

Enhanced processing of threat stimuli under limited attentional resources

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Abstract

The ability to process stimuli that convey potential threat, under conditions of limited attentional resources, confers adaptive advantages. This study examined the neurobiology underpinnings of this capacity. Employing an attentional blink paradigm, in conjunction with functional magnetic resonance imaging (fMRI), we manipulated the salience of the second of two face target stimuli (T2), by varying emotionality. Behaviourally, fearful T2 faces were identified significantly more than neutral faces. Activity in fusiform face area (FFA) increased with correct identification of T2 faces. Enhanced activity in rostral anterior cingulate cortex (rACC) accounted for the benefit in detection of fearful stimuli reflected in a significant interaction between target valence and correct identification. Thus, under conditions of limited attention resources activation in rACC correlated with enhanced processing of emotional stimuli. We suggest that these data support a model in which a prefrontal “gate” mechanism controls conscious access of emotional information under conditions of limited attentional resources.

Introduction

Humans share with other animals a striking ability to detect a threatening stimulus. This capacity confers an adaptive advantage allowing organisms to commit attentional resources during goal-directed behaviour, whilst retaining an ability to quickly respond to potential harm. Several researchers have proposed that the emotional significance of stimuli is evaluated pre-attentively (Dolan RJ, 2002; Palermo R and G Rhodes, 2007; Vuilleumier P, 2005; Vuilleumier P and G Pourtois, 2007). The central idea here is that stimuli tagged with emotional significance are prioritized for access to selective attentional mechanisms that operate within a limited-capacity system.

There is compelling behavioural data (Anderson AK and EA Phelps, 2001) demonstrating an emotional modulation of attention using an attentional blink paradigm, which involves rapid serial presentation of visual stimuli (RVSP). A common finding in this paradigm is increased difficulty detecting a second target if it follows closely in time a first target (Raymond JE et al., 1992). The aforementioned study showed that normal subjects were more likely to detect a second target if it was emotional, whereas patients with amygdala lesions do not show this effect (Anderson AK and EA Phelps, 2001). Clinical neuropsychological studies on patients with unilateral neglect, who typically have right-hemispheric damage, and who fail to attend to stimuli in the left half of space, have reported a dramatic reduction in this behavioural deficit when presented with a left hemifield stimulus that is emotionally salient (Vuilleumier P and S Schwartz, 2001, 2001). Finally, anxious individuals are more likely than controls to display attentional biases toward threatening stimuli (Bishop S et al., 2004; Bishop SJ et al., 2004).

In principle, the emotional significance of a stimulus can influence attentional processing through two distinct mechanisms: either by boosting activity in cortical regions that code for the stimulus itself, or via influences from other cortical areas that impose priorities on attentional processing. In support of the first mechanism, numerous studies have found increased activity in cortical visual processing areas when participants view emotionally provocative images, compared to when they view neutral images (Lane RD, EM Reiman et al., 1997; Lang PJ et al., 1998; Paradiso S et al., 1999; Vuilleumier P and S Schwartz, 2001, 2001). Likewise, activity in the fusiform face area shows an increase when participants view emotionally expressive compared to neutral faces (Breiter HC et al., 1996; Vuilleumier P et al., 2001). Other studies have found increased fusiform activity in response to fear-conditioned faces (Armony JL and RJ Dolan, 2002; Morris JS et al., 2001).

Nevertheless emotional information processing may benefit from a control mechanism that acts as a “gate” in modulating allocation of attentional resources. In the case of control on access to emotional processing, potential influences are likely to involve

prefrontal cortex, in particular the ventromedial regions and rostral cingulate cortex. These areas show close reciprocal connections with subcortical limbic regions such as the amygdala and ventral striatum (Groenewegen HJ and HB Uylings, 2000; Wise RA, 2004), regions strongly implicated in early stages of processing emotional material. For example, focusing attention on the spatial location of an emotionally relevant stimulus is associated with increased activity in bilateral VMPFC (Armony JL and RJ Dolan, 2002). One interpretation of the latter finding is that VMPFC is associated with directing spatial attention toward emotionally significant targets. Several other studies have found increased activity in the anterior cingulate cortex (rACC) during selective attention to emotional information (Elliott R et al., 2000; Lane RD et al., 1997). In addition, rACC activity increases when participants are required to ignore emotional information, compared to when they have to ignore neutral information (Whalen PJ et al., 1998). In the present study, we employed fMRI in conjunction with an attentional blink paradigm, to investigate how these two distinct mechanisms control increased detection of threatening targets under conditions of limited attentional resources.

Methods

Experimental design

In an attentional blink (AB) task subjects searched for two targets within an RSVP of 15 distracter items. Each stimulus was presented centrally for 70ms with no interstimulus interval. The first stimulus (T1) comprised a scene (either indoor or outdoor) and the second target (T2) comprised a face (either neutral or fearful). The distracter items were scrambled images of the scene and face together, with each greyscale stimulus subtending $8.5^\circ \times 8.5^\circ$. All face stimuli were selected from the KDEF database (D. Lundqvist and J.-E. Litton, personal communication; photographic face set available from the Department of Neurosciences, Karolinska Hospital, Stockholm, Sweden). The scrambled images originated from a pool of scene and face images (mixed in 50% proportion) and were created by dividing each quadrant of images into 25 squares randomly scrambling their position. Thin black grids were drawn over the scrambled and intact images to occlude the boundaries of blocks.

