

# Habituation of attentional networks during emotion processing

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Dysfunctional emotion processing is a key aspect of many neuropsychiatric disorders. This dysfunction may be due to an abnormal magnitude of neural substrate activation during emotion processing or due to an altered time course of the neural substrate response. To better understand the temporal characteristics of the neural substrate activation underlying implicit emotion processing, nine healthy female controls were repeatedly exposed to pictures of affective faces while performing a gender identification task in an fMRI. As the salience of the stimuli decreased with repeated exposure, brain areas implicated in a right hemispheric spatial

attention network (including the posterior parietal cortex (BA 40) and the frontal eye fields (BA 6)) habituated while brain areas lateralized to the left hemisphere (including the angular gyrus (BA 39), posterior superior temporal gyrus (BA 39) and insula (BA 13)) sensitized. These results provide strong evidence that the time course of activation is a critical component when assessing the function of neural substrates underlying emotion processing (specifically whether habituation is altered) in neuropsychiatric patients. *NeuroReport* 13:1255–1258 © 2002 Lippincott Williams & Wilkins.

**Key words:** Attention; Emotions; Face; Functional magnetic resonance imaging (fMRI); Habituation; Hemispheric laterality

## INTRODUCTION

Repeated exposure to a stimulus without meaningful consequences causes a decrease in neural response known as habituation [1–3]. It has been proposed that this reduced response involves a re-allocation of attentional resources [2,3]. In other words, as the salience of a novel object decreases, the attention allocated to that object will also decrease [3,4].

Mesulam has proposed the existence of a distributed large-scale network responsible for allocating attentional resources to novel objects in the visual field [5]. This attentional network consists of three cortical epicentres: the posterior parietal cortex, the frontal eye fields, and the cingulate gyrus. The parietal component of the network creates a salience map of the external world that is utilized by the frontal component in order to preferentially allocate attention to the various novel stimuli located on the map. The cingulate gyrus then extrapolates the motivational relevance of each novel stimulus and sustains the level of effort needed for the execution of attentional tasks. Thus, the phenomenon of spatial attention is created by the interaction between the different components of this attentional network.

Altered processing of affective stimuli makes the concept of a salience map particularly important. This notion may be especially relevant to the understanding of emotion processing in patients with schizophrenia [6], Huntington's

disease [7], Alzheimer's disease [8], and obsessive-compulsive disorder [7], all of whom show impairment in assessing the salience of certain affective stimuli in the external world. An increased or decreased sensitivity to specific emotional valences has been proposed to underlie these patient's dysfunctional emotion processing [9]. However, a recent study [10] hypothesized this dysfunction may also involve a failure to habituate to particular affects. In order to examine this hypothesis, it is critical to first determine how normal human volunteers habituate during emotion processing.

Utilizing fMRI and a test/retest design, this study repeatedly presented pictures of affective faces to nine healthy female controls while they performed a gender identification task. The aim of the study was to examine whether neural substrates underlying implicit emotion processing undergo significant habituation. Recently, Wright *et al.* [3] assessed habituation to repeatedly presented emotional faces by concentrating on activation within the amygdala and found that the amygdala differentially habituates depending on the affective valence of the face. In contrast, this study focuses on the top-down modulation of implicit emotion processing (i.e. on the interaction between attentional networks and habituation). It was hypothesized that areas involved in Mesulam's attentional network [5] (the posterior parietal cortex, the frontal eye fields, and the cingulate gyrus) would habituate as the salience of the affective pictures decreased with repeated exposure.

## MATERIALS AND METHODS

**Subjects:** Nine right-handed healthy female participants with a mean ( $\pm$  s.d.) age of  $31.2 \pm 7.6$  (range 23–44) years and an average education level of  $15.6 \pm 1.8$  (range 13–18) years participated in this study. All participants were screened for a history of psychiatric, neurological, and visual disorders by one of the investigators (MPP). Each participant provided informed consent as established and approved by the UCSD Institutional Review Board (000730).

**Task paradigm:** For each block, subjects viewed six colored images of emotionally expressive faces (three males and three females presented in a counter-balanced order) taken from a standard set of pictures of facial affect [11]. Each face was shown for 2.5 s with a 0.5 s inter-trial interval during which subjects were asked to determine whether the image showed a male or female by pressing the left or right button of a mouse. The faces in each block all displayed a particular facial expression (either happy, angry, fearful, or contempt). Following each block of pictures was a nine second presentation of a fixation black cross (baseline condition during which subjects were instructed not to press any buttons). All images were back projected onto a screen with a gray background in the MRI room within a  $6^\circ$  subtended visual angle. The duration of a single functional run was 324 s during which each block of pictures (happy, angry, fearful, or contempt) were presented three times in a pseudo-randomized order. After completion of the task, each subject was immediately re-tested using the same task, thereby exposing them to a particular affective face a total of six times.

