Neural responses to salient visual stimuli

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SUMMARY

The neural mechanisms involved in the selective processing of salient or behaviourally important stimuli are uncertain. We used an aversive conditioning paradigm in human volunteer subjects to manipulate the salience of visual stimuli (emotionally expressive faces) presented during positron emission tomography (PET) neuroimaging. Increases in salience, and conflicts between the innate and acquired value of the stimuli, produced augmented activation of the pulvinar nucleus of the right thalamus. Furthermore, this pulvinar activity correlated positively with responses in structures hypothesized to mediate value in the brain–right amygdala and basal forebrain (including the cholinergic nucleus basalis of Meynert). The results provide evidence that the pulvinar nucleus of the thalamus plays a crucial modulatory role in selective visual processing, and that changes in perceptual salience are mediated by value-dependent plasticity in pulvinar responses.

1. INTRODUCTION

The salience of a stimulus is determined by its behavioural significance, e.g. its appetitive (positive) or aversive (negative) quality, as well as by its perceptual features. Stimuli related to survival (e.g. food, sex and pain) possess an innate salience which is thought to depend on the activity of evolutionarily selected value systems in the brain (Edelman 1987; Friston *et al*. 1994). Since a stimulus may vary in importance during the lifetime of a phenotype, it is critical for neural systems that confer value to be adaptive and flexible. The neural mechanisms involved in the selective processing of salient stimuli are uncertain, but both animal and human studies suggest the involvement of structures such as the amygdala (LeDoux *et al*. 1984, 1988; Bechara *et al*. 1995; LaBar *et al*. 1995), thalamus (Robinson & Petersen 1992), basal forebrain (Hars *et al*. 1993) and orbitofrontal cortex (Thorpe *et al*. 1983).

Classical conditioning is a simple form of associative learning in which a neutral stimulus acquires behavioural significance (and therefore salience) by being temporally paired with an innately salient unconditioned stimulus. This type of conditioning has been demonstrated across the phylogenetic scale from gastropod molluscs (Hawkins *et al*. 1983) to humans (Hodes *et al*. 1985), and the synaptic changes involved (Kandel & Schwartz 1982) represent one of the simplest forms of value-dependent neural plasticity (Friston *et al*. 1994). In mammals, this plasticity of neural response appears to involve neuromodulatory cholinergic projections, predominantly from the nucleus basalis of Meynert in the basal forebrain (Pirch *et al*. 1992; Hars *et al*. 1993; Acquas *et al*. 1996).

Primate lesion studies, employing conditioning paradigms, suggest that the amygdala is critically involved in conferring aversive and appetitive values on stimuli (Weiskrantz 1956; Jones & Mishkin 1972). Rodent experiments (LeDoux *et al*. 1984, 1988; Campeau & Davis 1995) and human neuropsychological studies (LaBar *et al*. 1995; Bechara *et al*. 1995) also implicate the amygdala in the formation of stimulus–reinforcement associations. Electrophysiological experiments in monkeys, on the other hand, suggest that the pulvinar nucleus of the thalamus has an important role in the processing of behaviourally significant or salient stimuli (Petersen *et al*. 1987; Robinson & Petersen 1992). A recent neurobiological model has proposed that the pulvinar may be crucial in the selective processing of sensory information (Olshausen *et al*. 1993). It is interesting that animal studies have indicated the critical importance of pathways between thalamus and amygdala in the mediation of conditioned responses (LeDoux *et al*. 1984).

The present study employed aversive classical conditioning (using loud noises) to manipulate the salience of different facial expressions (happy, fearful and neutral) presented to normal human subjects during positron emission tomography (PET) neuroimaging. Facial expressions of emotion are innate (Meltzoff & Moore 1977; Field *et al*. 1982), universal across cultures (Darwin 1872; Ekman 1982), and evoke automatic mimicry (Lundqvist & Dimberg 1995). This suggests that the neural mechanisms underlying the expression and perception of facial emotion are evolutionarily determined or 'hard-wired' (Ekman 1982). After conditioning to the loud noises, happy expressions (i.e. innately appetitive stimuli) acquire an aversive quality, while the negative quality of fearful expressions (i.e. innately aversive stimuli) is enhanced.

