simple perceptive failure. Instead, it is suggestive of a specific failure in orienting attention according to the successfully perceived eye-gaze. It is also important to note that patients with schizophrenia demonstrated a trend for a benefit reduction for the very concrete, elliptical eyes as well, emphasizing that their benefit reduction from congruent gaze cues cannot be attributed solely to their difficulty with ambiguous stimuli.

Gaze cognition is pivotal in social interaction, in that it enables us to decipher the inner thoughts of others from the direction of their attention. Any form of compromise would be devastating to the victims. The social inadequacy often seen in patients suffering from chronic schizophrenia might in part be attributable to the compromise in gaze cognition such as demonstrated in the current study. A deeper understanding of the symptoms related to gaze in schizophrenia might offer some strategy to rescue from their social isolation.

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Altered Brain Activation by a False Recognition Task in Young Abstinent Patients With Alcohol Dependence

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Background: Heavy alcohol intake induces both structural and functional changes in the central nervous system. Recent research developments converged on the idea that even in patients with alcohol dependence without apparent structural brain changes, some cognitive impairment exists, and associated functional change could be visualized by neuroimaging techniques. However, these data were from old (more than 50 years) patients using working memory and response inhibition tasks. Whether young abstinent patients show aberrant signs of brain activation is a matter of interest, specifically by the long-term memory retrieval task.

Methods: Subjects were 9 young patients with alcohol dependence with long-term abstinent (8 males and 1 female) and age- and education-matched 9 healthy controls (7 males and 2 females). We used a modified false recognition task in a functional MRI study.

Results: The young patients with alcohol dependence showed reduced activation in the right dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), left pulvinar in the thalamus, and in the right ventral striatum, although behavioral performances and regional patterns of brain activation were similar between patients and controls.

Conclusions: Long-term memory retrieval induced altered activations in prefrontal lobes, ACC, thalamus, and ventral striatum in young patients with alcohol dependence. These findings were correspondent to deficits of goal directed behavior, monitoring the erroneous responses, memory function, and drug-seeking behavior. Furthermore; these reduced activations can be considered as latent "lesions," suggesting subclinical pathology in alcoholic brains.

Key Words: Abstinent Patients With Alcohol Dependence, Episodic Memory, Thalamus, Prefrontal Cortex, Functional Magnetic Resonance Imaging.

HEAVY ALCOHOL INTAKE is associated with both structural and functional changes in the central nervous system (Tarter and Edwards, 1985; Parsons, 1996; Sullivan, 2000, 2003; Sullivan and Pfefferbaum, 2005; Oscar-Berman, 2000). Classical postmortem studies have demonstrated a constellation of changes in alcoholic brains (Courville, 1966; Harper, 1998), which entail a variety of neuropsychological impairments, and correlations between these structural changes and behaviors have been investigated by quantitative neuroimaging techniques. However, attempts to establish direct links between "lesions" and specific cognitive function have come up with inconsistent results. One possible reason for these failures is that the "lesions" might not necessarily be related to cell loss (Jensen and Pakkenberg, 1993) and could represent shrinkage or disruption of neuronal processes (Harper, 1998). The advent of functional neuroimaging techniques has made it possible to investigate the pathology with no apparent structural changes, and several PET studies consistently showed hypometabolism in the frontal lobes (Gilman et al., 1990; Volkow et al., 1992; Wang et al., 1993; Dao-Castellana et al., 1998). Moreover, correlations between poor performance in neuropsychological testing of frontal functions and brain metabolism in detoxified patients have also been demonstrated (Adams et al., 1993, 1995).

Collectively, research developments seemed to converge on the idea that even in alcoholic brain without apparent structural brain changes, some cognitive impairment exists, and associated functional change could be visualized by neuroimaging techniques. However, these data were from relatively old (more than 50 years) patients, and comparable data from young patients were few (Tapert et al., 2001, 2003, 2004).

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Whether young patients with alcohol dependence show signs of brain dysfunction is a matter of interest, as this could provide clues to the progression of alcoholic brain damage, which has long been a subject of controversy. As early as 1966, Courville indicated that the neuropathology of alcoholic brains resembled the shrinkage that occurs with normal chronological aging, and this was replicated in later studies (Pfefferbaum and Rosenbloom, 1993; Harper, 1998). These findings have led to the "premature aging" theory of alcoholic brains, but whether manifestation of alcoholism and aging are similar or synergistic is still an open question. Research focused on young alcoholic subjects could be expected to shed light on this subject.

As for the investigation of specific "lesions" in patients with alcohol dependence, functional magnetic resonance imaging (fMRI) is considered to be the superior technique. However, fMRI studies to detect the latent lesions have been surprisingly few. Three fMRI studies examined brain function concerned with working memory (Pfefferbaum et al., 2001; Desmond et al., 2003; Tapert et al., 2004), and 1 report was about simple motor task (Parks et al., 2003). Pfefferbaum et al. (2001) investigated brain activation patterns by spatial working memory task, revealing that the control group exhibited activation of the dorsal stream, while the alcoholic group showed activation of the ventral stream and declarative memory systems. A subsequent study by this group demonstrated that nonamnesic patients showed brain activations in the right superior cerebellar hemisphere and left prefrontal cortex (PFC) during the verbal working memory task with a high relative to a low memory load (Desmond et al., 2003). Moreover, using the spatial working memory task, Tapert et al. (2004) reported that adolescents with alcohol use disorders showed greater brain response in bilateral parietal cortices and diminished response in other regions than controls, although groups did not differ on behavioral measures of task performance.