**fMRI acquisition:** MRI were obtained using a 1.5T whole body system (Siemens, Erlangen). High-resolution structural T1-weighted sagittal images of the whole brain (MPRAGE, TR = 11.4 ms, TE = 4.4 ms, flip angle =  $10^\circ$ , FOV =  $256 \times 256$ , 1 mm in-plane resolution, 1 mm slice thickness) were collected. Thirty-two slices of T2\*-weighted functional images were obtained in the transverse plane using gradient-recalled echo planar imaging (TE = 40 ms, flip angle =  $90^\circ$ ,  $64 \times 64$  pixel, FOV =  $220 \times 220$  mm, 3.4 mm in-plane resolution, 3 mm slice thickness) every 3000 ms (TR) for 112 repetitions. Functional images were co-registered to structural images and transformed into Talairach space [12].

**Data analysis:** The Analysis of Functional Neuroimages (AFNI) software package was used to process all structural and functional images. Echoplanar images were co-registered using a 3D co-registration algorithm to the whole brain image that resulted in the smallest amount of image translation and rotation relative to all other images. The percent signal change during the presentation of the faces relative to the baseline cross was used as the measure of differential blood oxygen level-dependent (BOLD) activation.

The AFNI program 3dDeconvolve was used to calculate the estimated impulse response function (i.e. BOLD response) for each of the four block types. A time-shifted reference function that coded 1 for the block type of interest and 0 for all other block types was used to analyze the

impulse response function occurring 3–9 s post stimulus onset at each voxel. The regressor coefficients for each time shift (i.e. 1, 2, and 3 TR lags) were summed and divided by the mean MR signal produced during the baseline condition to yield a percent signal change for each block type. Next, a Gaussian spatial filter with FWHM of 3.4 mm was applied to the voxel-wise percentage signal change data to account for individual variations in brain anatomy. The functional data of each participant were normalized to Talairach coordinates in order to make group inferences. Finally, percentage signal change served as the dependent variable in a  $4 \times 2$  mixed model ANOVA with facial expression (happy, angry, fearful, and contempt) and test number (test and re-test) used as fixed factors and participants as a random factor.

In the cluster analysis, a joint probability threshold adjustment method based on Monte-Carlo simulations was used to protect against false positive identification of BOLD activation [13]. As a result of these simulations, a voxel-wise *a priori* probability of  $p < 0.05$  and a minimum cluster volume threshold of  $350 \mu\text{l}$  with a connectivity radius of 3.4 mm were used to protect against false-positive detection of significant cluster-wise BOLD activation at  $p < 0.05$ . Areas that survived statistical thresholding were used to define functionally derived regions of interest (fROIs). For each fROI we obtained the cluster-wise average percentage signal change for each subject; examined the percentage signal change across test one and test two in a within-subjects repeated measures ANOVA; and used the ANOVA results to determine significant differences in cluster-wise average percentage signal change (brain activation while viewing affective faces compared to baseline cross fixation) across all subjects.

The percentage signal changes across the fROIs were extracted for each subject and were subjected to a repeated measure ANOVA (test/re-test) in order to extract the F and *p* values for each cluster. Furthermore, in order to assure that the variance in percentage signal change was due to habituation, the raw time series data for each fROI was extracted from each subject. The average time series data (of each fROI) from all nine subjects was then calculated and graphed jointly with a face regressor reference function. The average percentage signal change for each block was computed and used to graph a trend line that assessed whether or not a particular fROI exhibited a pattern consistent with habituation.