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In humans, psychophysiological studies suggest predominantly right hemisphere involvement in aversive classical conditioning (Johnsen & Hugdahl 1993). Right hemisphere activations in orbitofrontal, dorsolateral prefrontal and temporal cortices have been reported in a previous PET study of aversive conditioning (Hugdahl *et al*. 1995). We predicted, therefore, on the basis of this human evidence as well as animal studies (LeDoux *et al*. 1984, 1988; Robinson & Petersen 1992; Hars *et al*. 1993), that aversive conditioning of faces would produce right hemisphere activations in the pulvinar, amygdala, basal forebrain, orbitofrontal cortex and brainstem nuclei. We also hypothesized, from the results of other psychophysiological experiments (Hamm *et al*. 1993), that there would be greater activation in the aversive conditioning of happy expressions compared with that of fearful or neutral expressions, i.e. where there was a conflict between the innate and the acquired value of the stimulus.

2. METHODS

Six healthy, right-handed, male subjects took part in the study. Subjects (mean age 32.7 years) were recruited by advertisement. They all gave informed consent and the study was approved by the local hospital ethics committee and ARSAC(UK). Each subject had 12 scans of the distribution of $H_2{}^{15}O$ which were obtained using a Siemens/CPS ECAT EXACT HR$^+$ PET scanner operated in high sensitivity 3-D mode. Subjects received a total of 350 MBq of $H_2{}^{15}O$ over 20 s through a forearm cannula. Images were reconstructed into 63 planes using a Hanning filter, resulting in a 6.4 mm transaxial and a 5.7 mm axial resolution (full width half maximum). Each scanning window lasted 90 s.

After initial realignment, mean PET images from each subject were scalp-edited and used as a template to edit all 12 individual PET images. Structural magnetic resonance images (MRIs) from each subject were co-registered into the same space. The scans were then transformed into a standard stereotactic space. The scans were smoothed using a Gaussian filter set at 12 mm full width at half maximum. The regional cerebral blood flow (rCBF) measurements were adjusted to a global mean of 50 ml dl^{-1} min^{-1}. A blocked (by subject) ANCOVA model was fitted to the data at each voxel, with condition effects for conditioning contingency and facial expression, and global CBF as a confounding covariate. Predetermined contrasts of the condition effects at each voxel were assessed using the usual *t*-statistic, giving a statistic image for each contrast. The PET data were analysed using statistical parametric mapping (SPM95) software from the Wellcome Department of Cognitive Neurology, London (Friston *et al*. 1995*a*, *b*).

In the period before scanning, subjects viewed a sequence of grey scale images of faces taken from a standard set of pictures of facial effect (Ekman & Friesen 1976). Images of a single face were presented on a computer monitor screen for 4 s at intervals of 15–25 s (mean 20 s). Two faces were shown during each sequence, with each face being repeated eight times in a pseudo-random order. The faces in a particular sequence had different identities but the same emotional expression. The expressions varied between happy, fearful and neutral across the sequences. Two different pairs of faces (A, B and C, D) were used, and all subjects saw the same 12 sequences of faces in a counterbalanced order.

Subjects were instructed to pay attention to the order of presentation of each pair of faces and immediately respond 'yes' if there was a consecutive repeat and 'no' if not. There were never more than three consecutive presentations of the same face. One face of a pair (the CS+) was always followed by a noise stimulus; the other face (the CS−) was always followed by silence. A 95 dB white noise burst was played for 1 s immediately after all eight presentations of the CS+ face in the conditioning acquisition sequence. The CS− face was always followed by at least 19 s of silence (i.e. before the next presentation of the CS+ face). In half the subjects, faces A and C were CS+; in the other half, faces B and D were CS+. The conditioning protocol is summarized in figure 1. Subjects were warned that noises would be played during the experiment, but they were not informed of the conditioning contingency. Subjects were told to attend equally to all stimuli throughout the experiment. After completion of all the scans, subjects were debriefed and their awareness of the conditioning contingency assessed.