In the present study, to visualize the subtle brain changes in the young and long-term abstinent patients, we conducted an fMRI study during a modified false recognition task, which tapped long-term memory retrieval process. The original version of the false recognition task was created by Deese (1959), which was revised by Roediger and McDermott (1995). Briefly, they presented a list of words to the subjects and later another list of words that included "old" (in the original list), related "new," and unrelated "new" words (not in the original list). The subject's task was to make old/new judgments for each word.

We chose this task because it was found in an earlier study to reliably activate anterior frontal lobes and other areas concerning memory (Schacter et al., 1997), which have been consistently shown to be impaired in patients with alcohol dependence, both functionally and structurally. Another reason for selecting this task was that it requires the subject's memory load to be large enough to reveal mild frontal dysfunction and other subtle impairments of related brain areas. Our modified procedure was similar to the original, except that we presented the test words in pairs for making the task more difficult to perform. We hypothesized that the subjects with alcohol dependence, even without apparent cognitive impairment, would perform the long-term memory task poorly and show reduced activations in some frontal and related areas.

MATERIALS AND METHODS

Participants

Nine young patients with alcohol dependence (8 males and 1 female) were recruited from outpatients who were participants in Alcoholics Anonymous group in Japan and met DSM-IV (American Psychiatric Association, 1994) criteria for alcohol dependence. In these young patients, the onset ages of alcohol dependence were less than 30-years old. They were assessed for eligibility for study with structured psychiatric interviews (detailed screening interviews), physical examination, medical history, complete blood count, and chemistry panel. Patients with alcohol dependence had been abstinent for a long period, an average of 39.8 ± 12.1 months at the time of scanning, which was confirmed from regular examination at outpatient clinic every 3 months by a medical doctor (MK), on the basis of the information from their family and constant values of γ-GTP in blood samples (Table 1).

Exclusionary criteria were a history of a DSM-IV psychiatric or substance disorder other than alcohol dependence, neurological illness, severe head trauma, and serious medical problems including alcoholic hepatitis, liver cirrhosis, and diabetes mellitus. The subjects with current use of medications that could affect the central nervous system, smoking more than 4 cigarettes per day, family history of bipolar I or psychotic disorders, and irremovable metal on the body were excluded. In addition, significant maternal drinking during pregnancy (more than 4 drinks per occasion or more than 7 drinks per week) were excluded, which was confirmed from the interview with their family members (specifically their mothers) to examine alcohol drinking or complications during pregnancy, birth weight or complication at birth, and whether subjects suffered from fetal alcohol syndrome or not. Patients with alcohol dependence who had antisocial personality disorder were also excluded.

Nine healthy control subjects (7 males and 2 females) were recruited from the local community and were initially screened by phone

Table 1. Demographic Characteristics of Subjects

	Controls (n = 9)		Alcoholics (n = 9)		
	Mean	SD	Mean	SD	p-value
Age (years)	32.6	7.2	34.6	6.5	NS
Years of education (years)	15.6	0.5	14.3	2.5	NS
Duration of lifetime drinking (years)			13.2	4.2	
Onset of alcohol dependence (age; years)			23.8	4.3	
Duration of alcohol dependence (years)			11.1	3.7	
Number of detoxified			3.5	1.2	
Family history positive [No. (%)]	1/9 (11.1%)		5/9 (55.6%)		
VIQ (WAIS-R)			102.6	6.7	
PIQ (WAIS-R)			98.3	4.5	

WAIS-R, Wechsler Adult Intelligence Scale-Revised; NS, nonsignificant.

and were evaluated further by a structured psychiatric interview and medical assessment. Subjects who met DSM-IV criteria for any Axis I disorder or substance abuse in the year before the study were excluded. The control subjects drink less than 14 standard drinks (SD) per week and less than 4 SD per occasion in males, and less than 7 SD per week and less than 3 SD per occasion in females, and who did not meet the DSM-IV criteria for alcohol use disorders. The control subjects who had antisocial personality disorders diagnosed by DSM-IV were also excluded. At the experimental day, the control subjects had no alcohol and they were also prohibited from alcohol drinking at the day before the experiment.

Group demographics are summarized in Table 1 and each group were mostly from upper middle-class social status. The patients with alcohol dependence and control groups were matched according to age (patients 34.6 ± 6.5 and controls 32.6 ± 7.2) and education (patients 14.3 ± 2.5 and controls 15.6 ± 0.5). Handedness was assessed by the Edinburgh Handedness Survey (Oldfield, 1971), and all participants were right-handed. Raven's Standard Progressive Matrices (Raven et al., 1983) was conducted in order to screen for remarkable cognitive impairment, and subjects who were in the lower 10th percentile were excluded from this study. In patients with alcohol dependence group, VIQ and PIQ on Wechsler Adult Intelligence Scale-Revised (Wechsler, 1987) was 102.6 and 98.3, respectively, which did not indicate severe alcohol-related cognitive impairments.

All participants gave written informed consent to participate as paid volunteers in this study after reading a detailed description of the study and having their questions answered. The experiments were conducted under a protocol approved by the Institutional Ethics Committee of the National Institute of Radiological Sciences of Japan.

Task Materials

The material consisted of 24 theme sets of 15 semantic associate words (a total of 360 words) and was largely based on the study lists used by Roediger and McDermott (1995). We modified some of the words because they would have been inappropriate for Japanese subjects. In preparation for the fMRI experiment, 10 healthy subjects were recruited and requested to rate the degree of association of the words from their theme words on a 5-point scale. We then averaged each of the association values to obtain a new association order for each theme set. We used 18 of the 24 theme sets in the study phase of the experiment, and the other 6 sets were used as unrelated new word sets in the test (MRI scanning) phase (see Umeda et al., 2005).

