junction

Note that the data analysis was time-locked to the pop-out, i.e. independent of when the pop-out appeared for each subject within each trial.

In addition, latency differences in seconds between neutral and fearful faces in the bilateral amygdala-hippocampal junction were obtained (see table 8.2). For the right amygdala-hippocampal junction \((x,y,z = 27, -15, -6)\) the mean estimated latency difference is on average -765 milliseconds, i.e. earlier for fearful faces than for neutral faces. For the left amygdala-hippocampal junction \((x,y,z = -27, -12, -9)\) the mean estimated latency difference is -532 milliseconds, i.e. earlier for fearful faces than for neutral faces.
Figure 8.2: Significant latency of the BOLD response differences between fearful and neutral faces in the bilateral amygdala-hippocampal junction. This SPM (thresholded at $p < 0.05$ uncorrected) is displayed on a coronal slice ($Y = -12$) in the center of the figure. On the left and right sides of the SPM, plots of fitted hemodynamic responses are given for the peak voxels of that cluster (upper parts). Peak coordinates, as included in the presented clusters: left amygdala-hippocampal junction ($x, y, z) = (-27, -12, -9)$ and right amygdala-hippocampal junction ($x, y, z) = (27, -15, -6)$ (see also table 8.2). Below these fitted hemodynamic responses, the regression parameter estimates for the canonical response ($\beta_1$) and derivative ($\beta_2$) are plotted. Positive values of $\beta_2$ indicate an earlier hemodynamic response and negative $\beta_2$ a later hemodynamic response (see methods for more details).
Discussion

In this study we investigated the neurobiological substrate of the emergence of conscious perception of biologically salient stimuli. Fearful and neutral faces appeared from dynamically decreasing random visual noise and were matched for luminance, contrast, brightness and spatial frequency information. We found latency differences between neutral and fearful faces of the evoked event-related BOLD responses around the moment of conscious perception: the latency of the BOLD response in the bilateral amygdala-hippocampal junction was found to be more than half a second earlier for fearful faces than for neutral faces.

The location of the latency of the BOLD response in bilateral amygdala (see table 8.2) is more posterior located than the amygdala activation involved in conscious fear perception, which is more anteriorly located (left amygdala \((x,y,z) = -24,3,-24\), right amygdala \((x,y,z) = 12,-6,-27\) (see chapter 7). Rather the location of the latency difference lies in the transition of the amygdala to the hippocampus, i.e. in the amygdala-hippocampal junction. Other studies have noticed the involvement of both amygdala and hippocampus in the (conscious) recognition of fear-related stimuli. For example, the process of recognizing fear might involve hippocampal dependent retrieval of fear relevant memory (LeDoux, 2000). This is supported by amygdala-hippocampal activations in aversive conditioning (Büchel et al., 1999) and other types of aversive learning (Peper et al., 2001). Recently, amygdala-hippocampal border activation was found to be activated in conscious perception of fearful faces (Critchley et al., 2000; Hempel et al., 2003; Phillips et al., 2004). Furthermore, animal studies have proposed the possibility that the hippocampus controls fear and anxiety independent of learning, i.e., the hippocampus may specifically influence some types of defensive fear-related behavior (Antoniadis and McDonald, 2001; Kjelstrup et al., 2002). These findings fit our amygdala-hippocampal response to unconditioned perception of fear. Amygdala and hippocampus also play a role in discriminating the emotional valence of faces (Gur et al., 2002). This concept of the amygdala-hippocampal junction is consistent with our finding that the recognition of a fearful face precedes its conscious awareness. Therefore, our findings support the hypothesis that the amygdala-hippocampal junction is a component of a neural network which is involved in the context dependent recognition of fear.

When assessing latency differences it is important to acknowledge the fact that the relationship between the detected hemodynamic response and real underlying neural activity is indirect. We are aware of the fact that fMRI only measures neuronal response indirectly. As discussed by Henson and colleagues (Henson et al., 2002) a difference in BOLD latency can be derived from a difference in the onset of neural activity or a difference in duration (with simultaneous onsets) of neural activity. As described in the methods section the BOLD response due
to the neural activity for full perception, i.e. from the moment of conscious awareness to the last picture presentation, is included in the GLM to capture signal changes initiated by a prolonged neural activity arising in the moment of conscious perception. However, our latency differences were derived from the event regressors (HRF and TD) that were aligned with the moment of pop-out. This regressor models hemodynamic correlates of neural transients around and prior to the emergence of conscious perception. Thus, neural activation prior to ‘conscious’ amygdala activation will induce a ‘preconscious’ BOLD response. This ‘preconscious’ activation manifests itself in a latency shift that is modeled by the time-derivative regressor in the GLM. Considering these aspects, we propose that our results coincide with an earlier onset of neuronal activation in the amygdala-hippocampal junction. Since the neuro-vascular coupling should be constant in a single region (see for review: Arthurs and Boniface, 2002), we suggest that the underlying neuronal activity in the amygdala appears earlier when perceiving a fearful face appearing through random visual noise as compared to neuronal activity when perceiving a neutral face. Interestingly, direct neuronal measurements, i.e. single neuron activity recordings, in the human hippocampus and amygdala during the recognition of faces (Fried et al., 1997) reflect the importance of both the amygdala and hippocampus in the processing of facial expressions. Although these findings of Fried and colleagues were not fear specific they indicate an amygdala-hippocampal interaction in the recognition of faces.

