Sustained Activation of the Hippocampus in Response to Fearful Faces in Schizophrenia

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Background: *In healthy individuals, the activity of the medial temporal lobe habituates rapidly with the repeated presentation of a stimulus. Using functional magnetic resonance imaging (fMRI), we tested the hypothesis that habituation of the medial temporal lobe is reduced in schizophrenia.*

Methods: *During fMRI scanning, fearful and happy faces were presented repeatedly to healthy control subjects (*n *= 16) and patients with schizophrenia (*n *= 18). Habituation of medial temporal lobe structures was measured by comparing the hemodynamic response occurring during the early and late portions of the presentation of each face.*

Results: *Control subjects demonstrated significant medial temporal lobe habituation to fearful but not to happy faces. In contrast, patients with schizophrenia did not demonstrate medial temporal lobe habituation in response to fearful or happy faces. In a direct, between-group comparison, right hippocampal habituation to fearful faces was significantly greater in control subjects than in the schizophrenia patients. Also, there were no significant differences between the patients and control subjects in the early medial temporal lobe response to fearful faces, suggesting that attenuated hippocampal habituation in schizophrenia is not associated with a reduction in initial activation.*

Conclusions: *These findings suggest that there is abnormal modulation of hippocampal responses to fearful faces in schizophrenia.*

Key Words: Schizophrenia, habituation, hippocampus, emotion, fMRI, faces

The attenuation of a neural response over time to a repeatedly presented stimulus represents a basic form of neural plasticity. Decrements in neural responses with repeated stimulus presentations have been demonstrated in nonhuman primates with single unit recordings in inferotemporal areas of monkey cortex (Brown et al 1987; Miller et al 1991) and in humans with functional neuroimaging techniques in extrastriate (Blaxton et al 1996; Buckner et al 1998; Schacter et al 1996), inferotemporal (Henson et al 2000), auditory cortex (Pfleiderer et al 2002), and medial temporal lobe structures (the amygdala/hippocampus complex) (Buchel et al 1999b; Fischer et al 2000, 2003; Hart et al 2000; Jessen et al 2002; Martin et al 1997; Phan et al 2003; Phillips et al 2001; Strange et al 1999; Wright et al 2001). Decrements in neural responses in the medial temporal lobe have been found with the repetition of emotionally salient stimuli, such as emotional facial expression and pictures (Breiter et al 1996; Fischer et al 2000, 2003; Hart et al 2000; Phan et al 2003; Phillips et al 2001; Wright et al 2001), and in studies using emotionally neutral stimuli (Buchel et al 1999b; Jessen et al 2002; Martin et al 1997; Strange et al 1999).

Habituation effects have been found more frequently in the right amygdala and hippocampus (Fischer et al 2000, 2003; Martin et al 1997; Wright et al 2001), consistent with evidence for a role of the right medial temporal lobe in responses to novelty (Martin 1999; Tulving et al 1994, 1996) and right hemispheric dominance in arousal and orienting mechanisms (Mesulam 1999). Also, laterality of medial temporal lobe responses in humans is influenced by a variety of factors that are specific to the individual and to the experimental stimuli used in the study. For example, in neuroimaging studies of amygdala responses to emotional stimuli, right-sided activation predominates during encoding of emotional or arousing information in men (Cahill et al 2001, 2004; Canli et al 2002a) and in response to nonlinguistic stimuli, such as objects (Martin et al 1997) and faces (Hariri et al 2002). Left-sided medial temporal lobe activation is more common during encoding of emotional or arousal information in women (Cahill et al 2001, 2004; Canli et al 2002a), anticipation of aversive stimuli (Phelps et al 2001), and in response to negatively valenced linguistic stimuli (Crosson et al 1999; Hamann and Mao 2002; Strange et al 2000). Also, studies of patients with medial temporal lobe lesions have found that right-sided anterior medial temporal lobe lesions impair recognition of negatively valenced facial expressions more than left-sided lesions do (Adolphs et al 2001; Anderson et al 2000).

The attenuation of medial temporal lobe responses with repetition has been hypothesized to relate to habituation of the orienting response—an initially novel stimulus is recognized, determined to be nonthreatening, and thus becomes less behaviorally salient to the organism over time (Bordi and LeDoux 1992; Kreiman et al 2000; Wilson and Rolls 1993). Repeated processing of a stimulus has been thought to lead to a "sharpening" of its cortical representation, allowing for more efficient stimulus processing (Miller et al 1991; Wiggs and Martin 1998). This "neural priming" might be associated with increases in effective connectivity (Buchel et al 1999b) and associative learning (Dobbins et al 2004).