Procedure

The overall procedure used in the present study was similar to that of the typical false recognition task (DRM paradigm), except that we presented the test words in pairs to make the task more difficult (Roediger and McDermott, 1995; Schacter et al., 1996b, 1997; Umeda et al., 2005).

First, each subject was individually asked to try to remember 18 theme sets of 14 semantic associate words (e.g., butter, toast, sandwich, eat...) in preparation for a later memory test in the scanner. The theme word (e.g., breakfast) and the third strongest associate (e.g., jam) from the 18 theme sets were not presented during the study phase and were used as related lures in the test phase.

Subjects listened to a total of 252 words at a rate of 1,700 milliseconds per word, with none of the words being presented more than once. The words were presented in order of decreasing strength of association with the theme word. Presentations of the theme sets were separated by 20-seconds intervals during which subjects answered simple arithmetic problems (e.g., "2 plus 3").

After a 10-minutes break at the end of the study phase, the test phase was begun by having the subjects lie on the flat scanner bed and asking them to make recognition judgments about words projected on a screen. The test words were presented in pairs from each theme set. A total of 24 pairs of words extracted from each of 24 theme sets were equally assigned to 1 of the 4 conditions with a counterbalance across 4 versions of the test list: (1) old word–old word pair (O–O), consisting of the first and second strongest associates, (2) old word–related lure pair (O–R), consisting of the theme word and the first strongest associate, (3) related lure–related lure pair (R–R), consisting of the theme word and the third strongest associate, and (4) unrelated lure–unrelated lure pair (U–U), consisting of the first and the second strongest associates. Therefore, none of the test words was presented more than once. The trials were pseudorandomly ordered so that there were never more than 3 trials of the same condition in a row. Subjects were instructed to respond with their left hand, pressing with their index finger to indicate "old" for both words in the pair, with their middle finger to indicate "old" for just the right word in the pair, with their ring finger to "old" for just the left word in the pair, and with their little finger to "new" for both words in the pair. They were also asked to respond while the words were being presented or after they were removed from the screen. The pair words were presented for 3 seconds and immediately followed by presentation of a cross hair with stimulus-onset asynchronies (SOAs) of 30 seconds. Before starting the scanning session, the subjects briefly practiced pressing the buttons and understanding the response mapping in order to minimize differences in response time between the different fingers and any impact of the difficult response mapping on the imaging results. All of the subjects completed the test within 20 minutes.

fMRI Data Acquisition

A Siemens Magnetom VISION system on 1.5 T was used to acquire high-resolution T1-weighted anatomical images (1 mm isotropic voxel) and gradient-echo echo-planar T2*-weighted images with blood oxygenation level dependent (BOLD) (Ogawa et al., 1992) contrast of 15 axial slices with 4 mm cubic resolution, a TE of 50.24 milliseconds, and flip angle of 90°. Our slice selection focused mainly on the PFC (including the slices from $Z = -3$ to 33) so that the adjacent areas of hippocampus were outside the scanning field. A single volume consisted of 15 slices and each volume was acquired continuously every 2,500 ms with an acquisition time of 1,460 ms. Each behavioral trial corresponded to 12 volumes. A total of 24 trials per subject were collected in 1 run (732.5 seconds), yielding a total of 293 volumes. The first 5 volumes were discarded to allow for T1 equilibration effects. The scanner was synchronized with presentation of the stimuli.

fMRI Data Analysis

The data were analyzed by statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) (Friston et al., 1995b). The time series was realigned by rigid body transformation, corrected for movement-related effects by modeling geometric deformations (Andersson et al., 2001), and sinc interpolated in time to correct phase advance during volume acquisition (Aguirre et al., 1998). To enable intersubject analysis, the images obtained were transformed to the Montreal Neurological Institute (MNI) standard space by using coregistered structural T1 scans with subsampling to an isotropic voxel size of 3 mm (Ashburner and Friston, 1999). We restricted the search volume for analysis to within the common area scanned across all subjects. The resulting images were smoothed in space with an isotropic 10 mm FWHM Gaussian kernel. In order to process the images as a time series, they were high-pass filtered at 1/120 Hz and estimated residual temporal auto-correlation. The BOLD response to the events of each response condition (O–O, O–R, R–R, and U–U) which included

at least 1 correct response was modeled with a Finite Impulse Response basis set of peristimulus time bins of 2.5 seconds duration that were equal to the scan repetition time. This general basis set captures any shape of the impulse BOLD response up to the frequency limit imposed by the bin size and smoothing (Henson, 2001). These functions comprised the covariates in a fixed-effects general linear model (Friston et al., 1995a; Worsley and Friston, 1995; Worsley et al., 1996) together with global changes in activity. Contrasts were performed on the parameter estimates between bin 1 (the onset of stimulus presentation) and bins 2 to 4 (from 5.0 to 10.0 seconds poststimulus presentation). They allowed a reasonable window during which the peak BOLD response including the late onset BOLD response was likely to have occurred. In this study, we used the model-free style of the BOLD as a method of analysis to detect activation areas with a long SOA of 30 seconds. The fMRI signal intensities obtained at the voxels in the whole image were compared by *t*-tests to determine whether a significant increase in signal had occurred since the onset of stimulus presentation. The resulting statistical maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. We determined activation areas to collect the highest *t*-value between bins 1 and 2 to 4 at each voxel for each condition. In the present study, we chose conditions O–O and R–R to analyze imaging data because of the unambiguous condition in the false recognition task. For assessments of the reliability of trends in an effect across subjects, the weighted time series for each subject's time bin of each contrast was entered into a 1-sample *t*-test across all subjects in each group with an intensity threshold of $p < 0.001$. This allows us to conduct random effects analysis, and the results from these random effects group analyses could be generalized from our sample of subjects to the population represented by this sample (Penny et al., 2003). We also conducted random effects analysis for group comparison between the 9 patients with alcohol dependence and the 19 normal volunteers by using a 2-sample *t*-test with an intensity threshold of $p < 0.001$. The maxima of activations were checked on normalized average images of EPI and T1 structural images and labeled using approximations to the system of MNI and Brodmann (1909) for consistency with previous studies.

