

# Human Amygdala Responses During Presentation of Happy and Neutral Faces: Correlations with State Anxiety

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**Background:** Previous functional imaging studies demonstrating amygdala response to happy facial expressions have all included the presentation of negatively valenced primary comparison expressions within the experimental context. This study assessed amygdala response to happy and neutral facial expressions in an experimental paradigm devoid of primary negatively valenced comparison expressions.

**Methods:** Sixteen human subjects (eight female) viewed 16-sec blocks of alternating happy and neutral faces interleaved with a baseline fixation condition during two functional magnetic resonance imaging scans.

**Results:** Within the ventral amygdala, a negative correlation between happy versus neutral signal changes and state anxiety was observed. The majority of the variability associated with this effect was explained by a positive relationship between state anxiety and signal change to neutral faces.

**Conclusions:** Interpretation of amygdala responses to facial expressions of emotion will be influenced by considering the contribution of each constituent condition within a greater subtractive finding, as well as 1) their spatial location within the amygdaloid complex; and 2) the experimental context in which they were observed. Here, an observed relationship between state anxiety and ventral amygdala response to happy versus neutral faces was explained by response to neutral faces.

**Key Words:** Amygdala, functional magnetic resonance imaging, human, state anxiety, happy faces, neutral faces

Numerous studies have demonstrated that the amygdala responds to facial expressions of emotion, with a particular emphasis on the study of fearful facial expressions (Breiter et al 1996; Morris et al 1996; Phillips et al 1997, 1998; Whalen et al 1998, 2001). The amygdala has also been shown to be responsive to other types of facial expressions (Anderson et al 2003; Yang et al 2002), including positive expressions (i.e., happy), when compared with either a neutral-face baseline (Breiter et al 1996; Canli et al 2002; Killgore and Yurgelun-Todd 2001; Yang et al 2002) or a low-level fixation baseline (Pessoa et al 2002; Whalen et al 1998).

To date, the experimental designs of studies reporting amygdala signal changes to happy facial expressions have included at least one negatively valenced facial expression. To determine whether the human amygdala is responsive to happy facial expressions in their own right (and not because of the presence of primary negative expressions in the experimental context), the present experimental design included only happy and neutral faces, as well as an interleaved fixation baseline condition. Previous behavioral research has demonstrated that the interpretation of neutral faces can vary depending on the presence of other primary expressions in the experimental context (e.g., Russell and Fehr 1987), so we were particularly interested in assessing amygdala response to neutral faces, given that they represent the most "potentially" negative stimulus in the current paradigm.

Previous neuroimaging research has demonstrated a relation-

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ship between amygdala activation and individual personality characteristics (Abercrombie et al 1998; Canli et al 2002; Fischer et al 2001; Johnson et al 1999; Schaefer et al 2002). Indeed, the results of one study (Canli et al 2002) suggest that amygdala responses are more variable to happy expressions (compared with fear) and that personality measures are particularly useful in explaining this variability. Therefore, we used such personality measures to assess their relationship with amygdala responses to happy versus neutral faces, as well as the unique contribution of each condition considered as a change from the fixation baseline. Consistent with our previous reports (Kim et al 2003; Whalen et al 1998, 2001), we assessed the current functional magnetic resonance imaging (fMRI) responses with a particular emphasis on spatial location within the amygdaloid complex.

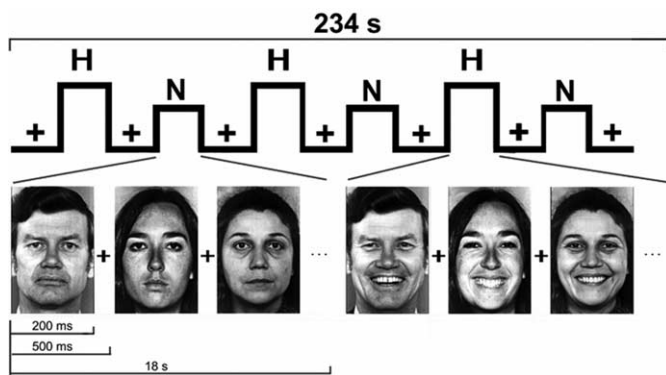
## Methods and Materials

### Subjects

Subjects were 16 right-handed (Oldfield 1971) adults (eight female; aged  $24.4 \pm 3.67$  years [mean  $\pm$  SD]). All subjects underwent a brief clinical interview to ensure an absence of current or past psychiatric, neurologic, or medical illness in themselves and an absence of psychiatric illness in first-degree relatives. This investigation was conducted in accordance with the guidelines of the Human Subjects Committee of University of Wisconsin-Madison; all subjects provided written informed consent for participation.