A trial began with presentation of a fixation cross for a variable time between (2000-4000ms) before the onset of the RSVP, which consisted of 15 images each displayed on a screen for 70ms. All images were scrambled pictures of scenes and faces (distracters) but two of the distracters were replaced by two intact target images: a T1 scene and a T2 face. At the end of RVSP subjects reported the identity of both targets by a key press in two response period of 4000ms each. During the T1 response period a display was shown with three options: NoScene, Indoor or Outdoor. Subjects indicated by a keypress whether no scene, an outdoor scene or an indoor scene was presented. For the T2 response subjects were shown the face that had been presented during the current trial together with two other faces of the same gender (male or female) and expression (neutral or fearful) and were asked to indicate by a key press the face shown at T2. A scene target (T1) and face target (T2) was presented in every trial. T1 was presented randomly between the 2nd to 7th position during the RVSP, where T2 was always presented after 5

distractors (350ms) from T1. A total of 144 trials were presented in 3 sessions of 48 trials each.

fMRI Scanning parameters

We acquired gradient-echo T2*-weighted images (EPI) on a 1.5 Tesla magnetic resonance scanner using a 30 degree tilted acquisition sequence designed to reduce signal dropout in orbitofrontal cortices. Image parameters were as follows: TE 50ms; TR 3.96s; slice thickness 2mm; inter slice gap 1mm. We collected 810 volumes (across 3 sessions) per subject. T1-weighted structural images co-registered with mean EPI images and averaged across subjects to allow group level anatomical localization. Images were analyzed using the statistical parametric software SPM2 (Wellcome Department of Imaging Neuroscience London <http://www.fil.ion.ucl.ac.uk/spm>). Pre-processing consisted of spatial realignment and normalization to a standard EPI template, and spatial smoothing (8mm kernel).

Behavioural Data Analysis

Following the standard procedure, used in AB data analysis, trials in which subjects reported that a T1 scene was not present (missed T1) were discarded. The experiment constituted a 2x2 factorial design with the first factor representing the task condition (emotional T2 and neutral T2) and the second representing the behavioural performance of each subject on a trial by trial basis (during the attentional blink task in the scanner correctly reported T2 (Correct-T2) and incorrectly reported T2 (Incorrect-T2)).

Because Correct-T2 includes 33% of correct responses purely by chance (forced response between 3 faces), the number of trials allocated to Correct-T2 on a chance base meant that reaction time (RT) was taken as index of confidence. This was based on the evidence that subjects showed a significant reduction in reaction time (RT) in Correct-T2 compared with Incorrect-T2. The normal RT's distributions for the two conditions (Correct-T2 and Incorrect-T2) overlapped for half of the areas (see figure 1 b). We used a median split to divide the Correct-T2 into confident (fastest response) and unconfident

correct hits (Strange BA and RJ Dolan, 2004). Only the confident Correct-T2 were included in the fMRI data analysis. A few trials in which the subjects did not press any key at T2 response period were also included in the IT2.

Imaging Data Analysis

We analyzed the fMRI data in an event-related design using the general linear model (GLM) within SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). After discarding the first six image volumes from each run to allow for T1 equilibration effects, image volumes were realigned and co-registered to each subject's structural scan. Subject-specific regressors of interest were assembled by convolving δ functions (corresponding to the time of onset of the beginning of the RVSP) with a canonical hemodynamic response function (HRF). We removed low frequency fluctuations by a high-pass filter with a cut-off at 128 s. A correction for temporal autocorrelation in the data (AR 1 + white noise) was applied. Four regressors of interest were built according to the trial type and the subjects' responses and were included in the GLM. The onset was locked to the beginning of the RVSP. Two nuisance regressors (T1 incorrect trials and T2 response period) were included in the GLM. Parameter estimates were used to calculate the appropriate linear contrast. These contrast images were then entered into a one-sample t test across all subjects (random effects analysis). The resulting Z statistic images were thresholded at $Z > 3.1$, corresponding to $P < 0.001$ uncorrected. We report results in a priori regions of interest (FFA, amygdala, striatum, ACC) previously identified in neuroimaging studies on emotional regulation of attention (Bishop S et al., 2004; Bush G et al., 2000; Lane RD, GR Fink et al., 1997; Salamone JD, 1994; Seymour B et al., 2005; Vuilleumier P and G Pourtois, 2007) at $P < 0.001$ uncorrected for multiple comparisons. We also performed a small volume correction (SVC) using a sphere of 10mm radius centered on coordinates of a priori regions of interest (rACC: [x= -38, y=-50, z=-22] (Bush G et al., 2000) and ventral striatum: [x= \pm 22 y=10, z=-10] (Seymour B et al., 2005)). The SVC procedure, as implemented in SPM2 using the family-wise error (FWE) correction ($p < 0.05$), allows results to be corrected for multiple non-independent comparisons with a defined region of

interest. Activations in other regions are only reported and discussed if they survive whole-brain correction for multiple comparisons at $P < 0.05$ (FWE).

We performed a region-of-interest (ROI) analysis in the bilateral FFA using the MarsBaR SPM toolbox: (<http://marsbar.sourceforge.net/>). The ROI's for the FFA area were defined by the SPM cluster ($P < 0.05$ whole-brain corrected for multiple comparisons) contrasting the activity during the entire task contrasted against the baseline. Definition of this ROI is thus orthogonal and unbiased with respect to all our contrasts of interests. Using the MarsBaR SPM toolbox, we obtained parameter estimates for all voxels within this region, for the group as a whole. These parameter estimates were averaged across the ROI, and specific effects tested using planned one-sample t tests.

Results

We recruited fifteen healthy subjects who underwent functional magnetic resonance imaging (fMRI) while performing a modified attentional blink task (Anderson AK and EA Phelps, 2001), (Raymond JE *et al.*, 1992). We presented subjects with 15 images each displayed on a screen for 70ms. All images were scrambled picture of scenes and faces (distractors) but two of the distractors were replaced by two intact target images (Marois R *et al.*, 2004). The participants' task was to identify both targets identity at the end of each trial. The first target (T1) was always a scene (either indoor or outdoor) followed, after 5 intervening distractors (350ms lag), by another target (T2) which was always a face (either neutral or fearful). This experimental design allowed us to identify the neurobiological underpinnings supporting an increased capacity to process emotional stimuli, under conditions of high attentional load

Our experimental paradigm elicited a robust attentional blink effect. For the entire scanning period participants were able to detect the T1 scene on 91.7% of the trials. After correct T1 detection subjects could correctly report the T2 face stimuli significantly more often when the face was fearful (Fearful-T2) compared to when it was neutral (Neutral-T2) 58.8% vs. 46.8% ($t_{(14)}=5.2$ $p<0.001$ two tailed paired t-test) (Fig 2a).