RESULTS

Behavioral Results

Even though participants of both groups recognized many of the old words as old and correctly rejected many of the unrelated new words as new, they tended to recognize both of the related lure words as old. In normal controls, the mean proportion of correct responses for each condition was 0.56 (SD = 0.25) for O–O, 0.19 (SD = 0.15) for O–R, 0.17 (SD = 0.21) for R–R, and 0.65 (SD = 0.27) for U–U. In patients with alcohol dependence, the mean proportion of correct responses for each condition was 0.48 (SD = 0.31) for O–O, 0.31 (SD = 0.14) for O–R, 0.26 (SD = 0.21) for R–R, and 0.65 (SD = 0.27) for U–U. A 2-way ANOVA (type of condition and group as factors) yielded no significant main effect of group [$F(1,16) = 0.66$, $p = 0.43$] and condition-by-group interaction ($F = 0.56$, $p = 0.64$), but a significant main effect of condition [$F(3,48) = 11.70$, $p < 0.001$]. Ryan's post hoc tests for factor of condition yielded significant differences between O–O and O–R [$t(48) = 3.10$, $p < 0.005$], O–O and R–R [$t(48) = 3.49$, $p < 0.005$], U–U and O–R [$t(48) = 4.60$, $p < 0.001$], and U–U and R–R [$t(48) = 5.00$, $p < 0.001$].

Imaging Results

Table 2 shows that those brain areas in both groups exhibited significant activation during the false recognition task. Overall, the regional patterns of brain activation were similar between the groups. In the O–O condition, significant activation areas found in both controls and patients were left anterior PFC (BA 10), bilateral posterior PFC (BA 9/44/45/46), bilateral frontal operculum (BA 47/13), cingulate cortex (BA 24), bilateral cuneus and precuneus (BA 7/19), left parietal cortex (BA 40), and bilateral basal ganglia. In addition to these common areas, right anterior PFC (BA 10) and bilateral temporal cortex (BA 22) showed significant BOLD signal increases in patients. In the R–R condition, significant activation areas found in both controls and patients were right anterior PFC (BA 10), bilateral posterior PFC (BA 9/44/45/46), bilateral frontal operculum (BA 45/47), cingulate cortex (BA 24/32), bilateral cunei and precunei (BA 7/19), and bilateral basal ganglia. In addition to these common areas, left anterior PFC (BA 10) and left parietal cortex (BA 40/39) showed significant BOLD signal increases in control and right parietal cortex (BA 40) showed significant BOLD signal increases in alcoholics.

We next compared the strengths of the activations among patients and controls to determine whether there were any differences in brain activation (Figs 1 and 2). Figure 1 shows those areas that exhibited a significant difference between the groups. The patients with alcohol dependence had significantly reduced activation in the right PFC and anterior cingulate cortex (ACC) in the O–O and R–R conditions, left pulvinar in the thalamus in the O–O condition, and right ventral striatum in the R–R condition (Table 2).

DISCUSSION

The primary goal of our study was to visualize the brain pathology of young abstinent patients with alcohol dependence before clinical symptoms of cognitive impairment emerge. The results demonstrated that the young patients showed reduced activation in several regions compared with normal controls in a false recognition task, despite similar behavioral performance. Structural brain changes lead to cognitive dysfunctions, but in patients with alcohol dependence, it is known that cognitive dysfunctions occur without any signs of structural changes by conventional neuroimaging technologies. Before the advent of functional neuroimaging techniques, only neuropsychological tests could reveal their impairment, and most frequently reported were frontal lobe dysfunctions. The "lesions" responsible for these impairments would be in the frontal lobe or subcortical regions densely connected with it. Elucidation of the latent "lesions" would lead to a better understanding of alcoholic brain damages

Table 2. Regions Showing Significant BOLD Signal Increases (Random Effects Analysis, $p < 0.001$, Uncorrected for Multiple Comparisons) During [Old Word] [Old Word] pair (O–O) and [Related Lure] [Related Lure] Pair (R–R) Conditions by MNI Coordinates