## RESULTS

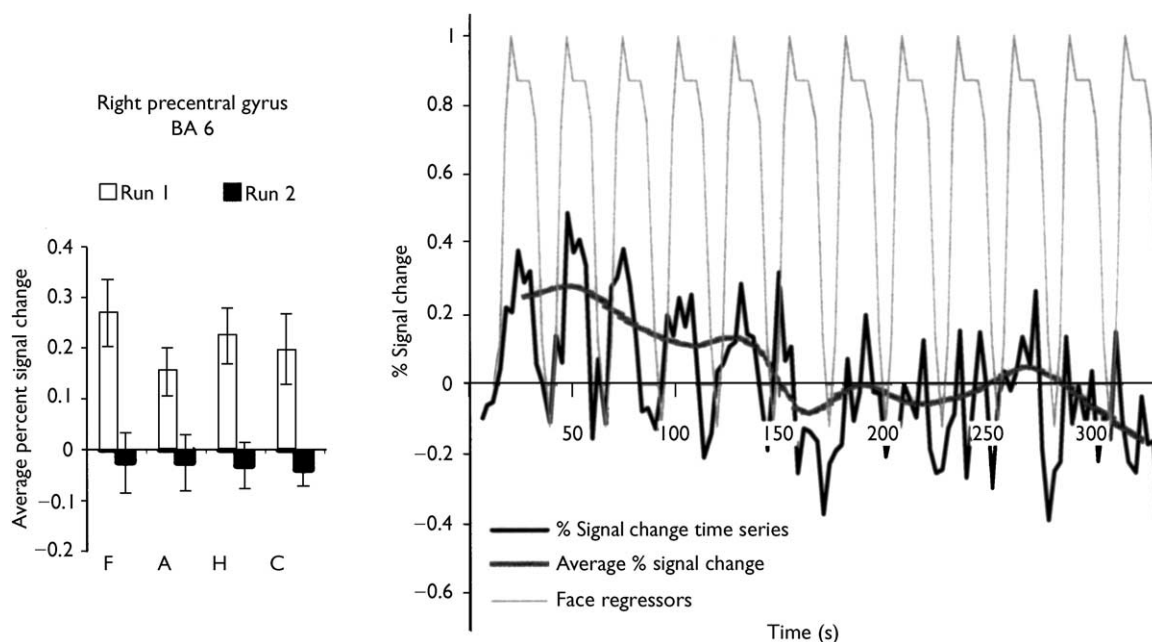
Consistent with previous studies [14–16], the presentation of faces resulted in bilateral fusiform gyrus activation, a brain region well known to contain neurons that selectively activate to faces [16].

The task-related activation (subtracting the baseline activation from the face activation; Table 1) located clusters in the brain that produced a significant difference in BOLD activation between the first test (T1) and the second test (T2). Two distinct patterns of activation can be seen: habituation to all face stimuli (Fig. 1), and sensitization to all face stimuli. First, areas in the right frontal and precentral gyrus (BA 9, 6), right insula (BA 13), right postcentral gyrus (BA 3, 5), right inferior parietal lobule (BA 40), left

**Table 1.** Location of cluster-thresholded areas that showed a significant effect of test/retest.

Cluster volume ( $\mu$ l)	x	y	z	L/R	Brain structure	Brodmann area	Pattern	F(1,9)	p value
1024	35	6	38	R	Middle frontal gyrus	9	-	24.0	0.001
576	9	-21	69	R	Medial frontal gyrus	6	-	8.3	0.020
<b>1536</b>	<b>51</b>	<b>0</b>	<b>28</b>	<b>R</b>	<b>Precentral gyrus</b>	<b>6</b>	-	<b>56.0</b>	<b>0.0001</b>
512	35	-7	51	R	Precentral gyrus	6	-	20.8	0.002
576	37	-23	22	R	Insula	13	-	21.8	0.002
512	31	13	18	R	Insula	13	-	12.8	0.007
704	29	-32	50	R	Postcentral gyrus	3	-	13.5	0.006
512	53	-16	36	R	Postcentral gyrus	3	-	25.1	0.001
832	34	-41	59	R	Postcentral gyrus	5	-	2.7	0.140
1856	46	-30	47	R	Inferior parietal lobule	40	-	33.8	0.0001
768	50	-35	25	R	Inferior parietal lobule	40	-	14.2	0.005
768	0	-60	-17	L/R	Declive (cerebellum)		-	26.6	0.0001
704	-26	-29	-8	L	Hippocampus, parahippocampal gyrus		-	32.2	0.0001
896	-31	-54	33	L	Angular gyrus, posterior superior, temporal gyrus	39	+	34.9	0.0001
640	-36	-7	48	L	Precentral Gyrus	6	+	20.2	0.002
512	-30	-25	9	L	Insula	13	+	28.5	0.0001

xyz coordinates are at the center of the cluster, cluster-wise F values are calculated with 8 degrees of freedom, the row in bold is illustrated in Fig. 1. - = habituation; + = sensitization.



**Fig. 1.** Habituation in the right frontal eye fields to the repeated presentation of faces (error bars in the bar graph represent the s.e.m. and x-axis labels define the four emotions tested: F, fear; A, anger; H, happy; C, contempt). The habituation during the first test is shown in the adjacent graph.

cerebellum, and left hippocampus/parahippocampal gyrus, were found to be significantly more activated during the presentation of faces during T1 compared to T2. Second, areas in the left angular and posterior superior temporal gyrus (BA 39), left precentral gyrus (BA 6), and left insula (BA 13), were significantly more active during the presentation of faces during T2 relative to T1.