From an evolutionary point of view a potential threatening object should be rapidly acknowledged thereby initiating a defensive response. It has been proposed that this initiation of a defensive (motor) response involves subconscious perception through a fast subcortical route including the amygdala (Le Doux, 1996). Subconscious perception through this direct subcortical pathway can effectively be studied using backward stimulus masking (Esteves and Ohman, 1993). Facial emotions signaling potential threat, e.g. fear or anger, have been studied in early skin conductance studies, which have revealed that masked fear related targets elicit an emotional response from subjects without conscious perception (Esteves et al., 1994). Subsequent functional imaging studies, both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have revealed that the amygdala responds without the subject being explicitly aware of the facial emotions signaling potential threat (Morris et al., 1998b; Whalen et al., 1998; Morris et al., 1999, 2001; Pasley et al., 2004). Besides the good spatial but low temporal resolution of PET and fMRI, event-related brain potential (ERP) and magnetoencephalography (MEG) studies investigated the time-course of conscious and subconscious perception in the amygdala (Streit et al., 2003; Liddell et al., 2004). ERP time courses show a dissociation between subconscious and conscious perception of threat related stimuli, i.e. fearful faces versus neutral faces (Liddell et al., 2004). MEG time courses have also shown an earlier and stronger effect in the
amygdala to emotional faces (Streit et al., 2003). These temporal correlate studies support the dual route model for the subconscious and conscious perception of emotional stimuli (Shevrin, 2001).

A recent study (Pasley et al., 2004) questions, among others, these empirical data on the functional significance of the subcortical pathway. The authors discuss that the cortical route, which includes the inferior temporal cortex (IT), can not be excluded from (i) subconscious amygdala activation in a blindsight patient (Morris et al., 2001; Goebel et al., 2001) or from (ii) passing information to the amygdala in masking studies (Morris et al., 1998b; Whalen et al., 1998), because IT retains information despite masking (Rolls, 1999). Addressing this controversy Pasley and colleagues measured brain activity in response to fearful faces in a binocular rivalry paradigm. In line with previous findings they support the double dissociation theory of subconscious and conscious perception of threat related stimuli. Using binocular rivalry it is shown that amygdala activation can occur without input from IT and appears to be mediated by the subcortical route (Pasley et al., 2004).

The results in table 8.1 demonstrate an earlier conscious behavioral response for fearful faces than for neutral faces. This shows that fearful faces are recognized earlier, i.e. through a more coarse representation (see chapter 7). Despite time locking to the conscious pop-out we additionally found early amygdala activation, by investigating the latency of the BOLD response. The bias for processing fear- and threat-related information in the amygdala (Adolphs, 2002) entails an earlier detection of this information, i.e., the neural activity arises earlier with a more coarse representation of the visual stimulus. However, this earlier detection does not imply that visual information concerning fearful faces reaches the amygdala earlier than for neutral faces because all visual information is processed via both subcortical and cortical routes. In addition to an earlier conscious response we therefore propose that the detection processes in the amygdala have an even lower threshold for fearful than for neutral faces, which generates a preconscious response in the amygdala-hippocampal junction leading to the observed latency difference between fearful and neutral faces. Therefore, our results show an earlier preconscious amygdala activation for fearful faces than for neutral faces. More specifically, we propose that this preconscious amygdala activation for threat-related information emerges through the thalamic-hippocampal-amygdala subconscious processing route (Liddell et al., 2004). Consequently, our results support the double dissociation theory of preconscious and conscious perception of threat related stimuli (Pasley et al., 2004).

In conclusion, we have shown on basis of the fMRI BOLD response that the amygdala preconsciously activates on perceiving fearful faces. In addition, our data proposes involvement of the thalamic-hippocampal-amygdala subcortical route for a preconscious and rapid amygdala response to threat-related stimuli.
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