		Alcoholics					Controls					Alcoholics < Controls				
			MNI coordinates					MNI coordinates					MNI coordinates			
Region of activation	Left/right	Brodmann area	*X*	*Y*	*Z*	*t*-value	Brodmann area	*X*	*Y*	*Z*	*t*-value	Brodmann area	*X*	*Y*	*Z*	*t*-value
[Old word] [Old word] pair condition																
Anterior prefrontal	L	10	−33	54	−6	4.89	10	−48	39	−3	6.27					
	R	10	36	54	−6	4.53	10	39	45	18	4.70					
Posterior prefrontal	L	9/44/45/46	−51	12	21	12.32	9/44/45/46	−54	9	33	11.53					
	R	9/44/45/46	51	12	24	5.98	9/44/45/46	54	27	33	10.02	9	51	30	33	3.13
Frontal operculum/insula	L	47	−45	21	−6	7.75	47	−33	24	−3	6.10					
	R	47	36	21	0	5.03	47	60	21	6	11.99					
Cingulate		32	−6	24	33	5.25	32	−3	18	36	10.32	24	6	24	27	4.96
Cuneus/precuneus	L	7/19	−12	−84	39	8.41	7/19	−6	−78	42	5.75					
	R	7/19	6	−78	38	14.25	7/19	12	−72	45	10.74					
Parietal	L	39	−30	−66	36	14.59	40	−51	−39	39	6.26					
	R	39	36	−63	39	12.05										
Basal ganglia	L	striatum	−15	−3	12	5.78	striatum	−21	−3	6	6.30	thalamus	−12	−30	6	3.47
	L	thalamus	−18	−30	15	5.57	thalamus	−9	−12	6	5.02	caudate	−15	21	6	3.14
	R	thalamus	6	−24	15	12.33	caudate	15	0	15	4.52					
	R	thalamus	18	−18	18	5.06										
	R	striatum	15	−3	15	4.68										
[Related lure] [Related lure] pair condition																
Anterior prefrontal	L	10	−36	42	3	5.01	10	−39	45	15	9.72					
	R	10	33	54	0	5.95	10	36	60	0	7.88					
Posterior prefrontal	L	9/44/45/46	−48	12	30	8.69	9/44/45/46	−51	3	33	10.95	46	−39	27	18	3.86
	R	9/44/45/46	51	9	21	9.88	9/44/45/46	54	21	30	7.82	46	39	48	12	4.23
Frontal operculum/insula	L	47	−51	24	−6	5.36	47	−57	9	3	12.12	13	−33	−24	18	4.39
	R	47	51	24	0	7.78	47	60	18	6	5.27					
Cingulate		24	3	30	30	5.03	32	0	21	39	7.97	24	−6	30	18	5.64
Cuneus/precuneus	L	7/19	−6	−81	42	8.22	7/19	−6	−81	42	9.32					
	R	7/19	15	−72	39	12.48	7/19	3	−81	27	12.28					
Parietal	L	40	−27	−72	39	7.08	40	−30	−75	42	6.07					
	R	40	30	−57	39	6.85	40	48	−36	36	12.22					
Basal ganglia	L	thalamus	−18	−33	9	4.80	putamen	−27	3	−3	5.40	caudate	−15	−24	18	3.74
	L	thalamus	−12	−6	12	4.66	caudate	−18	−6	21	5.17					
	L						thalamus	−15	−6	12	4.91					
	R	striatum	18	−3	15	4.79	caudate	15	−3	24	5.97	striatum	18	3	3	4.32
	R						thalamus	6	−27	3	4.98					
	R						putamen	27	3	0	4.63					

BOLD, blood oxygenation level dependent; MNI, Montreal Neurological Institute.

Fig. 1. Areas showing reduced activation in chronic alcoholics than in normal controls (random effects analysis, $p < 0.001$, uncorrected for multiple comparisons) in the right prefrontal cortex [51,30,33], anterior cingulate cortex [6,24,27], and pulvinar [−12,−30,6] in the thalamus in the old word–old word pair (O–O) condition, and the right prefrontal cortex [39,48,12], anterior cingulate cortex [−6,30,18], and right ventral striatum [18,3,3] in related lure–related lure pair (R–R) condition.

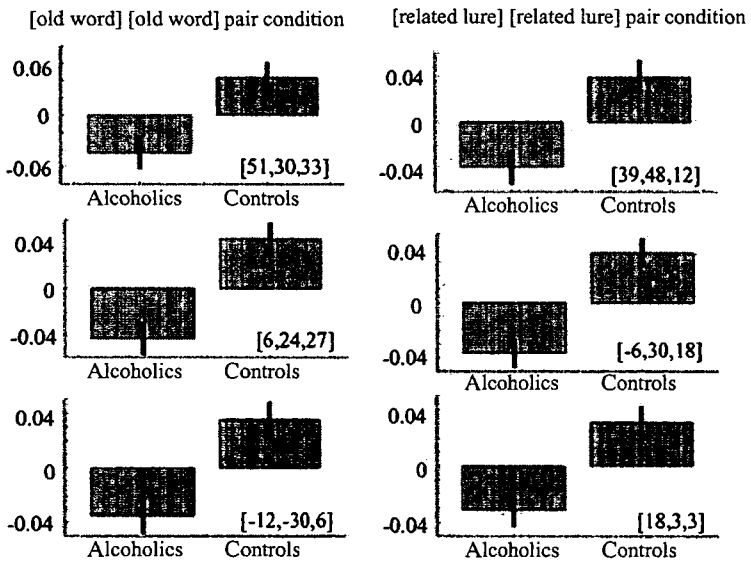

Fig. 2. Effect size at each peak coordinate showing reduced activation in patients with chronic alcoholics than in normal controls (random effects analysis, $p < 0.001$, uncorrected for multiple comparisons) in the right prefrontal cortex [51,30,33], anterior cingulate cortex [6,24,27], and pulvinar [−12,−30,6] in the thalamus in the old word–old word pair (O–O) condition, and the right prefrontal cortex [39,48,12], anterior cingulate cortex [−6,30,18], and right ventral striatum [18,3,3] in related lure–related lure pair (R–R) condition.

and, moreover, contribute to a strategy of treatment and rehabilitation of patients with alcohol dependence. With these backgrounds, we tried to visualize the latent "lesions" by using fMRI. Relationship between false recognition task and frontal lobe has been demonstrated in both lesion and functional neuroimaging studies (Schacter et al., 1996a, 1997). We predicted that our modified false recognition task could reveal behavioral impairment in patients as well as visualize the "lesions." Contrary to our expectation, the behavioral results of patients and controls were comparable. In addition, the overall activation patterns of the 2 groups were similar, and in line with those in reports of false recognition tasks (Table 2). However, significant differences in the degree of activation were observed in several regions (Fig. 1).