The 2x2 fully factorial design employed in our experiment allowed us to study how the emotional valence of the T2 face, that was either fearful or neutral (Fearful-T2 vs. Neutral-T2), impacted upon correct or incorrect T2 face detection (Correct-T2 vs. Incorrect-T2). Reaction times (RT's) for T2 targets were analyzed by repeated measures ANOVA. We detected a shortening in reaction times (RT's) for correct T2 (mean value 2.76 ± 0.20 sec) relative to incorrect T2 detection (mean value 2.95 ± 0.28 sec), a reduction that was statistically significant ($F_{(1,14)}=22.6$ $p<0.001$) (Fig 2b). By contrast the emotional valence of the T2 face stimulus (fearful vs. neutral) did not produce significant changes in RT's ($F_{(1,14)}=2.8$ $p=0.11$).

Our experimental design included a forced choice decision task for three faces at the time of T2 response. Accordingly, one third of trials, classified as Correct-T2, can be attributable to chance alone. In order to address this issue, we used a median split based on RTs in the fMRI analysis as measure of confidence for correct T2 identification. This procedure was motivated by evidence that subjects showed a significant reduction RT's for Correct-T2 compared to Incorrect-T2 detection and that the normal RT's distribution for the two conditions (Correct-T2 and Incorrect-T2) overlapped for half of the areas (see figure 1 b and methods section). Such a procedure has been previously used (Strange BA and Dolan RJ, 2004) to deal with similar confounds in event-related fMRI design, where the accurate trials categorization is critical to achieve a robust estimation of the GLM.

For the imaging data we first contrasted BOLD activity during the period in which subjects were engaged in the task versus the resting period, a contrast that enabled us to identify stimulus responsive regions. This contrast revealed significant activation within both right and left fusiform face regions (FFA) (R-FFA ([x= 30, y=-48, z=-24] Z=5.88, 25-voxels) and L-FFA ([x= -38, y=-50, z=-22] Z=5.28, 97-voxels) $p < 0.05$ whole-brain corrected for multiple comparisons (FWE)). The location of these two clusters of activity is consistent in location with FFA activity previously reported (Kanwisher N et al., 1997; Kanwisher N et al., 1999) (Fig3 a). These clusters were then used to define regions of interest (ROIs) in which we performed a statistical analysis between the different conditions during the AB task.

Activity in both FFA's significantly predicted subjects' ability to report correct face identity in the response period (R-FFA $Z=3.27$ $p < 0.05$, L-FFA $Z=5.32$ $p < 0.05$) (Fig3 b). Neither the left or right FFA showed increased activity for fearful face T2 compared to neutral (Fearful-T2 vs. Neutral-T2), although we observed trend level effect in the L-FFA ($Z=2.01$ $p=0.11$). Nevertheless, in trials where the T2 were incorrectly reported L-FFA showed a significant increase in activity ($Z=2.56$ $p < 0.05$) for fearful T2, targets versus neutral T2 (Fearful-T2_Incorrect-T2 vs. Neutral-T2_Incorrect-T2). No significant interaction between valence of the target T2 (Fearful-T2 vs. Neutral-T2) and increased

performance in T2 detection was observed suggesting that the FFA activity cannot fully account for the behavioural increase in T2 fearful face detection.

Using a voxel based analysis we then identified regions showing an increase in activity for fearful T2 faces versus neutral T2 faces (Fearful-T2 vs. Neutral-T2). Bilateral ventral striatum showed a significant increase in BOLD activity: R-striatum ([x= 20, y=16, z=0] Z=4.08, 68-voxels, p<0.001 uncorrected and p<0.05 SVC), L-striatum ([x= -26, y=14, z=-4] Z=3.63, 8-voxels, p<0.001 uncorrected and p<0.05 SVC). Both simple contrasts: Fearful-T2_Correct-T2 vs. Neutral-T2_Correct-T2 and Fearful-T2_Incorrect-T2 vs. Neutral-T2_Incorrect-T2 also showed statistically significant striatal activation.

The fully factorial design of our experiment allowed us to examine how the emotional valence of T2 (Fearful-T2 vs. Neutral-T2) modulated accuracy in T2 detection (Correct-T2 vs. Incorrect-T2), the principal experimental goal of the study. The most direct way to determine at a neural level an effect of T2 valence on T2 response accuracy is to identify brain areas showing a significant interaction between the two factors across all trial conditions ([Fearful-T2_Correct-T2 – Fearful-T2_Incorrect-T2] > [Neutral-T2_Correct-T2 – Neutral-T2_Incorrect-T2]). This interaction contrast identifies brain areas specifically activated when emotional T2 stimuli are correctly reported, rather than responding to the valence of T2 stimuli alone. The rostral anterior cingulate cortex (rACC) showed significantly enhanced activity within this interaction ([x=14, y=40, z=22] Z=3.59, 25-voxels p<0.001 uncorrected and p<0.05 SVC). rACC was significantly more active when subjects correctly reported the T2 identity in the fearful face condition as showed by the simple effect (Fearful-T2_Correct-T2 vs. Fearful-T2_Incorrect-T2) ([x=10, y=38, z=18] Z=4.25, 32-voxels p<0.001 uncorrected and p<0.05 SVC).