The 12 PET scans corresponded to the presentation of each of the four faces (A, B, C, D) in each of the three emotional conditions (fearful, happy, neutral). The start of the PET scanning window was timed to coincide with the

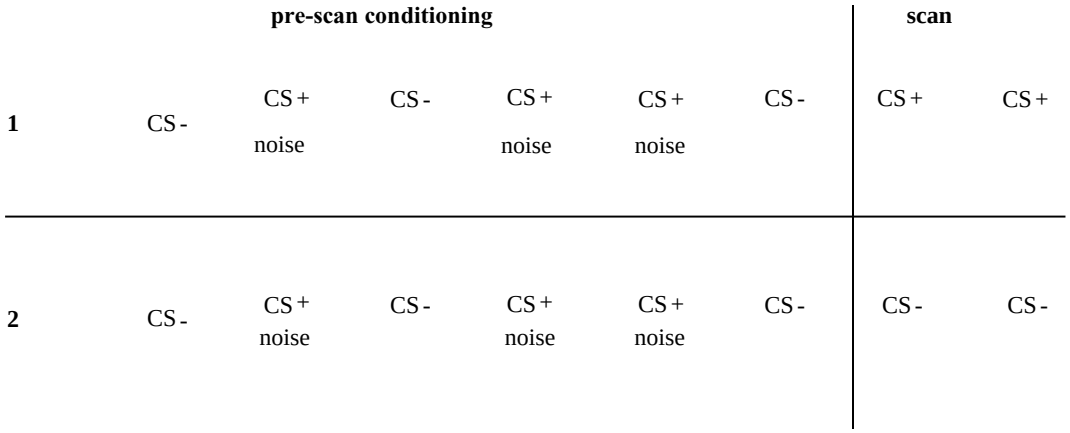

Figure 1. Diagram of conditioning protocol. Two different faces, CS+ and CS−, are shown in two sequences, 1 and 2. During the 5 min pre-scan conditioning phase, CS+ presentations are always temporally paired with a 95db white noise burst; CS− presentations are never paired with noise. During the scanning phase, the CS+ face is presented (without the noise) in sequence 1; the CS− face is presented in sequence 2. The interstimulus interval ranges from 15 to 25 s, with the scanning phase seamlessly following the conditioning phase. It is important to note that the pre-scan conditioning phases are identical for sequences 1 and 2.

end of the conditioning acquisition sequence. During the scan, four presentations of one of the preceding faces were made at 15 s intervals. No noises were played during this phase (extinction). Subjects were not informed that there were separate phases of acquisition and extinction. In six scans, the face (CS+) which had been paired with noise was presented in the extinction sequence; in the other six scans the face (CS−) explicitly unpaired with noise was presented (figure 1).

Throughout the acquisition and extinction phases, subjects' skin conductance responses (SCRs) were monitored to index autonomic conditioning. SCRs were measured with Biodata galvanic skin response equipment using Ag/AgCl electrodes attached to the palmar surface of the middle phalanges of the index and middle fingers of the right hand. Readings of skin conductance (in microSiemans) were taken every 500 ms and stored digitally on computer. All SCRs were square-root transformed to attain statistical normality (Levey 1980). Using the SCR in the 4 s period prior to presentation as a baseline, the maximal SCR deflection in the 0.5–4 s period following a face presentation was assigned as the value for the SCR to that face. The mean SCRs for CS+ and CS− faces were calculated for each of the 12 sequences, and the differences of these means tested using a paired *t*-test.

3. RESULTS

All subjects demonstrated differential conditioned SCRs. The mean CS+ SCR was 0.431 μS; the CS− mean was 0.366 μS. The difference between the means was highly significant ($p < 0.001$). There was considerable variability in the time-course and magnitude of SCRs, both between subjects and within subjects across time, as has been reported in other studies (LaBar *et al.* 1995). All subjects reported awareness of the conditioning contingency, and stated that the CS+ presentation became a predictor of the noise burst.