Regions where we observed reduced task activation in the patients with alcohol dependence, i.e., prefrontal lobe, anterior cingulate, thalamus, and ventral striatum, represent areas that have been reported to be damaged in neuropathological and neuroimaging literature. Among the above regions, the prefrontal lobe has been most frequently suggested to contribute to performance in the false recognition task, which requires an effortful recollection process. Several studies have indicated that a variety of memory deficits in patients with frontal lobe lesions may be attributable to deficient search and retrieval processes (Wheeler et al., 1997; Eskes et al., 2003). Furthermore, PET studies have revealed that right frontal lobe regions are consistently activated during episodic retrieval of recently studied items and also suggest that such activations may reflect intentional or effortful retrieval processes (Cabeza and Nyberg, 2000). It is conceivable that the hypoactivation of right frontal regions during the false recognition task in our patients with alcohol dependence reflects the latent lesion in this area, because its hypoactivation was not severe enough for behavioral impairment to emerge. Atrophy in alcoholic brains is most prominent in the frontal lobes, extending back to the parietal lobes (Courville, 1966). Moreover, Volkow et al. (1994), using ^{18}F FDG PET, showed a persistent metabolic reduction in basal ganglia and parietal lobes in patients with alcohol dependence. Paller et al. (1997) also reported widely distributed glucose hypometabolism in the cerebral cortex including frontal and parietal lobes on FDG PET in Korsakoff patients. In functional imaging studies, Desmond et al. reported that they found increased activation in left frontal and right cerebella regions in alcoholic subjects using verbal working memory compared with nonalcoholic control subjects (Desmond et al., 2003). They explained this might reflect compensatory increase in alcoholic subjects in order to maintain the comparable level of performance as controls. In this study, however, patients with alcohol dependence were much older (50 ± 8.2) and abstinent period was much shorter (32 to 732 days) than the present study. These demographic differences in subjects would be of importance, because older and less abstinent brain in patients might need more activation to achieve the behavioral compensation.

The ACC is an important component of the human medial prefrontal neural circuit that monitors ongoing processing in the cognitive system for signs of erroneous outcomes. Alcohol consumption in moderate doses induces a significant deterioration of the ability to detect erroneous responses (Ridderinkhof et al., 2002). The detection of response errors, response conflict, unfavorable outcomes, and decision uncertainty elicits largely overlapping clusters of activation foci in an extensive part of the posterior medial frontal cortex (pMFC), and monitoring-related pMFC activity serves as a signal that engages regulatory processes in the lateral PFC to implement performance adjustments (Ridderinkhof et al., 2004). Alcohol intoxication dose-dependent fMRI activation decreases were observed in anterior and posterior cingulate during visual perception task (Calhoun et al., 2004). Hypoactivation in anterior cingulate observed in our study could be interpreted in line with these observations.

The thalamus is vulnerable to alcohol, as manifested by overall volume reduction (Kril et al., 1997), reduction in the size of specific nuclei (Harding et al., 2000), and reduced neuronal size and number in the anterior nuclei (Belzunegui et al., 1995; Harding et al., 2000). The medial nucleus of the thalamus, where reduced activation was observed in this study, was the region responsible for the alcoholic Korsakoff syndrome. This is intriguing in the context of the continuum hypothesis, which indicates Korsakoff syndrome is an extreme form of alcoholic brain damage (Harper, 1983; Bowden, 1990).

The striatum, as well as the thalamus, is densely connected with the frontal lobe. Because the striatum includes groups of dopamine neurons, this structure has often been described in the context of the reward system, which plays a crucial role in drug-seeking behavior. For example, activation of the striatum and medial PFC induced by alcohol-associated cue has been shown to associate with an increased risk for relapse in abstinent patients with alcohol dependence (Braus et al., 2001; Grusser et al., 2004). Furthermore, a decreased monoaminergic system in this area was demonstrated in alcoholic brains by a PET study (Gilman et al., 1998). These findings suggested that some dysfunction in this region exists in patients with alcohol dependence.

Taken together, regions where we observed reduced activation in patients with alcohol dependence during the false recognition task were consistent with the lesions reported in a large body of literature of alcoholic neuropathology. Therefore, it is likely that the reduced activation could reflect subclinical alcoholic brain pathology, which might be in situ or a disruption of input from other areas. Our relatively young patients retained the ability to perform the false recognition task but responded abnormally at the neuronal level. These findings would indicate that the patients did have damage in the areas needed to perform the task, but they were so subtle that they retained the ability to perform the task normally. One possible factor responsible for this result could be the long abstinence period of our subjects. There have been several studies that showed that longer abstinence leads to greater improvement in functional lesions and/or cognitive functions (Sullivan et al., 2000). For example, 1 longitudinal FDG PET study evaluated the effect of abstinence and relapse on metabolic changes and neuropsychological test performances on 2 occasions separated by 10 to 32 months. The abstinent subjects showed improvement in glucose metabolism and in neuropsychological test results, while the relapsing patients exhibited further decline in both measures (Johnson-Greene et al., 1997). Moreover, Dupont et al. (1996) compared perfusion on ^{123}I IMP SPECT with performances on Raven's Progressive Matrices in recently detoxified subjects and long-term (mean 7.7 years) abstinent patients. Reduced perfusion was observed with both short- and long-term abstinence, despite nearly normal

neuropsychological task performances in the long-term abstinent patients. Our results are essentially in accordance with these reports, revealing abnormal functional neuroimaging despite normal cognitive function in young patients with alcohol dependence. The regions of reduced activation in the subjects may be precursors of impaired performance, and performance of more demanding task might be affected. These are questions raised by our study that will require future attention.

