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Reduced Amygdala Activation in Young Adults at High Risk of Alcoholism: Studies from the Oklahoma Family Health Patterns Project

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Abstract

Background—Risk of alcoholism is higher in those with a positive family history (FH+) and in those showing behavioral disinhibition, possibly reflecting altered limbic system function.

Methods—We performed functional magnetic resonance imaging (fMRI) in 17 nonabusing young adults, 9 with FH+ and high in disinhibition versus 8 with a negative family history (FH−) and low in disinhibition. We probed limbic system reactivity with a recognition task using faces expressing fear versus geometric objects.

Results—Subjects with FH− had robust activation to the faces in the region of the right and left amygdalar complexes (p's < .05), while subjects with FH+ had no such activation (p's > .46). The blood oxygenation level-dependent (BOLD) signal in the region of the amygdala was correlated with scores on the self-report measure of temperament in the combined groups (r = .51, p < .04).

Conclusions—Behaviorally disinhibited temperament, found in many with FH+, may be associated with amygdalar hyporesponsiveness and a failure to avoid risky decisions, increasing the person's liability for alcohol abuse.

Keywords

Alcoholism; amygdala; behavioral disinhibition; fMRI; risk factors

Alcoholism affects 13% of individuals during their lifetimes (Kessler *et al.* 2005). Offspring of alcoholics (positive family history [FH+]) have 2 to 4 times the risk of future alcohol abuse relative to individuals with a negative family history (FH−) (Lieb *et al.* 2002; Merikangas *et al.* 1998), and twin-adoption studies implicate a genetic contribution to the disorder (Cloninger *et al.* 1981; Hesselbrock 1995). This calls for identifying characteristics of healthy, young individuals with FH+ that may contribute to their risk. Individuals with FH+ often display a behaviorally undercontrolled temperament (Dawes *et al.* 1997; Sher *et al.* 1991), a blunted stress cortisol response (Lovallo *et al.* 2000; Sorocco *et al.* 2006; Vanyukov *et al.* 1993), and reduced amygdala volumes (Hill *et al.* 2001), suggesting a dysregulation of neural functions underlying motivation of behavior (Koob 2003).

The Oklahoma Family Health Patterns Project (OFHP) studies nonabusing FH+ and FH− individuals in relation to behavioral undercontrol. Subjects with FH+ in this cohort score lower

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than FH− subjects on the California Personality Inventory Sociability Scale (CPI-So) (Gough 1994) (28.5 ± .59 vs. 32.8 ± .49, $t = 5.67$, $p < .0001$), similar to alcoholic patients (Cooney *et al.* 1990), indicating a predominant pattern of behavioral disinhibition among the FH+ subjects. There are no published functional magnetic resonance imaging (fMRI) studies in FH+ subjects.

Accordingly, we used an emotive face identification task shown to activate the amygdala (Hariri *et al.* 2002) on FH + subjects with low CPI-So scores versus FH− subjects with high CPI-So scores drawn from the parent project. We predicted deficient amygdalar responses in the FH+ subjects.

Methods and Materials

Subjects included 9 with FH+ (5 female subjects) and 8 with FH− (3 female subjects) 23.5 years of age (Table 1). Volunteers were scanned at the Research Imaging Center at the University of Texas Health Science Center San Antonio. Subjects and parents signed consent forms approved by the supervising Institutional Review Boards and were paid for participating.

Subjects were free of Axis I and II disorders (clusters A and C) by DSM-IV criteria (American Psychiatric Association 1994). Subjects with FH+ had a biological parent that met DSM-IV criteria for alcohol use disorders by Family History Research Diagnostic Criteria (FH-RDC) (Andreasen *et al.* 1977). Subjects with FH− had an absence of alcohol or substance use disorders in parents and grandparents. Subjects were excluded for possible fetal exposure to alcohol or drugs.

Behavioral disinhibition was indexed by low scores on the CPI-So scale (Lovallo *et al.* 2006). Groups scoring ≥30 are highly norm-abiding (research scientists, students in nursing and engineering), while scores <30 are seen in deviant groups (marijuana smokers, shoplifters, alcoholics and offspring, pathological gamblers) (Gough 1994). Table 2 shows a progressive relationship between family density of alcoholism and prevalence of low CPI-So scores in the OFHP sample ($n = 175$; $\chi^2 = 10.1$, $p < .007$). The present sample of FH+ and FH− subjects had strongly differing CPI-So scores (26.3 and 33.5, respectively).