Table 1. *Brain regions with a significantly greater neural response to CS+ stimuli than CS−*

(Talairach coordinates, Brodmann areas and *Z*-scores are shown. All activations are significant at $p < 0.001$ (uncorrected), in a one-tailed *t*-test.)

region	coordinates (x, y, z)	*Z*-score
right orbitofrontal cortex (BA10)	12, 50, −12	4.1
right pulvinar	14, −34, 4	3.6
right superior frontal gyrus (BA46)	48, 26, 12	3.6
right anterolateral thalamus	16, −10, 8	3.28

In the contrast of rCBF values for all CS+ minus all CS− conditions, four brain regions, all in the right hemisphere, showed significant activations ($p < 0.001$, uncorrected): these were the pulvinar nucleus of the thalamus, orbitofrontal cortex (BA10), superior frontal gyrus (BA46) and an anterolateral thalamic region (figure 2 and table 1). The activation centred on $x = 14$, $y = -34$, $z = 4$ lies almost totally within the region of the right pulvinar nucleus as defined by a standard stereotaxic atlas (Tailarach & Tournoux 1988). A single area showing significantly greater activation in the CS− compared to the CS+ conditions was located in the right pons (coordinates $x = 14$, $y = -24$, $z = -28$).

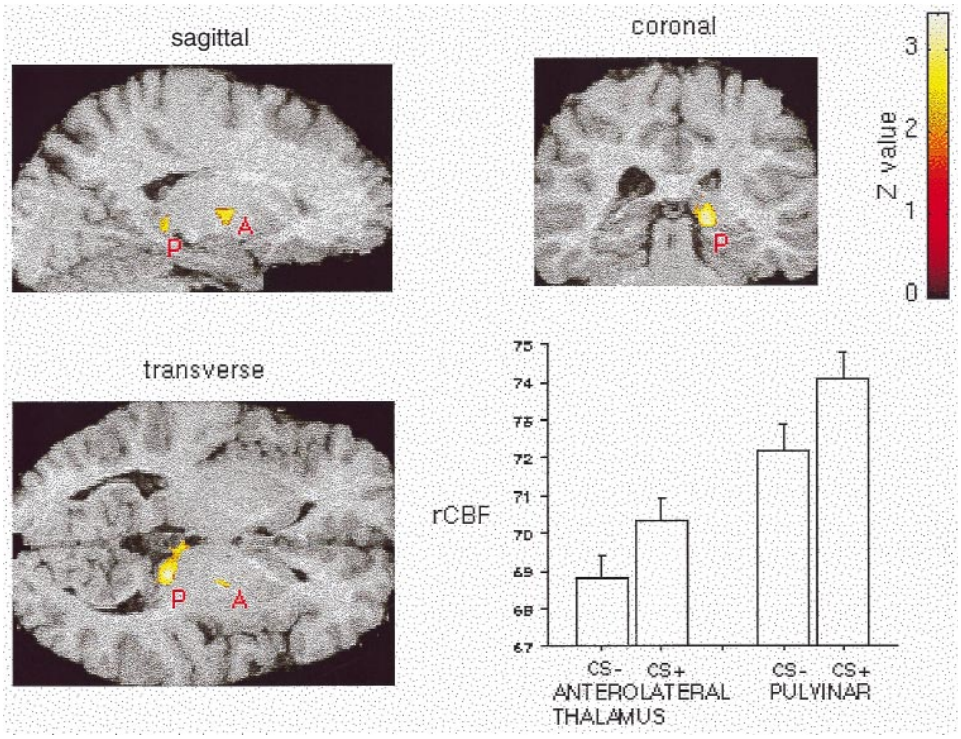

Figure 2. A statistical parametric map (SPM) showing activation of the pulvinar (P) and an anterolateral region of the right thalamus (A), together with a graphical representation of the regional cerebral blood flow (rCBF) values. The SPM is the result of a contrast of selected brain regions with a greater neuronal response to the CS+ stimuli relative to the CS−. An uncorrected p value of 0.01 was used as the threshold. Views of the brain