In summary, the present study demonstrated diminished response in several regions in relatively young abstinent patients with alcohol dependence in a false recognition task. Because our subjects show no apparent cognitive impairment and their task performance was comparable with that of healthy controls, these regions can be considered as latent "lesions," implicating some dysfunctions. These can be consequences of heavy drinking, but another possibility might be that they were premorbid risk factors for alcoholism. In the present study, the effect of antisocial personality disorder on cognitive function was excluded. However, the other comorbid personality disorders with alcoholism may have an impact on neuropsychological results and brain activations. The effect of premorbid factors including personality disorders on the performance of the subjects with alcoholism would be of importance in future study.

Our analyses in the present study were focused on the PFC, but areas outside PFC, such as the hippocampus, are also crucial for comprehensive understanding of alcoholic pathology. Notwithstanding the limitations, an implication from our results is that understanding the activation of brain circuitry during certain tasks may help explain the behavioral characteristics of patients with alcohol dependence, including impairments as revealed by neuropsychological testing. Further, insights into this issue could help in the design of interventional methods such as cognitive behavioral therapies for patients with alcohol dependence.

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Unilateral Amygdala Lesions Hamper Attentional Orienting Triggered by Gaze Direction

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The newly discovered deficit in a bilateral amygdala-damaged case, of not being able to allocate attention to the critical feature of a face (Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. 2005. A mechanism for impaired fear recognition after amygdala damage. Nature. 433:68–72.), has opened a new window into the function of the amygdala. This case implies that the amygdala might be essential in detecting potentially relevant social stimuli, and directing attention accordingly. In this study, we have sought to test this implication by investigating the behavioral performance of 5 unilateral amygdala-damaged subjects on spatial cueing tasks. The tasks employed central gaze and arrow direction as cues to trigger attentional orienting in peripheral target detection. Although age-matched normal controls demonstrated a significant congruency effect such that targets presented congruently to cue direction elicited faster detection, amygdala subjects demonstrated no such congruency effect for gaze cues in the face of a significant congruency effect for arrow cues. The results suggest that the social valence of a stimulus is critical for amygdala involvement in visual processing. The results also support the implicated role of the amygdala in detecting and analyzing relevant social stimuli, and orienting attention accordingly.

Keywords: amygdala laterality, arrow, social cognition, spatial cueing

Introduction

The amygdala has captured much interest for its intriguing function in processing the emotional valence of a stimulus, and modulating perception, behavior, and memory based on such valence. In the growing field of social cognition, a rather specific role of the amygdala in recognizing fearful faces has been repeatedly demonstrated in both neuropsychological (Adolphs et al. 1994, 1999) and neurofunctional (Morris et al. 1996; Whalen et al. 1998) studies. More specifically, the importance of the eye region in fearful faces has been emphasized through functional neuroimaging studies where fearful eyes (Morris et al. 2002), and even fearful eye-whites (Whalen et al. 2004) have been shown to be sufficient in activating the amygdala. Recently, a further role of the amygdala has been identified in a bilateral amygdala-damaged case, SM, who failed to make gaze fixations on the critical feature of faces, that is, the eyes, thereby hampering her ability to decipher emotion expressed through faces (Adolphs et al. 2005). The finding from this case thus indicates that the amygdala does not merely process incoming emotional stimulus but actually participates in seeking for relevant stimulus from the environment, and allocating attention toward it. Indeed, a number of functional neuroimaging studies have demonstrated that aversive faces that escape conscious awareness, as when unattended to due to competing stimuli (Vuilleumier et al. 2001; Anderson et al. 2003; Williams et al. 2004), when subliminally presented (Morris et al. 1998; Whalen et al. 1998; Nomura et al. 2004), or even when unperceived due to blindsight (Morris et al. 2001), are nonetheless captured by the amygdala as seen in its activation. However, to date, few neuropsychological investigations have addressed the impact of amygdala lesion on attention; Anderson and Phelps (2001) have reported that left (and bilateral) amygdala lesions diminish the attentional enhancement normally seen to aversive over neutral words. Vuilleumier et al. (2004) have demonstrated that the enhancement of fusiform activation, which is normally present to fearful over neutral faces, was absent in left and right amygdala-damaged subjects, irrespective of attentional factors (i.e., whether the stimuli faces were attended to or not). The effect of amygdala lesion on attentional orienting behavior, such as implicated through the case of SM (Adolphs et al. 2005), is an intriguing issue that has not yet been fully addressed.

A potential experimental paradigm to test the implicated role of the amygdala in orienting attention toward relevant stimuli is the spatial cueing task using cues such as gaze and arrow direction (Friesen and Kingstone 1998; Tipples 2002). In these tasks, where central gaze/arrow is used to trigger attentional orienting, normal subjects have repeatedly demonstrated faster reaction times (RTs) in detecting peripheral targets presented congruently to the cue direction, opposed to incongruently presented targets. Given the numerous data of amygdala involvement in gaze processing (Brothers and Ring 1993; Young et al. 1995; Broks et al. 1998; Kawashima et al. 1999; George et al. 2001; Morris et al. 2002; Adams et al. 2003; Hooker et al. 2003; Whalen et al. 2004; Adolphs et al. 2005), the employment of gaze direction in such tasks would have an additional value of directly examining the impact of amygdala lesion on gaze processing. On the other hand, arrow cues would give us the opportunity to investigate whether any compromise that might be present in amygdala-damaged subjects is selective to gaze, or generalizes to other relevant signals. When considering the nature of the amygdala function in optimizing adaptation and survival, social cues such as fearful faces and gaze direction might not necessarily be the only relevant stimuli to "capture the amygdala's attention"; nonhuman animates (snakes), objects (guns), natural phenomenon (lightening), words ("caution"), and symbols (skull and crossbones) might all equally capture attention for better adaptation and survival. Likewise, an arrow sign is an overlearned symbol that can effectively modulate orienting behavior in healthy subjects (Tipples 2002), a phenomenon most likely attributable to the conveyed intention behind the arrow sign: "Look over there!"