We probed limbic system response with a face identification task known to robustly increase blood oxygenation level-dependent (BOLD) signals in the region of the amygdala (Hariri *et al.* 2002). Subjects viewed trios of fearful faces (Ekman and Friesen 1976) selected from 12 such stimuli, 6 of each gender, for 5 sec, in 5 blocks of 6 trials over 5 min. To ensure attention to the faces, subjects pressed a button to indicate which bottom face was identical to the top face (Figure 1A). The sensorimotor control used geometric shapes (Figure 1B). Perceptual control blocks used sets of shapes viewed for 5 sec each. Response accuracy and reaction time were monitored.

Scanning was carried out on a Siemens 3T MRI (Siemens, Munich, Germany). Functional imaging used a gradient-echo, echo-planar sequence, acquiring 30 slices (4 mm thick, 1 mm gap) parallel to the anterior commissure-posterior commissure (AC-PC) plane (repetition time/echo time [TR/TE] = 2500/30 msec, 128 × 128 × 5 mm, and field of view [FOV] = 256 mm). For anatomical reference, we acquired a higher resolution coplanar T1-weighted series (TR/TE = 500/20 msec, flip angle = 90°, 128 × 128 × 5 mm, FOV = 256 cm) and a high-quality three-dimensional (3-D) image (TR/TE = 33/12 msec, and flip angle = 60°, 1 mm isotropic). Image analyses were performed using FSL software (Smith *et al.* 2004) (www.fmrib.ox.ac.uk/fsl/; Oxford, UK) and in-house utilities. Images were spatially registered to the middle data point in that time series to combat motion artifacts and were smoothed using a nonlinear algorithm applied to voxels thought to be of the same tissue type (3 mm kernel) to preserve image structure.

Data were subjected to multiple regression using a prewhitening technique to account for the intrinsic temporal autocorrelation of BOLD signals. Least-squares coefficients were generated for each intracranial voxel independently for the emotion and sensorimotor control conditions, and contrasts between these coefficients were used to create the statistical images. These were spatially normalized to a standard stereotactic space to facilitate multisubject analysis based on the high-resolution anatomical image (Kochunov *et al.* 2002). Group maps were thresholded based on the magnitude ($z \geq 2.0$) and extent (cluster $p < .01$) of activation.

Anatomically defined regions of interest (ROIs) were drawn bilaterally for amygdala and fusiform face areas. The amygdala ROI was an 8-mm cube centered on the maximum activation reported with the identical task: left −28, −6, −16; right 30, −4, −16 (Hariri *et al.* 2002). The fusiform ROI was a comparably sized region placed on a putative face-processing area (Grill-Spector *et al.* 2004). Regions of interest were overlaid on each subject's BOLD data to determine percent signal change from the sensorimotor control to the emotion condition. To account for amygdala volume and focus on activated voxels, analysis was confined to signal change in positive voxels.

Multisubject analyses used a mixed-effects model, with subject as a random factor, providing *z*-images reflecting the high- and low-risk group activation patterns and yielding between-group contrasts.

Results

Face identification activated regions implicated in facial processing: posterior fusiform gyri, inferior parietal lobules, frontal eye fields, striate and extrastriate cortex, anterior cingulate gyrus, hippocampal and parahippocampal gyri, and amygdalas (Haxby *et al.* 2002; Ridderinkhof *et al.* 2004).

A family history (FH) group × hemisphere × ROI (amygdala, fusiform) multivariate analysis of variance (MANOVA) revealed a main effect for ROI [$F(1,15) = 10.63$, $p < .005$] and an FH × ROI interaction [$F(1,15) = 4.99$, $p < .04$] (Figure 2A). The FH− group produced a greater percent signal change for facial versus geometric control stimuli for right [$F(1,15) = 5.21$, $p < .04$] and left [$F(1,15) = 4.22$, $p < .05$] amygdalas but not for either fusiform ROI (p's > .46) (Figure 3). Since hemispheres did not differ ($p > .64$), ROIs were then combined across hemispheres. The CPI-So scores were correlated with amygdala ROI activation ($r = 0.51$, $p < .04$, two-tailed), indicating the influence of behavioral disinhibition on amygdala hyporesponsivity.

Confounder analyses showed no effect of sex, age, or their interactions with FH group for either ROI. Family history groups did not differ in recognition accuracy or reaction times (p's > .16), ruling out attention differences. Results were not attributable to depression or frontal executive function, as Beck Depression Inventory (BDI) and Stroop Color and Word Test scores were uncorrelated with amygdala or fusiform activation (p's ≥ .09), and FH group remained significant after their inclusion as covariates (p's < .05).