are shown for orthogonal slices at the pixel with coordinates $x = 18$, $y = -36$, $z = 4$. The graph displays the adjusted mean rCBF values (with bars showing two standard errors) in ml dl^{-1} min^{-1} for the CS+ and CS− conditions at the pixels maximally activated in the pulvinar ($x = 14$, $y = -36$, $z = 4$) and anterolateral thalamus ($x = 16$, $y = -10$, $z = 8$).

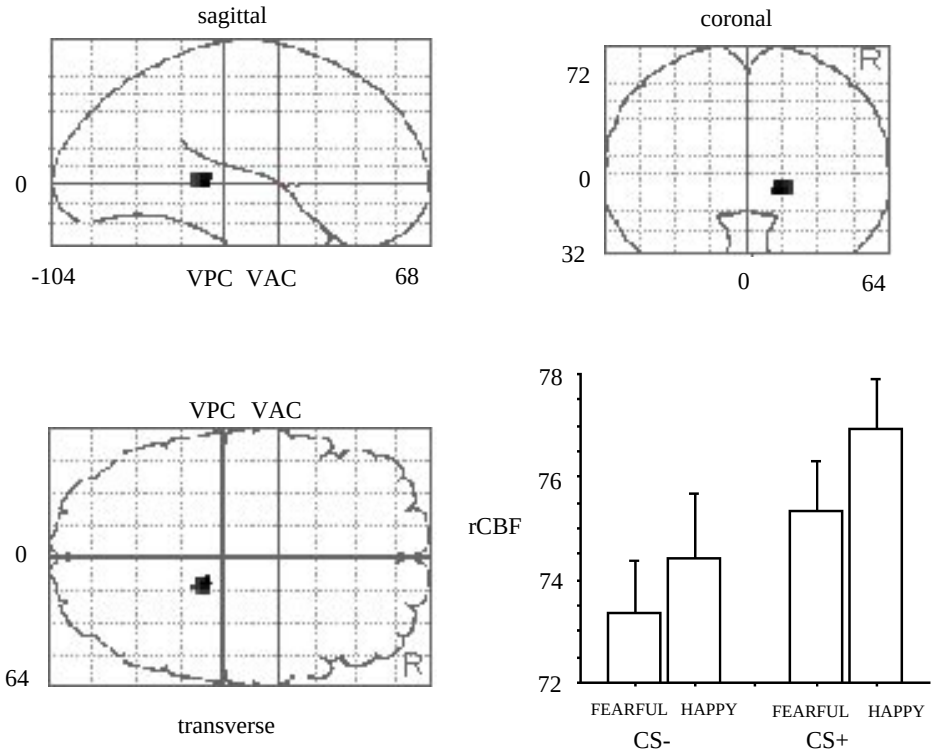

Figure 3. An SPM showing selective activation of the right pulvinar in an interaction of conditioning and emotional expression, together with a graphical representation of the rCBF values. The SPM is the result of two orthogonal contrasts, the first being identical to that in figure 1, and the second selecting brain regions showing a greater neural response to happy expressions than fearful expressions. A threshold of $p < 0.01$ was used for both contrasts, giving a significance level of $p < 0.0001$ (uncorrected) for the interaction. The activation is displayed in orthogonal views of a transparent representation of the brain, showing that the right pulvinar is the only significant region. Talairach coordinates and reference planes are shown: VAC = vertical plane through the anterior commissure; VPC = vertical plane through the posterior commissure. The graph displays the adjusted mean rCBF values (with bars showing two standard errors) in ml dl^{-1} min^{-1} at the pixel in the right pulvinar maximally activated in the orthogonal contrasts ($x = 16$, $y = -36$, $z = 0$). The interaction effect is demonstrated by the significantly larger difference between happy and fearful in the CS+ condition compared to the CS− condition.