### Stimuli and Apparatus

Face stimuli consisted of happy and neutral expressions of six individuals, three female (Ekman and Friesen 1976; identities used were C, EM, GS, MF, SW, and WF) normalized for size and luminance. For four subjects, stimuli were back-projected onto a screen within the imaging chamber and were viewable by a mirror (1.5 in  $\times$  3.5 in [3.8 cm  $\times$  8.9 cm]) approximately 6.5 in (16.5 cm) from the subject's face. The remaining 12 subjects viewed stimuli through Avotec Silent Vision 4000 Enhanced, High Resolution Fiber Optic Video System (Avotec, Inc., Stuart, Florida) goggles centered and focused above the subjects' eyes.



**Figure 1.** Temporal layout of face presentations within one scan. H, happy; N, neutral; +, fixation.

Within each of the current effects, examination of individual subject data verified that subjects who viewed stimuli via back-projection did not represent extreme scores but rather were normally distributed among the responses for the group. Head stabilization was achieved by supporting the subject's head with pillows.

### Procedure

Subjects passively viewed blocked presentations of faces during two functional scans (see Figure 1). During each scan, 18-sec blocks alternated between presentations of happy (H) and neutral (N) faces. Within a scan, face presentation blocks were interleaved with 18-sec blocks during which a fixation point (+) was presented on an otherwise blank screen. An example of a typical scan consisted of the following: +N+H+N+H+N+H+. The order of happy and neutral face blocks was counterbalanced within and across subjects. Each scan lasted 4 min 14 sec.

During each 18-sec block, subjects viewed 36 happy or neutral stimuli (six presentations of six individual faces, matched for presentation number and identity). Each face stimulus was presented for 200 msec at an interstimulus interval of 300 msec (i.e., two per second), for consistency with previous studies (Breiter et al 1996; Kim et al 2003; Whalen et al 2001). The background color of the screen was black across all blocks.

Upon exiting the scanner, subjects were again presented with the face stimuli in an 18-sec blocked format and were asked to label the expression and then provide a valence rating for the block (scale 1–9: 1 = very positive, 3 = positive, 5 = neither negative nor positive, 7 = negative, 9 = very negative). Subjects provided ratings of blocks of faces, rather than individual faces, to facilitate comparison of these data with their blocked fMRI data (see also Kim et al 2003). One block of each expression was presented (in the same order as their first functional scan), during which subjects provided one label and valence rating for each block of faces at the midpoint of the block.

Subjects also completed the following behavioral scales: Edinburgh Handedness Inventory (Oldfield 1971), Beck Depression Inventory (BDI; Beck et al 1961), State-Trait Anxiety Inventory (STAI, STAI; Spielberger et al 1988), the NEO Five-Factor Inventory (NEO-FFI [Neuroticism and Extraversion subscales only]; Costa and McCrae 1991), and the Positive and Negative Affect Scale (PANAS; Watson et al 1988).

### Image Acquisition and Analysis

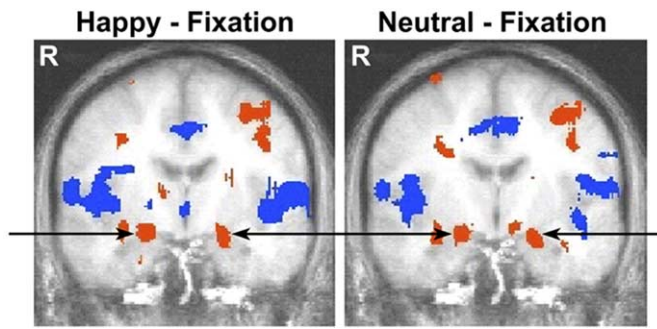
Subjects were scanned with a General Electric Signa 3.0 Tesla fMRI scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a quadrature head coil. For each subject, a whole-brain, high-resolution, T1-weighted anatomic scan (three-dimen-