Discussion

Our behavioural results replicate previous findings (Anderson AK and EA Phelps, 2001) in showing an increase in detection of arousing, compared to neutral, words in the attentional blink, but extends these findings to a more ecological context of face processing. Moreover, the findings support a model that suggests an overlap in face identity and face expression recognition processes, in contrast with a view that propose two distinct parallel mechanisms (Calder AJ and AW Young, 2005). Reaction time for the correctly reported target was significantly shorter, supporting a more complete and accurate processing of these targets.

While previous fMRI studies have examined the neurobiology of the attentional blink effect using neutral stimuli (Marois R et al., 2000; Marois R *et al.*, 2004) the present study is the first to investigate the mechanisms underlying a reduced blink effect for emotional T2 items. The fMRI data show a significant increase in FFA activity for faces that subsequently would have been correctly reported. These results support claims that detection and identification of faces, critically depends on FFA activity (Kanwisher N *et al.*, 1997; Kanwisher N *et al.*, 1999; Grill-Spector K et al., 2004). Moreover in trials where a fearful face was incorrectly reported L-FFA showed increased activity for fearful faces compared to the neutral ones. This finding is in keeping with previous findings of a reported increase in FFA activity for fearful unattended faces versus neutral unattended faces (Vuilleumier P, 2005; Vuilleumier P *et al.*, 2001) in a spatial divided attention task. Our results extend these findings to the domain of non-spatial attention, and support a model that proposes enhanced processing of emotional stimuli even under conditions where they do not reach full awareness (Vuilleumier P and G Pourtois, 2007). The data also show that FFA activity is critically associated with the correct face identification. An important caveat is that because FFA activity did not show an interaction between valence of the target T2 and increased performance in T2 detection these observations cannot fully explain our behavioural increase in T2 fearful face detection.

Comparing brain activity in trials where the T2 target was a fearful face with trials where T2 was a neutral face was associated with activity increase in bilateral ventral striatum. These region is implicated in anticipation of reward (O'Doherty JP, 2004; Schultz W, 2006) and anticipation of both aversive stimuli as well as painful stimulation (Jensen J et al., 2003; Salamone JD, 1994; Seymour B *et al.*, 2005). Previous neuroimaging studies have also shown that ventral striatum is more active when subjects are exposed to unpleasant visual stimuli (Paradiso S *et al.*, 1999). It has been suggested that striatum is implicated in responding to arousing stimuli (Horvitz JC, 2002). Furthermore, evidence from animals and humans literature, show that ventral striatum plays a key role in instrumental learning and goal-directed behaviour (Hollerman JR et al., 2000). Thus, our data are in keep with a role for the striatum in motivation and adaptation of behavior related to affective situations (Everitt BJ et al., 1999; Robbins TW and BJ Everitt, 1996; Schultz W, 2006).

The rostral anterior cingulate cortex (rACC) showed an increase in activity in the critical interaction contrast that sought to identify brain areas underpinning an increase in detection for fearful T2 targets seen in our behavioural findings. The rACC (Brodmann areas 24 a-c and 32) is considered to have distinct anatomical and functional characteristics compared with the more caudal anterior cingulate cortex (cACC) (Bush G *et al.*, 2000). At neuroanatomical level this area shares reciprocal connections with amygdala, nucleus accumbens, anterior insula, and orbitofrontal cortex. At a functional level convergent evidence shows that rACC has a primary role in processing emotional information and regulating emotional responses (Bush G *et al.*, 2000). In particular rACC activity is implicated in awareness for emotional material (Carrette L et al., 2001; Lane RD *et al.*, 1997; Lane RD et al., 1998; Simpson JR, Jr. et al., 2001), attention to emotional stimuli (Fichtenholtz HM et al., 2004; Vuilleumier P et al., 2001) and rating of affect intensity (Taylor SF et al., 2003). During anxiety, altered response of rACC has been associated with an impaired processing of treat-related attentional competitors (Bishop S et al., 2004) and with appraisal of emotional material (Kalisch R et al., 2006). More generally, rACC has been shown playing a key role in selective attention to emotional information (Elliott R *et al.*, 2000; Lane RD, GR Fink *et al.*, 1997). Our

behavioural manipulation highlights a role for rACC in early stages of emotional processing (Kalisch R *et al.*, 2006). In this regard the results extend the functional role of rACC to include mediating selective detection of potential threat under conditions of limited attentional capacity, as elicited by the attentional blink paradigm.

A previous study (Anderson AK and EA Phelps, 2001) using a word RVSP with either a neutral or an arousing T2 demonstrated that patients with left amygdala damage did not have a significant behavioural advantage in emotional T2 detection. A theoretical model of emotional modulation of AB predicts that amygdala may play a key role in mediating this effect (Fragopanagos N *et al.*, 2005; Palermo R and G Rhodes, 2007). In our study we did not find a statistically significant amygdala activation either in the critical interaction ($[\text{Fearful-T2_Correct-T2} - \text{Fearful-T2_Incorrect-T2}] > [\text{Neutral-T2_Correct-T2} - \text{Neutral-T2_Incorrect-T2}]$) or in the main effect of fearful versus neutral T2, even at a more liberal threshold of $P < 0.05$ uncorrected. This negative finding does not exclude a possible involvement of amygdala in our task. In fact the statistical power of the analysis was limited by the number of events and brief presentation of the target. This may have rendered it more difficult to detect rapid changes in amygdala, particularly when considering the low signal to noise ratio in this subcortical area (LaBar KS *et al.*, 2001). Additionally, all faces, even neutral ones especially when presented briefly may have potential emotional significance and can activate amygdala (Wright P and Y Liu, 2006).

Finally, our data suggests a model in which early control exerted by rACC is required for enhanced processing of threat targets. In fact the stimulus driven activity in visual areas, although necessary for the correct T2 process, does not appear sufficient to explain enhanced behavioural processing of the fearful T2 targets. One possibility is that enhanced activity in rACC, triggered by subcortical areas (e.g. striatum) sensitive to stimulus valence, mediates correct target identification by gating the access of the potentially threatening stimulus to full awareness.