The interaction between emotional expression and aversive conditioning was examined by applying orthogonal contrasts in SPM95. This conjunction analysis allows the identification of brain areas where changes in activity due to conditioning are significantly modulated by the category of the facial expression. Regions identified by the contrast of CS+ minus CS− conditions were therefore subjected to a second contrast of two different emotional categories, i.e. (all happy CS+ minus all happy CS−) minus (all fearful CS+ minus all fearful CS−). This analysis revealed a highly significant interaction, representing an enhanced response in the pulvinar to the aversive conditioning of happy expressions compared to fearful (figure 3).

A key aspect of the theoretical model presented in Friston *et al*. (1994) is that stimuli which acquire value or salience are defined by their ability to elicit responses in neuronal systems mediating value (i.e. the amygdala, lateral hypothalamic area and the nucleus basalis). Specifically, connections to the amygdala and the nucleus basalis from sensory neural systems are selectively strengthened when stimuli acquire value. This strengthening is itself value-dependent and depends on reinforcement by stimuli that have innate or pre-existing value. We therefore hypothesized that activity in the amygdala and nucleus basalis would be significantly correlated with thalamic activity. To test this, the rCBF values at the voxel of maximal activation in the right pulvinar ($x = 14$, $y = -34$, $z = 4$) were used as a covariate of interest to identify those regions whose activity could be predicted significantly by rCBF changes in this structure. The right amygdala (two foci: $x = 20$, $y = -12$, $z = -12$ and $x = 22$, $y = -6$, $z = -24$), right basal forebrain in the region of the nucleus basalis of Meynert ($x = 12$, $y = -10$, $z = -8$), right orbitofrontal cortex ($x = 10$, $y = 24$, $z = -8$) (BA11), right hippocampal gyrus (BA35) and bilateral fusiform gyri (right: $x = 24$, $y = -68$, $z = -12$) (BA19) covaried positively with the right pulvinar (figure 4); an area in right orbitofrontal cortex (BA10) with maximal activation at $x = 20$, $y = 58$, $z = -8$, showed negative covariance with the pulvinar. All results are significant at $p < 0.001$ (uncorrected).

4. DISCUSSION

Our findings provide compelling empirical evidence for a recent neurobiological model of selective visual processing (Olshausen *et al*. 1993). The model postulates that the pulvinar nucleus of the thalamus has a crucial controlling role in the coordination of neural processing in sensory and association cortices. Other

evidence for the model includes (i) the pulvinar's extensive reciprocal connections with visual cortical areas and other brain regions (Ungerleider *et al*. 1983); (ii) electrophysiological recordings in monkeys of pulvinar responses to visual salience (Petersen *et al*. 1987; Robinson & Petersen 1992); (iii) human studies showing attentional deficits with pulvinar lesions (Rafal & Posner 1987); and (iv) PET experiments demonstrating pulvinar activation in a selective attention task (LaBerge & Buchsbaum 1990). The specific responses to visual salience recorded in the pulvinar nucleus in the present study are consistent with these previous findings, and provide general support for the model. Our PET data do not have sufficient temporal or spatial resolution, however, to test more specific predictions.

Our study also provides evidence for stimulus-specific neural plasticity in the responses of the pulvinar nucleus, as indicated by the conditioning-induced changes in neural responsiveness. Identical stimuli and the same explicit task were used in the CS+ and CS− conditions during scanning, and the experimental design controlled for time, order, and non-specific arousal effects. Consequently, the only difference between the CS+ and CS− conditions was the experimentally induced change in salience, occurring outside the scanning window. We use plasticity here to refer to experience-dependent changes in the physiological (haemodynamic) response to stimuli. Differential haemodynamic responses, elicited by the faces, were experience-dependent in the sense that they could only be explained by associative learning prior to scanning.