sional spoiled gradient; 256 × 256 in-plane resolution, 240-mm field of view [FOV]; 124 × 1.1-mm axial slices) was acquired for transformation and localization of functional data to Talairach space (Talairach and Tournoux 1988). An echo planar imaging sequence (repetition time = 2000 msec, echo time = 33 msec, 60° flip angle) was used to collect functional data, with 18 contiguous 3-mm-thick coronal oblique slices (.5-mm interslice gap; 64 × 64 in-plane resolution, 180-mm FOV). This functional acquisition scheme provided for slices with roughly isotropic voxels (2.812 × 2.812 × 3.0 mm [+ .5-mm skip], or 27 mm<sup>3</sup>) that were centered over the amygdala and tilted approximately 30° in an anterior direction. These slices covered the medial prefrontal cortex (mPFC) in an anterior direction, extending posteriorly to the posterior extent of the splenium of the corpus callosum. Thus, we did not image the frontal or occipital poles, posterior cingulate, or much of the parietal lobe.

Standard software (AFNI; Cox 1996) was used to perform a random-effects analysis of functional data. Raw functional blood oxygen level-dependent (BOLD) images were motion-corrected, yielding estimated rotations and translations of less than 1° and 1.5 mm for every subject. Next, functional data were spatially smoothed with a Gaussian kernel with 6 mm full-width half maximum. A linear model with boxcar regressors, lagged by 2 repetition time (TR) intervals, for happy and neutral conditions was used to generate linear contrast maps of happy versus neutral, happy versus fixation, and neutral versus fixation. Each contrast map was then converted to units of percent signal change and spatially normalized into Talairach space. Percent signal change contrast maps were also averaged across runs to create one averaged percent signal change map per subject. Contrast maps were then analyzed across subjects with voxel-wise one-sample *t* tests. Voxel-wise bivariate correlations across subjects were calculated between happy versus neutral percent signal change (or the change of either from the fixation baseline) and raw scores of the behavioral measures. Data from one female subject was excluded from the analysis of state anxiety (Figure 3) because she was found to have signal changes that were more than 2 SDs above the group mean and twice that of the next highest subject's signal change at this locus.

Given this study's focus on responses within the amygdala, we first defined the anatomic boundaries of this region. The amygdala boundaries constituted a search volume of approximately 3500 mm<sup>3</sup> bilaterally (Mai et al 1997). Because we discuss response distinctions made between dorsal versus ventral amygdala, we note that the dorsal/ventral cut-off within Talairach space was  $z = -10$  mm (see Kim et al 2003). The maximally activated voxels of all reported results were statistically significant at a threshold of  $p < .05$ , corrected for multiple comparisons, as stipulated by Monte Carlo simulations (AlphaSim within AFNI), based on the search volume stated above.

Susceptibility-related signal "dropout" attributable to B0 inhomogeneity is of particular concern within the amygdala (Ojemann et al 1997). We set acquisition parameters and took precautions to avoid susceptibility-related signal dropout in the amygdaloid region as follows: 1) relatively small and roughly isotropic voxels were acquired to reduce intravoxel signal dephasing; 2) data were acquired in coronal slices to minimize through-plane signal dephasing; and 3) a relatively short echo time (TE) of 33 msec was used to minimize phase dispersion at the time of echo. Parameters similar to these, used in the current and in our previous studies (Kim et al 2003; Whalen et al 2001), have recently been reported to provide optimal coverage of the amygdaloid region (Chen et al 2003). In addition, we verified that



**Figure 2.** Happy and neutral faces (compared with fixation) demonstrate similar signal increases in the dorsal amygdala/substantia innominata (SI) region. The overlap in spatial location in response to these two expressions explains why a direct contrast did not reveal significant activation to happy versus neutral faces within the dorsal amygdala/SI. Activation is presented here at  $y = -7$  (which best approximated their respective maximally activated voxels), but these activations comprised the entire anterior–posterior extent of the dorsal amygdala/SI extending from  $y = 0$  to  $y = -9$ . Image threshold  $p = .05$ , corrected. Positive activations are depicted in red, negative activations in blue. Image shown in radiologic convention (right = left, left = right).