In conclusion, using a modification of an attentional blink task in which we manipulated the emotional valence of a face T2 target, we observed a significant increase in correct

detection of fearful compared to neutral targets. These data replicate previous findings using words as arousing stimuli (Anderson AK and EA Phelps, 2001). Our behavioural results demonstrate that even when humans are unable to detect non-threatening stimuli due to attentional overload, they retain the ability to detect emotional items. Our imaging data indicates that although activity in visual areas like FFA is necessary for the correct stimulus detection, it does not account for the increased detection of threatening targets. Instead frontal rACC activity mediates a control on attention and awareness for emotional items even in conditions in which normal attentional capacity is limited.

Figures and legends

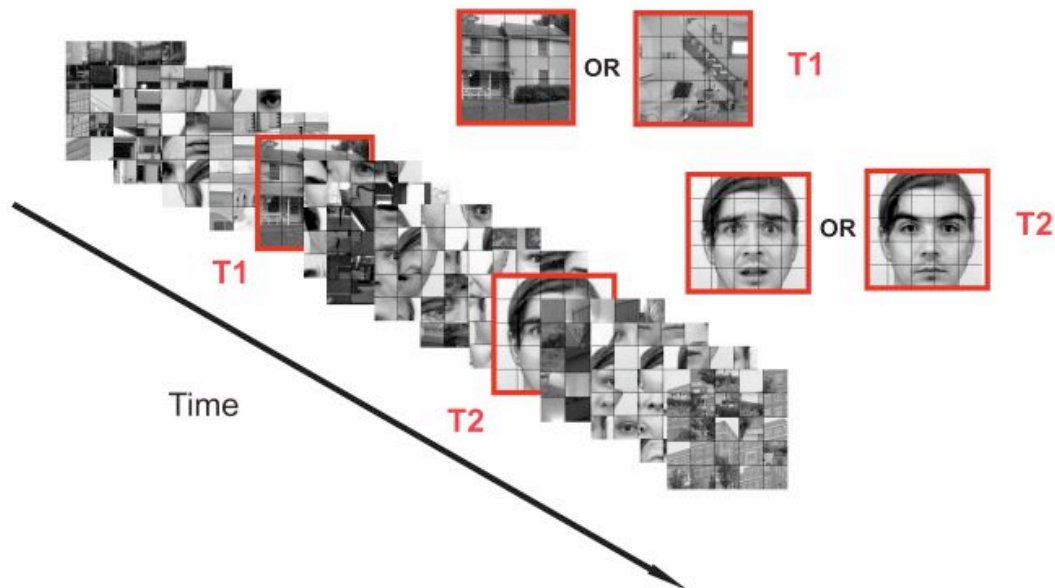


Figure 1 Task

Subjects were asked to search for two targets (T1 and T2) embedded in between 13 distractors items at fixation for 70ms each with no interstimulus interval. The first stimulus (T1) was a scene (either indoor or outdoor) and the second target (T2) was a face (either neutral or fearful). The distractors were scrambled images of the scene and face together. The two targets were always separated by 5 distractors (350ms). At the end of the rapid visual stimuli presentation (RVSP) subjects were asked to report by a keypress whether no scene, an outdoor scene or an indoor scene was presented (T1 response 4 sec). Subsequently they were asked to identify the identity of the face T2 by keypress in a forced choice between 3 faces: one of these was the one presented in the trial (T2 response 4 sec). *Note that the red frame is shown here only for the purpose of display and was not part of the original stimuli.*

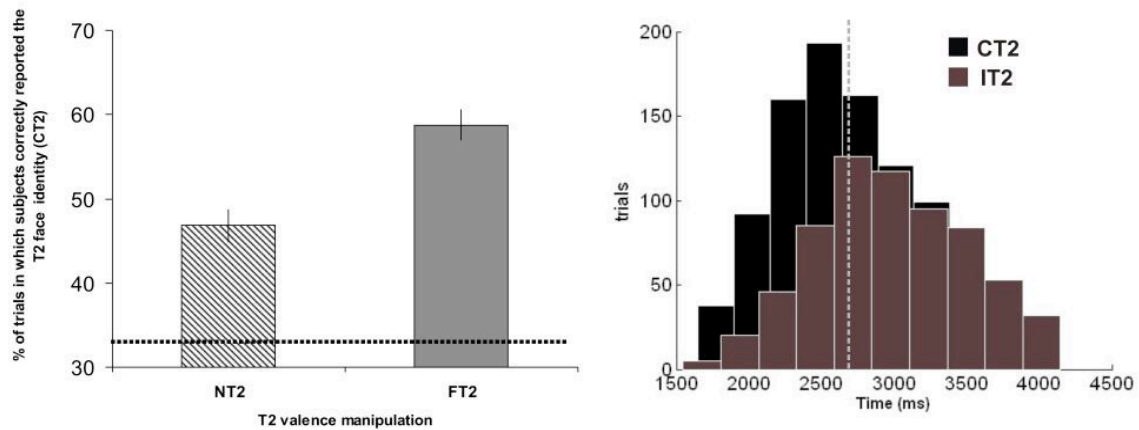


Figure 2 Behavioral results

a) Behavioral results (main)

The graph shows the x percentage (%) increase of trials in which the subject correctly reported the T2 face identity (Correct-T2) for a T2 fearful face condition (Fearful-T2 58.8% ; S.E. 1.85) respect to a T2 neutral face condition (Neutral-T2 46.8% ; S.E. 1.95) Fearful-T2 vs. Neutral-T2 ($t_{(14)}=5.2$ $p<0.001$ two tailed paired t-test).) In both the T2 detection was significantly above chance level of 33% (forced choice between tree faces) represented in the graph with a dashed line (Neutral-T2: $t_{(14)}=7.05$ $p<0.001$, Fearful-T2: $t_{(14)}=13.9$ $p<0.001$ two tailed one-sample t-test).

b) Behavioral results (RT)

The histograms represent the reaction time (RT) distributions for number of trials. In black is shown the condition in which the T2 face was correctly reported (Correct-T2) and in brown the condition in which the T2 face was incorrectly reported (Incorrect-T2). The two distributions partially overlap with the RT mean value significantly shorter in the Correct-T2 versus the Incorrect-T2 ($F_{(1,14)}=22.6$ $p<0.001$). The dashed line represent the median split for the Correct-T2 condition (see experimental procedure).