Discussion

The fMRI data supported our prediction of reduced amygdala responsivity in FH+ persons who are behaviorally disinhibited, providing a perspective on risk in FH+. In human and nonhuman primates, faces are provocative social stimuli that cause robust activation of the amygdala and parahippocampal gyrus (Adolphs *et al.* 2005; Hariri *et al.* 2002; Kobatake and Tanaka 1994), further highlighting the hyporeactivity of these FH+ subjects. One study found FH+ subjects to have reduced amygdala volumes compared with FH− subjects (Hill *et al.* 2001). Therefore, we analyzed only activated voxels in these subjects, indicating that the

reduced amygdala activation to faces in these FH+ subjects was not a function of volume differences.

A larger sample will allow a test of the dual impact of FH status and CPI-So scores on amygdala and prefrontal networks, since these work in tandem during motivated decision making (Bechara and Damasio 2002; Damasio 1994; Kringelbach 2005). We exclusively used fearful faces here, and testing a full range of facial emotions will help tease apart the effects of emotions from the impact of faces alone.

Other OFHP studies provide converging evidence of FH+ and behavioral disinhibition. Individuals with FH+ and low CPI-So scores have high interference on the Stroop task, and FH+ male subjects show high attention to financial gains in the Iowa Gambling Task (Lovallo *et al*. 2006), indicating mildly impaired executive cognitive functioning and appetitive response biases. Individuals with FH+ and low CPI-So scores show blunted stress cortisol responses (Sorocco *et al.* 2006), indicating reduced outputs from the amygdala to the hypothalamus (Herman *et al.* 2003; Schulkin *et al.* 1994), consistent with the amygdala hyporesponsiveness seen in this fMRI study.

The present data highlight the effect of disinhibitory tendencies in FH+. Deficient amygdala activation could cause inadequate signaling to prefrontal and hypothalamic areas involved in motivated behaviors. Amygdala hyporesponsiveness in persons at risk for alcoholism may therefore accompany a shift in approach-avoidance tendencies toward approach behaviors with a deficit in avoidance (Koob 2003). Such persons may fail to form aversive associations to negative consequences of alcohol intake, instead finding greater attraction to its positively hedonic aspects. The net result could be a long-term pattern of less cautious behavior and risky decisions about intake of alcohol and illicit drugs.

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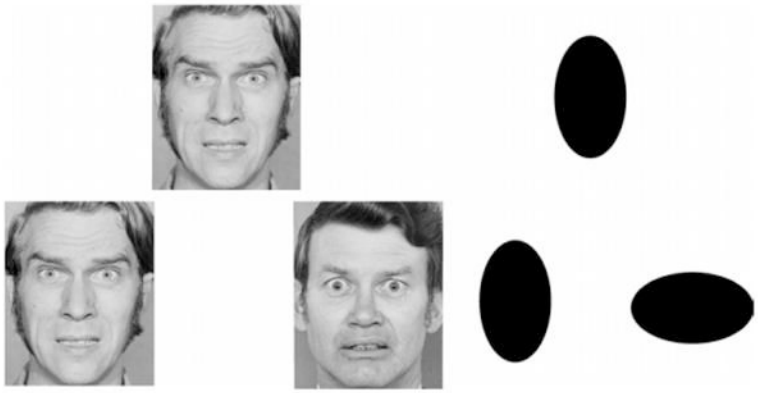

Figure 1.
Stimulus displays for emotion-matching and control tasks.

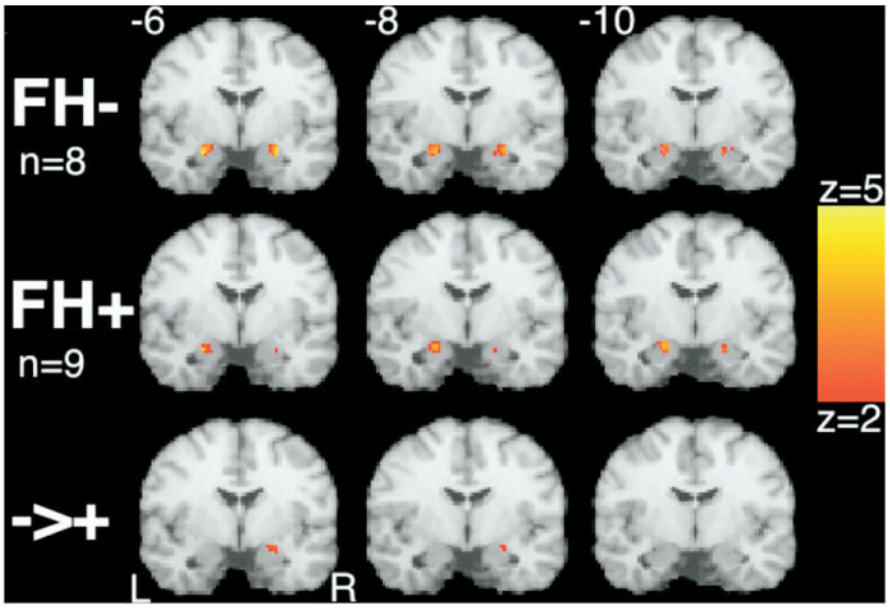

Figure 2.