all subjects moved less than 1.5 mm (i.e., half a voxel) in all directions (anterior–posterior, right–left, inferior–superior), thereby ruling out movement-related susceptibility “edge” effects. Finally, because differences in signal quality across subjects might mimic a correlational finding, we verified that there was no significant relationship between state anxiety scores and baseline signal levels across subjects (i.e., fixation condition) at the reported left and right amygdala correlational loci (both  $p > .20$ ).

## Results

### Behavioral Measures

Mean valence ratings of happy faces ( $1.63 \pm .719$ ; range = 1–3; mode = 1) were significantly more positive than those of neutral faces [ $5.75 \pm .856$ ; range = 4–7; mode = 6;  $t(15) = -11.716$ ,  $p < .0001$ ]. The behavioral measures administered yielded the following mean scores: Edinburgh Handedness Inventory: 94.44% Right  $\pm .05$ ; Beck Depression Inventory:  $2.26 \pm 2.29$ ; STAI:  $29.5 \pm 4.7$ ; STAI:  $29.38 \pm 3.69$ ; NEO-FFI Neuroticism subscale:  $12.31 \pm 4.3$ ; NEO-FFI Extraversion subscale:  $31.31 \pm 5.13$ ; PANAS Positive Affect subscale:  $28.56 \pm 6.84$ ; PANAS Negative Affect subscale:  $11.78 \pm 2.33$ . There were no gender differences within any of these measures (all  $p > .10$ ). These behavioral measures indicate that all subjects were right-handed, all subjects perceived happy faces as positive in nature, and all scores for depression and anxiety were within normal limits.

### fMRI Data: Convergence with Previous Studies

When considered as a change from the low-level fixation condition, both happy and neutral faces produced significant signal increases across the dorsal amygdala/substantia innominata (SI) region (see Figure 2). The localization of these effects within the dorsal amygdala/SI is consistent with the dorsal nature of previously reported loci (Breiter et al 1996; Pessoa et al 2002; Whalen et al 1998). In addition, consistent with previous reports (Breiter et al 1996), these signal increases habituated significantly to repeated presentations within scans [i.e., block 1 > block 2 > block 3; run 1:  $F(2,14) = 15.50$ ,  $p = .000012$ ; run 2:  $F(2,14) = 7.28$ ,  $p = .0027$ ] and showed a trend toward decreases across scans [i.e., scan 1 > scan 2;  $F(1,15) = 5.63$ ,  $p = .016$ ; not

significant after cluster threshold correction]. Given the similar responsiveness seen to both conditions, we did not observe a significant signal difference to happy versus neutral faces within the dorsal amygdala/SI region.

There was a signal increase to happy versus neutral faces in the anterior and ventral amygdala [ $t(15) = 3.516$ ,  $p = .0031$ , max voxel:  $x = 25$ ,  $y = 0$ ,  $z = -14$ ], in a location consistent with a previous report (Yang et al 2002). This activation did not exceed corrected statistical thresholding, because it was rather spatially circumscribed (e.g., this locus comprised only  $17 \text{ mm}^3$  that exceeded  $p < .01$ , uncorrected). Furthermore, at this locus, a significant difference between happy versus neutral faces was observed only during the second scan [happy versus neutral, scan 1:  $t(15) = 1.094$ ,  $p = .29$ ; happy versus neutral, scan 2:  $t(15) = 3.574$ ,  $p = .0028$ ].

At the posterior border of the right ventral/amygdala hippocampus, there was a main effect of gender: female subjects were more responsive to all face stimuli compared with male subjects [ $F(1,14) = 2.34$ ,  $p = .00032$ ,  $x = 21$ ,  $y = -8$ ,  $z = -17$ ]. This effect differs from that observed in the dorsal amygdala/SI, where magnitude of responsivity to these stimuli was similar for male and female subjects. This effect is not discussed further owing to 1) a lack of a significant gender  $\times$  expression interaction; and 2) its posterior location and contiguity throughout the hippocampus (reflecting perhaps a gender difference in greater medial temporal lobe responsivity rather than specifically in the amygdala).