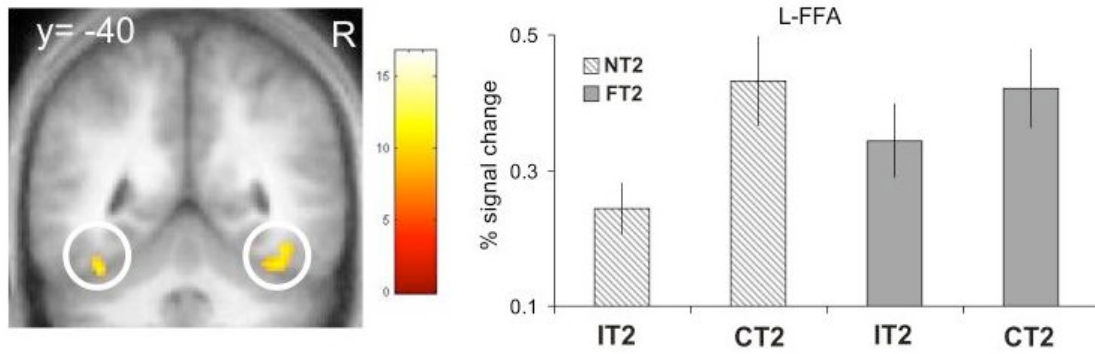


Figure 3 FFA

a) Coronal section of SPMs showing both fusiform face areas (FFA) contrasting activity during the entire task against the baseline (R-FFA ($[x= 30, y=-48, z=-24]$ $Z=5.88$, 25-voxels L-FFA ($[x= -38, y=-50, z=-22]$ $Z=5.28$, 97-voxels $p<0.05$ whole-brain corrected for multiple comparison FWE). Both clusters were used to identify respective regions of interests used in a ROI's analysis that revealed a significant increased activation in the Correct-T2 versus Incorrect-T2 (R-FFA $Z=3.27$ $p<0.05$, L-FFA $Z=5.32$ $p<0.05$). L-FFA showed a non-significant trend for Fearful-T2 versus Neutral-T2 ($Z=2.01$ $p=0.11$) with a significant simple effect in the Incorrect-T2 condition Fearful-T2_Incorrect-T2 versus Neutral-T2_Incorrect-T2 ($Z=2.56$ $p<0.05$)

b) Plot of signal percentage changes for the L-FFA cluster.

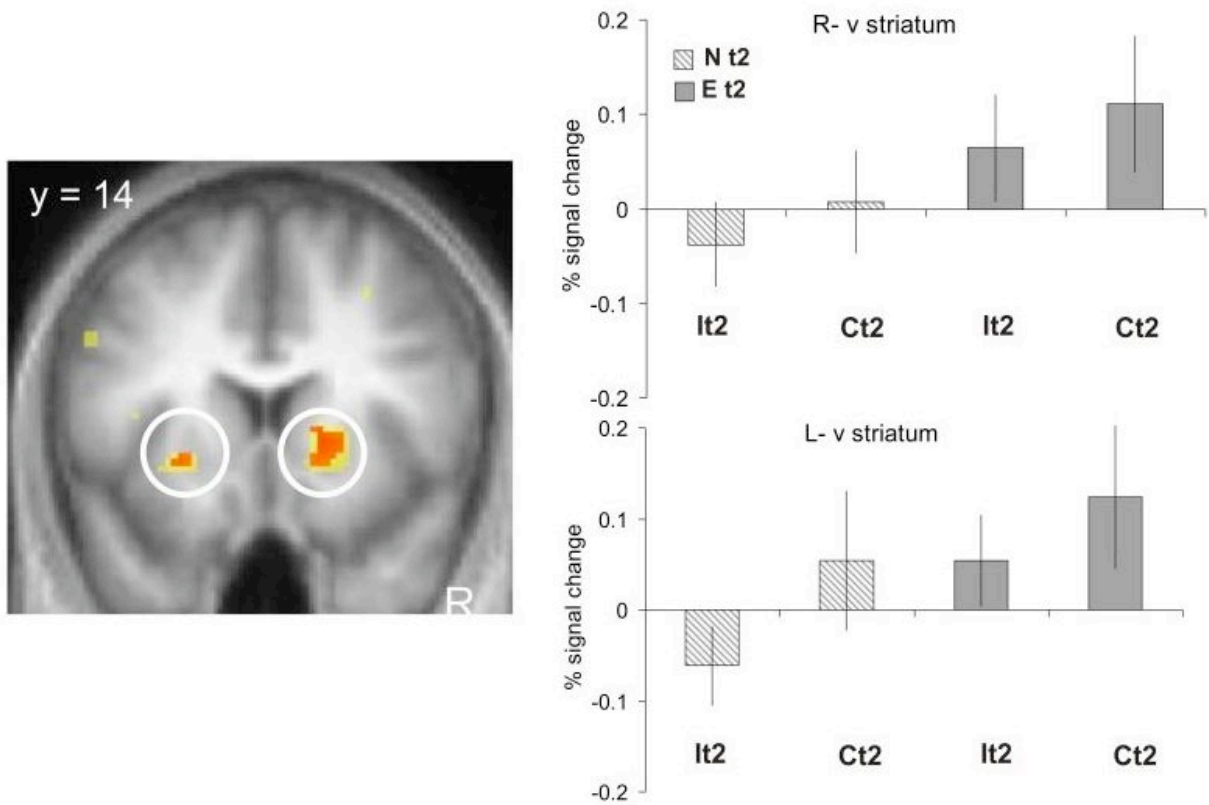


Figure 4 Striatum

a) SPM showing response in both ventral striatum nuclei for the Fearful-T2 versus Neutral-T2 statistical contrast R-striatum ($[x = 20, y = 16, z = 0]$ $Z = 4.08$, 68-voxels, $p < 0.001$ uncorrected), L-striatum ($[x = -26, y = 14, z = -4]$ $Z = 3.63$, 8-voxels, $p < 0.001$ uncorrected and $p < 0.05$ SVC).