Group amygdala activation patterns. Effect of FH of alcoholism on amygdala activity in healthy young adults during a face identification test using fearful face stimuli. Statistical parametric maps reflecting bilateral amygdala activation for FH− individuals (left: −24, −6, −16 and right: 26, −6, −16) and FH+ individuals (−18, −10, −16 and 26, −6, −16). These illustrate heightened amygdala response in the FH− versus the FH+ group for the right amygdala (FH− > FH+: 24, −6, −12). FH, family history; FH−, negative family history; FH+, positive family history.

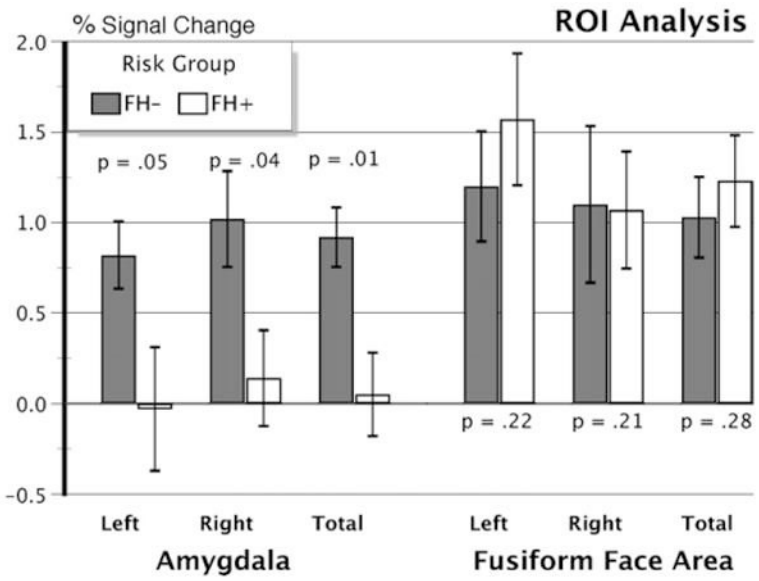

Figure 3.

Mean percent signal change in ROIs. Bars show mean ± SEM for ROIs comprising bilateral amygdala and fusiform gyrus. The FH+ group showed amygdala hypoactivation relative to the FH− group. In contrast, the fusiform ROIs did not differ between FH groups. The average sizes for the left and right amygdala ROIs were 23 and 21 voxels, respectively. ROI, region of interest; FH+, positive family history; FH−, negative family history; FH, family history.

Table 1

Sample Characteristics

Family History	FH−	FH +	*p* Values
N (M/F)	8 (5/3)	9 (4/5)	
Age (Years)	24 (1.2)	23 (1.1)	
Education (Years)	16 (.8)	14.2 (.4)	.09
SES	42 (5.0)	37 (5.6)	
Shipley Vocabulary	30 (1.7)	27 (2.8)	
CPI-So	33.5 (.7)	26.3 (1.8)	.003
BDI	2.4 (.7)	6.8 (1.9)	.06
EPI-Neuroticism	4.3 (1.3)	5.6 (1.0)	
AUDIT	3.5 (1.1)	3.6 (1.2)	
Alcohol Intake (oz/mo)	44 (15)	58 (12)	
Caffeine (mg/day)	156 (37)	102 (38)	
Tobacco (% Using Weekly)	25	22	

Entries (mean ± SEM) unless given otherwise. SES scores shown are considered “Middle Class.” Only *p*'s < .10 are shown.

FH−, negative family history; FH+, positive family history; M, male; F, female; SES, Hollingshead & Redlich Socioeconomic Status Score; Shipley Vocabulary, Shipley Institute of Living Vocabulary Score; CPI-So, California Personality Inventory Sociability Scale; BDI, Beck Depression Inventory; EPI, Eysenck Personality Inventory; AUDIT, Alcohol Use Disorders Identification Test.

Table 2

Family Density of Alcoholism in Relation to Behavioral Disinhibition

	CPI-So Score	
Family Density	**< 30**	**≥ 30**
0	23%	77%
1	59%	41%
2	75%	25%
3–6	77%	23%

Entries show the percentage of persons in a larger sample from the parent study ($n = 140$) representing four levels of family density of alcoholism and the percentages of those subjects that scored in the low (< 30) versus high (≥ 30) range on the Sociability scale of the California Personality Inventory as an index of behaviorally disinhibited temperament. $\chi^2 = 10.1$, $p < .007$.

CPI-So, California Personality Inventory Sociability Scale.