There is a large body of evidence for abnormalities in neural and behavioral habituation in schizophrenia. It has been proposed that the clinical and cognitive abnormalities of schizophrenia stem from a "failure of inhibition" within specific limbic circuits (Deutsch et al 2001; Freedman et al 1996; Frith 1979). Patients with schizophrenia exhibit deficits in measures of inhib-

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Table 1. Demographic Characteristics of Subjects

	Control (n = 16)		Schizophrenia (n = 18)	
	Mean	SD	Mean	SD
Age (y)	43.9	4.1	45.4	7.1
Mean parental SES[a]	2.9	1.3	3.4	1.1
Verbal IQ[b,c]	108.5	11.7	99.5	12.4
PANSS Total			58.0	10.1
PANSS Positive Subscale			13.8	5.0
PANSS Negative Subscale			17.1	5.0
PANSS General Subscale			27.1	5.4
SAPS			18.7	19.2
SANS			36.6	13.6

SES, socioeconomic status; IQ, intelligence quotient; PANSS, Positive and Negative Symptom Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

[a]Estimated with the Hollingshead Index.

[b]Estimated with the North American Adult Reading Test.

[c]Significant difference between schizophrenia and comparison subjects ($p < .05$).

itory gating, including a failure to demonstrate normal attenuation of the P50 evoked response (Freedman et al 1996) and the acoustic startle reflex (Akdag et al 2003), deficits in prepulse inhibition of acoustic startle responses (Braff et al 1992; Ludewig et al 2003), and impaired smooth pursuit eye movements (Friedman et al 1995; Holzman 2000). Also, patients with schizophrenia demonstrate attenuated "negative priming," thought to be one measure of cognitive inhibition (Peters et al 1994; Williams 1996). In one positron emission tomography (PET) study, an increase in regional cerebral blood flow (rCBF) was found in patients with schizophrenia in cortical regions of the right hemisphere in response to the repeated presentation of a visual noise pattern, whereas healthy control subjects demonstrated decreased rCBF in the same regions (Heckers et al 2002). Thus, in schizophrenia, deficits in habituation are found at the behavioral, neurophysiologic, and neural systems level, although it has not been determined whether the normal habituation of medial temporal lobe activity with stimulus repetition occurs in schizophrenia.

In the present study, we hypothesized that habituation of activity of medial temporal lobe structures is reduced or absent in schizophrenia. We tested this hypothesis by measuring habituation in the medial temporal lobe in schizophrenia and healthy control subjects with an experimental paradigm and analysis method that has demonstrated medial temporal lobe habituation reliably in healthy individuals (Fischer et al 2003; Wright et al 2001). We limited our study sample to men to control for the effects of gender on laterality of medial temporal lobe responses.

Methods and Materials

Subjects

This study was approved by the institutional review boards of the Massachusetts General Hospital and Massachusetts Department of Mental Health. Written informed consent was obtained from all subjects before their enrollment in the study.

Eighteen men with DSM-IV–defined schizophrenia were recruited from the Massachusetts General Hospital Schizophrenia Research Program. The diagnosis of schizophrenia was made by psychiatrists using the Structured Clinical Interview for DSM-IV (SCID; First et al 1995), and ratings of symptom severity were also obtained with standard symptom rating scales (Table 1). All patients were chronically ill; 13 of the 18 had mild, residual positive symptoms (hallucinations and/or delusions). All patients were being treated with a stable dose of antipsychotic medication for at least 4 weeks; 15 were being treated with second-generation antipsychotics (9 of these were receiving clozapine), whereas 3 were being treated with conventional antipsychotics. The mean daily neuroleptic dosage measured in chlorpromazine equivalents (Woods 2003) was 550 mg (SD = 287). One patient was taking anticholinergic medication (benztropine). Patients did not have a history of significant head trauma, seizure disorders, or other major neurologic illness. No subject met DSM-IV criteria for alcohol or other substance abuse within the previous 3 months. Sixteen healthy male control subjects were recruited from the community through advertisements. Control subjects were enrolled only if they did not have an Axis I psychiatric disorder (as determined by the SCID) and did not have a history of major medical or neurologic illness. None of the control subjects was taking psychotropic medications.

There were no significant between-group differences in age, level of education attained, or mean parental socioeconomic status (Table 1). There was a significant between-group difference in mean verbal intelligence quotient (IQ) [$t(32) = .887$, $p < .04$] as estimated by the North American Adult Reading Test (Blair and Spreen 1989). Of the 18 schizophrenia subjects, 13 were right-handed (4 were left-handed, and 1 was ambidextrous), and 15 of the 16 healthy control subjects were right-handed (1 was ambidextrous).

Procedure

During the study, subjects lay on a padded scanner bed and wore earplugs. Each functional magnetic resonance imaging (fMRI) run was 2 min long and consisted of an 80-sec block in which a happy or fearful face was repeatedly presented, preceded and followed by a 20-sec block of a cross-hair (Figure 1). During the 80-sec face block, one face of a male or female person with a fearful or happy expression was presented twice per sec or 160 times (stimulus duration, 200 msec; interstimulus interval, 300 msec). Subjects were instructed to focus their gaze on the center of the screen in which the fixation cross was located. Facial stimuli consisted of eight photographs of faces with happy or fearful expressions (Ekman and Friesen 1976). These eight photographs included four distinct identities (two male, two female), each displayed with two expressions (fearful, happy). The order of runs was counterbalanced with respect to facial expression and gender. The experiment consisted of four of these 2-min runs for each subject; thus each subject viewed a total of four faces.

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