b) Plot of signal percentage changes for the both ventral striatum nuclei clusters.

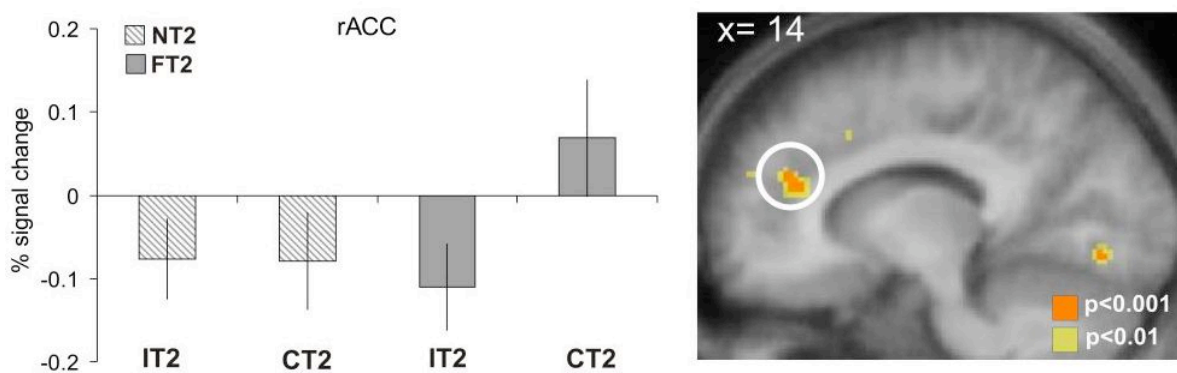


Figure 5 rACC

a) Plot of signal percentage changes for the rACC cluster.

b) Sagittal SPM image during the interaction contrast ($[\text{Fearful-T2_Correct-T2} - \text{Fearful-T2_Incorrect-T2}] > [\text{Neutral-T2_Correct-T2} - \text{Neutral-T2_Incorrect-T2}]$) showing the activity of the rACC ($[x=14, y=40, z=22]$ $Z=3.59$, 25-voxels $p<0.001$ uncorrected and $p<0.05$ SVC) is modulated by the T2 identification (Correct-T2 vs. Incorrect-T2) selectively in the when the T2 stimulus was a fearful face (Fearful-T2). rACC is significantly more active simple effect (Fearful-T2_Correct-T2 vs. Fearful-T2_Incorrect-T2) ($[x=10, y=38, z=18]$ $Z=4.25$, 32-voxels $p<0.001$ uncorrected and $p<0.05$ SVC) .

Tables

Abbreviations:

Fearful-T2: Fearful face target T2

Neutral-T2: Neutral face target T2

Correct-T2: Correctly identified face target T2

Incorrect-T2: Incorrectly identified face target T2

Table 1. Brain areas significantly more active during interaction contrast ([Fearful-T2_Correct-T2 – Fearful-T2_Incorrect-T2] > [Neutral-T2_Correct-T2 – Neutral-T2_Incorrect-T2])

All values $p < 0.001$ uncorrected with all clusters exceeding an extent threshold of 5 voxels
 *Statistically significant activations - regions that survive to the SVC for multiple comparisons FWE $p < 0.05$ (see Methods for more details)

Region	Laterality	x	y	z	z-score
rACC *	R	14	40	22	3.59
Cerebellum	L	32	-76	-30	4.04
Inferior postcentral sulcus	R	56	-10	26	3.89
Lingual gyrus	R	14	-78	-8	3.69

Table 2. Brain areas significantly more active during interaction contrast (Fearful-T2 > Neutral-T2)

All values $p < 0.001$ uncorrected with all clusters exceeding an extent threshold of 5 voxels
 *Statistically significant activations - regions that survive to the SVC for multiple comparisons FWE $p < 0.05$ (see Methods for more details)

Region	Laterality	x	y	z	z-score
Ventral striatum *	R	20	16	0	4.08
	L	-28	14	-4	3.63
Lingual gyrus	R	8	-78	4	3.59

Table 3. Brain areas significantly more active during interaction contrast (Correct-T2 > Incorrect-T2)

All values $p < 0.001$ uncorrected with all clusters exceeding an extent threshold of 5 voxels
 *Statistically significant activations - regions that survive to the SVC for multiple comparisons FWE $p < 0.05$ (see Methods for more details)

Region	Laterality	x	y	z	z-score
Posterior insula	L	-42	-8	16	4.64
	L	-32	-2	2	4.05
Inferior frontal sulcus	R	30	54	10	4.98
	R	44	48	2	3.91
Superior frontal sulcus	L	-26	46	38	4.14
Orbitofrontal cortex	R	32	42	-16	3.51
	L	-34	22	-20	4.21
ACC	R	2	32	28	3.67
Pre-SMA	L	-4	10	46	3.67
Cerebellum	L	-36	-68	-46	3.50
Inferior parietal gyrus	R	66	-42	22	4.98