### fMRI Data: Correlations with State Anxiety

Figure 3A presents loci within the right ( $r = -.646$ ,  $p = .009$ ;  $x = 19$ ,  $y = -5$ ,  $z = -21$ ) and left ( $r = -.685$ ,  $p = .005$ ;  $x = -22$ ,  $y = -5$ ,  $z = -18$ ) ventral amygdala showing a significant negative correlation between STAI scores and response to happy versus neutral faces. Within Talairach space (Talairach and Tournoux 1988; Mai et al 1997), these loci were within the basolateral complex (BLC), which in the human is located within the ventral amygdala (see Methods). Figure 3B and C present scatterplots depicting the negative relationship between state anxiety and response to happy versus neutral faces for these left and right ventral amygdala loci. Greater levels of state anxiety were associated with smaller signal changes to happy versus neutral faces, indeed even reversing (i.e., neutral > happy) in the most highly state-anxious subjects.

To illustrate the relative contributions of response to happy and/or neutral faces to this subtractive finding, Figure 3D–G present separate state anxiety–amygdala response scatterplots depicting responses to happy faces (vs. fixation) and neutral faces (vs. fixation) for the left and right loci depicted in Figure 3A. Figure 3D and E suggest that the relationship between state anxiety and amygdala response to happy faces is not compelling within either the right ( $r = -.060$ ,  $p = .83$ ; Figure 3D) or left ( $r = -.174$ ;  $p = .535$ ; Figure 3E) amygdala. Figure 3F and G show a significant positive relationship between state anxiety and amygdala response to neutral faces within the right ( $r = .480$ ,  $p = .035$ ; Figure 3F) and left ( $r = .473$ ,  $p = .038$ ; Figure 3G) amygdala. Thus, the observation that signal “change” between happy and neutral faces is related to levels of state anxiety (Figure 3B and C) can be explained as a greater level of amygdala reactivity to neutral faces with greater levels of state anxiety (Figure 3F and G).

No other behavioral measures showed a significant relationship with amygdala responsivity to happy versus neutral faces (or either condition compared with fixation).



neutral faces. Assessment of responsivity to each face type as a change from the fixation baseline showed that a positive relationship between state anxiety and amygdala response to neutral faces was the basis of this effect in the present experimental context.

### Considering Human Amygdala Response to Happy Facial Expressions

First, fMRI responses to happy and neutral faces were not uniform across the human amygdaloid complex. Consistent with previous studies, the dorsal amygdala/SI demonstrated signal increases to both happy faces (Breiter et al 1996; Pessoa et al 2002; Whalen et al 1998) and neutral faces (Breiter et al 1996; Pessoa et al 2002). The human dorsal amygdala/SI region comprises the central nucleus of the amygdala, as well as basal forebrain cell groups, such as nucleus basalis of Meynert and sublenticular extended amygdala neurons. These neuronal groups might constitute a functional unit whose activity is related to the arousal properties of presented stimuli (Detari and Vandervolf 1987; Whalen et al 1994; Kapp et al 1992). Thus, signal increases to faces in this region can be observed to a host of expressions (Breiter et al 1996; Pessoa et al 2002; Whalen et al 1998, 2001) and in the present experimental context did not discriminate between happy and neutral faces.

The human ventral amygdala comprises the BLC. The BLC has been shown to be critical to the detection and convergent processing of stimuli that predict biologically relevant outcomes (LeDoux et al 1990; Schoenbaum et al 1999). Within the ventral amygdala a trend toward signal increases to happy versus neutral faces was observed, consistent with a previous report (Yang et al 2002).

Human amygdala lesion patients are not impaired in their processing of happy faces (Adolphs et al 1994, 1995), which suggests that amygdala response to these stimuli might play more of a monitoring role rather than being causally related to behavioral outcomes. Of course, this point can only speak to the behavioral outcomes that have been measured to date. Like negative expressions, happy expressions offer predictive information concerning the ensuing probability of threat (or a positive outcome). Thus, human ventral amygdala response to happy faces converges with the demonstrated role of the BLC in appetitive conditioning in animal subjects (e.g., Schoenbaum et al 1999).