In order to examine whether the signal changes were truly due to habituation, the voxel-wise time series data for each subject and from each fROI were extracted and averaged across the fROI. As shown in Fig. 1, the face related signal change attenuated significantly across blocks during the first test in the region of the right frontal eye fields (BA 6). Similar patterns of habituation were seen in the other fROIs.

**DISCUSSION**

The repeated presentation of affective faces induced significant habituation of face-related activation in a highly lateralized right hemispheric neural network comprising the right frontal and precentral gyrus (BA 9, 6), right insula (BA 13), right postcentral gyrus (BA 3, 5), and right inferior parietal lobule (BA 40). The right hemisphere has been shown to be highly involved in spatial attention [5,17] as well as in the processing of salient facial expressions [7,18]. Furthermore, this lateralized substrate is mainly composed of brain areas implicated in Mesulam’s attentional network [5]: the posterior parietal cortex (including the inferior parietal lobule) and the frontal eye fields (BA 6 along with neighboring pre-frontal and pre-motor areas). Thus, these

results support the idea of a salience map, where each face is processed by the visual cortex and then assigned a weight (based on its emotional significance) by the inferior parietal lobule. The frontal eye fields then decide how much attention should be allocated to each face based on this weight. The habituation observed in the right inferior parietal lobule and right frontal eye fields functionally corresponds to a gradual reduction in the emotional value or weight elicited by each face with repeated exposure.

Interestingly, some areas, including the left angular and posterior superior temporal gyrus (BA 39), left precentral gyrus (BA 6), and left insula (BA 13), exhibited a significant increase in face-related activation during the second test, consistent with sensitization. This sensitization was lateralized to brain areas within the left hemisphere. Others have shown a similar shift in brain activity, from the right to the left hemisphere, as the novelty of a visuospatial stimulus decreases [1,4,19]. We propose that this shift in brain activity is partly due to the brain encoding the pictures of the faces during the first test and is involved in the recognition process during the second test. Increased activation was found in the left hippocampus, left parahippocampal gyrus, and the right middle frontal gyrus (BA 9), areas involved in the encoding of pictures [1,20], only during the first test. These brain areas rapidly habituated during the second test. Meanwhile, the left angular and posterior superior temporal gyrus (BA 39), left pre-central gyrus (BA 6), and left insula (BA 13), all exhibited an increase in activation during the second test. These areas are functionally connected with each other [21] and are involved in many aspects of cognition, including object recognition [1,16,21]. This combined pattern of activation is consistent with the hypothesis that the pictures of the faces were encoded as unfamiliar objects during the first test and recognized as familiar objects during the second test.

Previous studies measuring implicit emotion processing have detected amygdala activation [13,22]. However, the amygdala did not produce any significant activation in our study. Other studies have similarly found the amygdala to either rapidly habituate [1,3,23] or cease to activate [7,15] when repeatedly exposed to the same affective faces. In comparison, we observed significant activation in the right prefrontal cortex (BA 6); an area which has been shown to attenuate the emotional response of the amygdala [3,24]. The current finding is consistent with the hypothesis that the prefrontal cortex filters out emotionally irrelevant information by inhibiting the amygdala.

What are the clinical implications of our findings? The results of this study showed a significant sensitization in the left angular gyrus during the retest condition. The angular gyrus has been shown to be cytometrically abnormal in both patients with schizophrenia [25] and with Huntington's disease [26]. Furthermore, previous investigations have shown that patients with various neuropsychiatric disorders are impaired in the recognition of face emotion [6–8]. This

study demonstrated that repeated presentations of affective faces are differentially processed (as a function of exposure over time) in healthy controls. This leaves open the possibility that the time course of emotional processing may be altered in patients, and this may be an important, although as yet unexplored, component of the pathophysiology of certain neuropsychiatric disorders.

## CONCLUSION

The repeated exposure to pictures of affective faces resulted in habituation of a highly lateralized right hemispheric neural network implicated in spatial attention. As the novelty of the affective faces decreased, there was a significant sensitization lateralized to brain structures in the left hemisphere. This study provides strong evidence that it is necessary for future studies (analyzing or comparing the processing of emotion in healthy controls and patients) to examine a possible role for differential habituation and sensitization effects in neuropsychiatric disorders.

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