References

- Anderson AK, Phelps EA. 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*. 411:305-309.
- Armony JL, Dolan RJ. 2002. Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia*. 40:817-826.
- Bishop S, Duncan J, Brett M, Lawrence AD. 2004. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci*. 7:184-188.
- Bishop SJ, Duncan J, Lawrence AD. 2004. State anxiety modulation of the amygdala response to unattended threat-related stimuli. *J Neurosci*. 24:10364-10368.
- Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR. 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*. 17:875-887.
- Bush G, Luu P, Posner MI. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 4:215-222.
- Calder AJ, Young AW. 2005. Understanding the recognition of facial identity and facial expression. *Nat Rev Neurosci*. 6:641-651.
- Carrette L, Martin-Loeches M, Hinojosa JA, Mercado F. 2001. Emotion and attention interaction studied through event-related potentials. *J Cogn Neurosci*. 13:1109-1128.
- Dolan RJ. 2002. Emotion, cognition, and behavior. *Science*. 298:1191-1194.
- Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. 2000. Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study. *Neuroreport*. 11:1739-1744.
- Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW. 1999. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. *Ann N Y Acad Sci*. 877:412-438.
- Fichtenholtz HM, Dean HL, Dillon DG, Yamasaki H, McCarthy G, LaBar KS. 2004. Emotion-attention network interactions during a visual oddball task. *Brain Res Cogn Brain Res*. 20:67-80.
- Fragopanagos N, Kockelkoren S, Taylor JG. 2005. A neurodynamic model of the attentional blink. *Brain Res Cogn Brain Res*. 24:568-586.
- Grill-Spector K, Knouf N, Kanwisher N. 2004. The fusiform face area subserves face perception, not generic within-category identification. *Nat Neurosci*. 7:555-562.
- Groenewegen HJ, Uylings HB. 2000. The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog Brain Res*. 126:3-28.
- Hollerman JR, Tremblay L, Schultz W. 2000. Involvement of basal ganglia and orbitofrontal cortex in goal-directed behavior. *Prog Brain Res*. 126:193-215.
- Horvitz JC. 2002. Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. *Behav Brain Res*. 137:65-74.
- Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. 2003. Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron*. 40:1251-1257.

- Kalisch R, Wiech K, Critchley HD, Dolan RJ. 2006. Levels of appraisal: a medial prefrontal role in high-level appraisal of emotional material. *Neuroimage*. 30:1458-1466.
- Kanwisher N, McDermott J, Chun MM. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci*. 17:4302-4311.
- Kanwisher N, Stanley D, Harris A. 1999. The fusiform face area is selective for faces not animals. *Neuroreport*. 10:183-187.
- LaBar KS, Gitelman DR, Mesulam MM, Parrish TB. 2001. Impact of signal-to-noise on functional MRI of the human amygdala. *Neuroreport*. 12:3461-3464.
- Lane RD, Fink GR, Chau PM, Dolan RJ. 1997. Neural activation during selective attention to subjective emotional responses. *Neuroreport*. 8:3969-3972.
- Lane RD, Reiman EM, Axelrod B, Yun LS, Holmes A, Schwartz GE. 1998. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J Cogn Neurosci*. 10:525-535.
- Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, Schwartz GE. 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*. 35:1437-1444.
- Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, Nangia V. 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology*. 35:199-210.
- Marois R, Chun MM, Gore JC. 2000. Neural correlates of the attentional blink. *Neuron*. 28:299-308.
- Marois R, Yi DJ, Chun MM. 2004. The neural fate of consciously perceived and missed events in the attentional blink. *Neuron*. 41:465-472.
- Morris JS, Buchel C, Dolan RJ. 2001. Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. *Neuroimage*. 13:1044-1052.
- O'Doherty JP. 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol*. 14:769-776.
- Palermo R, Rhodes G. 2007. Are you always on my mind? A review of how face perception and attention interact. *Neuropsychologia*. 45:75-92.
- Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD. 1999. Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *Am J Psychiatry*. 156:1618-1629.
- Raymond JE, Shapiro KL, Arnell KM. 1992. Temporary suppression of visual processing in an RSVP task: an attentional blink? *J Exp Psychol Hum Percept Perform*. 18:849-860.
- Robbins TW, Everitt BJ. 1996. Neurobehavioural mechanisms of reward and motivation. *Curr Opin Neurobiol*. 6:228-236.
- Salamone JD. 1994. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav Brain Res*. 61:117-133.
- Schultz W. 2006. Behavioral theories and the neurophysiology of reward. *Annu Rev Psychol*. 57:87-115.

- Seymour B, O'Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, Dolan R. 2005. Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat Neurosci.* 8:1234-1240.
- Simpson JR, Jr., Drevets WC, Snyder AZ, Gusnard DA, Raichle ME. 2001. Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. *Proc Natl Acad Sci U S A.* 98:688-693.
- Strange BA, Dolan RJ. 2004. Beta-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. *Proc Natl Acad Sci U S A.* 101:11454-11458.
- Taylor SF, Phan KL, Decker LR, Liberzon I. 2003. Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage.* 18:650-659.
- Vuilleumier P. 2005. How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci.* 9:585-594.
- Vuilleumier P, Armony JL, Driver J, Dolan RJ. 2001. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron.* 30:829-841.
- Vuilleumier P, Pourtois G. 2007. Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia.* 45:174-194.
- Vuilleumier P, Schwartz S. 2001. Beware and be aware: capture of spatial attention by fear-related stimuli in neglect. *Neuroreport.* 12:1119-1122.
- Vuilleumier P, Schwartz S. 2001. Emotional facial expressions capture attention. *Neurology.* 56:153-158.
- Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL. 1998. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry.* 44:1219-1228.
- Wise RA. 2004. Dopamine, learning and motivation. *Nat Rev Neurosci.* 5:483-494.
- Wright P, Liu Y. 2006. Neutral faces activate the amygdala during identity matching. *Neuroimage.* 29:628-636.