We found predominantly right-sided differential responses in our aversive conditioning paradigm, consistent with psychophysiological experiments that show a right hemisphere advantage in the aversive conditioning of facial expressions (Johnsen & Hugdahl 1993). This result may conceivably have been influenced by the choice of emotionally expressive faces as stimuli, since a number of neuropsychological studies (DeKosky *et al*. 1980; Bowers *et al*. 1985; Rapcsak *et al*. 1989) implicate the right hemisphere in processing facial emotion. However, since other functional imaging data show predominantly right-sided activations with aversive conditioning of auditory tones (Hugdahl *et al*. 1995), the significance of the lateralization of response in the present study is unclear.

Activity in a right orbitofrontal region (BA10) correlated negatively with the response in the pulvinar. Single unit recordings in monkeys (Thorpe *et al*. 1983) show that neurones in the orbitofrontal cortex have rapid reversal of their responses during visual discrimination reversal learning, while rodent studies reveal that the medial prefrontal cortex is crucially involved in the extinction of conditioned responses (Morgan *et al*. 1993). These studies suggest, therefore, that the orbitofrontal cortex may be involved in reversing the enhanced thalamic responses to stimulus salience. Interestingly, a similar region of orbitofrontal cortex was also significantly activated in the CS+ condition (table 1). Since rCBF is integrated over a 90 s period in PET, a possible explanation is that both the conditioned response and the dynamic processes involved in extinguishing that response produce similar activations in the same scan. Neuroimaging techniques with greater temporal resolution may help to distinguish these components.

Only one area, located in the right pons, showed greater activity in the CS− than the CS+ condition. A projection from the amygdala to this region of the brainstem is known to be involved in fear-potentiated startle responses (Davis 1992). The activity measured in the right pons could conceivably be the result of a similar neuromodulatory process. However, the precise functional significance of the decrease in pontine rCBF in the CS+ condition is unclear. Like the orbitofrontal activation, the pontine response may be related to the extinction phase of conditioning.

Interactions between emotional category and conditioning have been demonstrated in psychophysiological experiments, which show a greater augmentation of startle response with aversive conditioning of pleasant pictures compared to unpleasant pictures (Hamm *et al*. 1993). We predicted, therefore, that the pairing of happy expressions with noise would produce larger and more significant responses than the pairing of fearful expressions with noise. This was confirmed by our results (figure 3). The interpretation of this finding is constrained by the limited temporal resolution of PET (see above). Psychophysiological experiments have also shown that aversively conditioned happy facial expressions tend to extinguish rapidly (Ohman & Dimberg 1978), whereas aversively conditioned fearful faces show resistance to extinction (Lanzetta & Orr 1986). Therefore, the enhanced response obtained with happy expressions in the present experiment may be partly related to the dynamic extinction phase of conditioning.

The pulvinar response to aversively conditioned facial stimuli was strongly correlated with activity in the amygdala. This correlated activity is consistent with a number of empirical and theoretical lines of evidence. Animal studies have indicated the importance of the amygdala and thalamo-amygdala pathways in emotional learning and, in particular, aversive (fear) conditioning (LeDoux *et al*. 1984, 1988; Campeau & Davis 1995). Human studies also implicate the amygdala in the mediation of conditioned responses (LaBar *et al*. 1995; Bechara *et al*. 1995). Moreover, humans with restricted amygdala lesions have selective deficits in recognizing fearful facial expressions (Adolphs *et al*. 1995; Calder *et al*. 1996), and an enhanced response in the human amygdala to faces expressing fear has been found in a functional imaging experiment with normal subjects (Morris *et al*. 1996).