Given the human neuroimaging data garnered to date, amygdala response to fearful expressions seems to be more fixed, automatic, and perhaps even preattentive (Anderson et al 2003; Canli et al 2002; Whalen et al 1998), whereas response of this system to happy expressions is perhaps more variable and elaborative (Canli et al 2002). In the present study, amygdala response to happy faces was significantly different than that observed to neutral faces only for later stimulus presentations (i.e., scan 2 only). Therefore, discrimination of happy versus neutral faces within the ventral amygdala was qualitatively different than that observed to fearful expressions in previous studies, in which discrimination was observed within initial stimulus presentations (Breiter et al 1996; Whalen et al 2001). This distinction in temporal profile might offer a hint at potential behavioral outcomes (in response to happy faces) that might be attenuated by amygdala lesions.

### Interpreting Amygdala Response as a Function of State Anxiety

A face constitutes a biologically relevant environmental “canvas” from which predictive information is routinely gleaned. Here, state anxiety levels were related to the level of ventral

amygdala reactivity to this source of potential predictive information. Indeed, this effect was located within the BLC, the portion of the amygdaloid complex most notably involved in detection and convergent processing of stimuli that predict biologically relevant and often aversive outcomes (Davis and Whalen 2001; LeDoux et al 1990). This result might be consistent with the notion that elevated state anxiety affects the ability to disengage visual attention from threat-related expressions (e.g., see Fox et al 2001). Though neutral faces are not necessarily threat-related, it is possible that directly contrasting neutral faces with only happy faces in the present study design (an alternating-block design intended to “polarize” categorical discrimination between expression conditions) created an experimental context in which state anxiety correlated with response to the most “potentially” negative predictive stimulus in the environment. Such a hypothesis would be consistent with data showing that primary facial expressions can serve as “anchors” for neutral faces, the latter being rated more negatively when presented with positively valenced expressions than when presented with negatively valenced expressions (Russell and Fehr 1987).

An alternative hypothesis would contend that the observed relationship between amygdala response to neutral faces and state anxiety was observed, not because of the status of happy faces as positively valenced per se, but because of their clarity of valence or category. To elaborate, happy expressions are discriminated more quickly and more accurately than any other expression (e.g., Ekman et al 1987; Pollak et al 2000, 2001). In addition, subjects report having more prior experience with these expressions compared with other primary expression categories (Bond and Siddle 1996; Whalen 1998). Thus, within the present experimental context, amygdala responsivity might begin to track the “least clear” expression category, varying as a function of state anxiety. This hypothesis would predict that amygdala response to neutral faces should show a similar relationship with state anxiety, even when these faces alternate with a clearly negative expression (e.g., anger).

The two hypotheses considered thus far treat response to neutral faces as a contrast effect, contextually dependent on the comparison expression within a given experimental paradigm. Alternatively, amygdala response that varies as a function of state anxiety might be related to the inherent uncertainty of neutral faces. That is, this effect might be more absolute than relative. Such a hypothesis would predict that this relationship between state anxiety and amygdala response to neutral faces would be observed regardless of the experimental context.

### Addressing Variability in a “Baseline” Condition

Identifying a source of variability influencing amygdala response to a “neutral” face baseline is both scientifically exciting and experimentally complicating. Documenting that such variability exists is just the first step. Upon knowing of its existence, one strategy is to try to counteract some of this variability. For example, some studies use 25% happy faces as a baseline condition when assessing responsivity to primary negative expression categories (e.g., Phillips et al 1998). Presumably, the use of such stimuli decreases variability in amygdala responsivity within the baseline, allowing for a cleaner comparison of primary expression stimuli. To the extent that state anxiety contributes to this variability, one could test such an assumption within the present experimental design, hypothesizing that substitution of 25% happy faces as the “neutral” face baseline would attenuate (at least to some degree) the relationship with state anxiety observed here.



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