The nucleus basalis of Meynert in the basal forebrain, which is implicated in ascending neuromodulation (Hars *et al*. 1993) and has strong anatomical connections to the amygdala (Russchen *et al*. 1985*a*), also showed correlated activity with the pulvinar. Single unit recordings in monkeys have revealed that, after conditioning, basal forebrain neurones with food-specific responses are stimulated by visual stimuli associated with food (Wilson & Rolls 1990). Also, neurotoxic lesions in the basal forebrain of

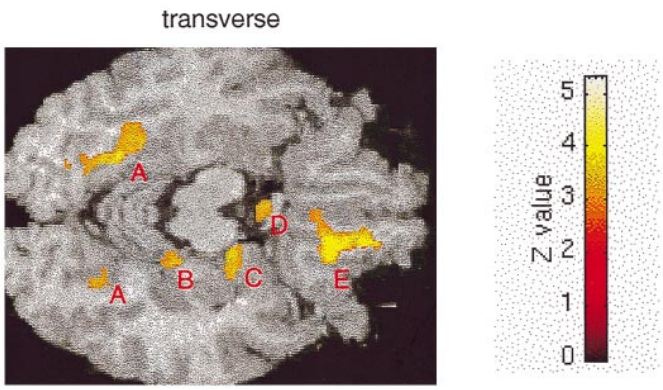

Figure 4. A statistical parametric map (SPM) of brain regions which show a positive correlation of neural activity with the right pulvinar. A = bilateral fusiform gyri (BA19), B = right hippocampal gyrus (BA35), C = right amygdala, D = basal forebrain in region of nucleus basalis of Meynert, E = right orbitofrontal cortex (BA11). The rCBF values (for all subjects and conditions) at the pixel of maximal activation in the right pulvinar ($x = 14$, $y = -34$, $z = 4$) were used as a covariate of interest, in a separate SPM analysis, to identify regions with activity that correlated positively with the pulvinar. The significance threshold was $p < 0.001$. Significantly correlated regions are shown in a transverse slice through the brain at the level $z = -12$.

monkeys have been shown to disrupt the formation of stimulus–reward associations (Roberts *et al*. 1992). Our finding of enhanced stimulus-specific connectivity between the thalamus, the amygdala and the basal forebrain is consistent, therefore, with these animal studies, and would also be predicted by Friston *et al*.'s (1994) model of value-dependent neural plasticity.

Although our study has shown a plasticity of thalamic response in relation to visual salience, the location of the underlying changes in synaptic strength is unclear. The finding of a correlation of activity between the pulvinar and the neuromodulatory systems in the amygdala and basal forebrain suggests that synaptic plasticity may be occurring within this system. The nucleus basalis of Meynert, which itself receives a significant afferent input from the amygdala (Russchen *et al*. 1985*a*), sends a strong cholinergic projection to the thalamus (Russchen *et al*. 1985*b*). Alternatively, the synaptic changes may be occurring in cortical areas projecting to the thalamus. Electrophysiological experiments in monkeys have shown that selective spatial attention to visual stimuli alters neural responses in extrastriate (Moran & Desimone 1985) and posterior parietal (Bushell *et al*. 1981) cortices. Future studies, using imaging techniques with higher temporal resolutions and employing pharmacological manipulations may be able to address this crucial question, and also further characterize the interactions between the thalamus, the neocortex, and the brainstem.

During the experiment, subjects were explicitly engaged in a memory task which had no relation to the conditioning paradigm, and were instructed to attend equally to all stimuli. This precludes an interpretation of the data purely in terms of voluntary changes in selective attention. If 'attention' is used in a more general sense to refer to enhanced processing of stimuli, then our experiment could be said to show an 'attentional' effect. However, the use of the term 'attention' in this broad sense does not help to discriminate the various aspects of emotional learning and conditioning addressed in this experiment.

An aversive conditioning paradigm was employed in this study to alter the salience or value of visual stimuli. We interpret the data as providing support for neurobiological models which postulate crucial roles for the thalamus, amygdala and basal forebrain in the selective processing of stimuli (Robinson & Petersen 1992; Hars *et al*. 1993; LeDoux 1993; Olshausen *et al*. 1993; Friston *et al*. 1994). Although other interpretations of the data are possible, it is striking that the neural structures activated in our paradigm accord with the anatomical predictions of these models. The empirical support provided for these theories indicates that the use of conditioning paradigms in functional neuroimaging may prove a powerful tool in elucidating the mechanisms involved in high-level neural organization.

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