The outstanding question that we have set out to address in this report is whether amygdala lesion affects attentional orienting triggered by relevant cues, and if so, whether there is any

distinction between social and nonsocial cues. Here, we have tested 5 subjects with unilateral amygdala lesions in spatial cueing tasks employing gaze and arrow cues. If indeed, social stimuli such as eyes enjoy preferential processing in the amygdala, the amygdala-damaged subjects might demonstrate impaired gaze-triggered, but intact arrow-triggered orienting. Conversely, if the amygdala processes relevant stimuli irrespective of social valence, orienting triggered by both cues might be uniformly hampered.

Materials and Methods

Subjects

Five subjects with unilateral amygdala lesion (right, 2; left, 3) participated in the study. The demographic data, such as the etiology, present medication, and present intelligent quotient (IQ) are shown in Table 1. Note that general attention, as indicated by the attention/concentration index of Wechsler memory scale-revised (WMS-R) (also shown in Table 1), is in the superior range for each subject. Case 1 demonstrates antisocial behavior, such as getting into numerous street fights, and lives on welfare. Case 2 became mildly depressive after recovery but is able to work full-time as a nurse. Case 3 presented with ictal fear at onset, which diminished within a month. He returned to his office work after recovery. Case 4 became emotionally withdrawn after surgery with some depressive symptoms, and is taking a long leave from work. Case 5 also became increasingly withdrawn after surgery, and is easily provoked. He has returned to his office job but remains socially withdrawn both at work and home. Magnetic resonance imaging (MRI) slices depicting the amygdala lesion are presented for each subject in Figure 1. Fifteen normal volunteers also participated as controls. The exclusion criteria were a psychiatric history and a neurological history. All participants had normal or corrected-to-normal vision.

Prior to the experiment, all 5 amygdala subjects were evaluated on conventional tests assessing spatial attention and visuomotor processing, as these functions are essential in performing the following experimental task. For spatial attention, Cancellation Test (for the numeral "3" and the Japanese character "ka"), and Tapping Span Test were administered, both of which were in the normal range based on the previously accumulated normative data (Table 2). Symbol Digit Modalities Test (SDMT) was used to assess visuomotor processing, tracking, and motor speed. In this test, a series of 9 geometric symbols, each of which were labeled with a number from 1 to 9, were presented. The subjects were required to substitute the symbols with the corresponding numbers as fast as possible within the given 90 s. The percentage of correct responses achieved (maximum 110) was evaluated. Again, the amygdala group performed within the normal range (Table 2). The performance of the amygdala subjects on the following experimental task can thus be concluded to be unconfounded by deficits in spatial attention or visuomotor processing capacities per se.

This study was approved by the ethical committee at our institutions, and all subjects gave their informed consent to participation.

Stimuli

The experiment was controlled by Superlab software, and the stimuli were presented on a 14-inch computer monitor. There were 3 blocks to the experiment, each with a different stimulus for the cue. The cues were black line drawings representing: Arrows for the first block, Eyes for the second, and Faces for the third block, as illustrated in Figure 2.

In the first, Arrow block, a cross subtending 3.9° horizontally and 1.9° vertically appeared in the center, of which the intersection served as the fixation point. This was displayed for 675 ms, followed by the cue display. In the cue display, arrowheads or vertical bars appeared at each horizontal end of the cross. Arrowheads (1.3° × 0.6°) at both ends pointed in the same direction, cueing either to the right or left. The vertical bars (1.3°) served as the neutral cue, similar to straight gaze in the second block. The cue was presented for either 100, 300, or 700 ms randomly (stimulus onset asynchrony; SOA), after which a target, X, subtending 0.6°, appeared either to the right or left of the cue, 7.1° from the fixation point. Note that the cue remained displayed throughout target presentation.

In the second, Eyes block, the fixation display was composed of one central circle subtending 0.4°, and 2 ellipses, the axes of which are 1.8° × 0.9°, and the center of which is 1.0° above, and 1.4° to the left and right of the central circle. The central circle was used as the fixation point, and was displayed for 675 ms, followed by the cue display. In the cue display, a black circle subtending 0.9°, appeared within each ellipse, positioned either centrally (straight gaze), or 11% off the center to the right or left (right/ left gaze). The cue was presented for either 100, 300, or 700 ms randomly, after which a target, X, subtending 0.6°, appeared either to the right or left of the cue, 7.1° from the central circle. Again, the cue remained displayed throughout target presentation. The third, Face block was identical to the Eyes block, except for the additional large circle subtending 8.0°, which surrounded the eyes and served as the facial outline.

Design

There were 3 cue-types (Arrows, Eyes, Faces), each in 3 separate blocks. The order of the blocks remained fixed among subjects. (The order was not counterbalanced in this study, due to the limited number of amygdala subjects. However, approximately 1 year after this experiment, Cases 1 and 3 were retested with different order [Case 1: Faces, Eyes, Arrows; Case 3: Eyes, Faces, Arrows]. Analyses of variance

Table 1
Demographic data

	Amygdala group					Normal group
	Case 1	2	3	4	5	(*N* = 15)
Age	48	40	59	28	42	45.0 ± 9.1
Gender	M	F	M	M	M	M 12, F 3
Handedness	R	R	R	R	R	R 14, L 1
Education (years)	12	14	13	16	16	15.5 ± 2.4
Etiology of lesion	Trauma	Encephalitis	Encephalitis	Hemangioma, postsurgery	Astrocytoma, postsurgery	
Side of lesion	R	R	L	L	L	
Duration of lesion (years)	31	3	6	2	2	
Medication (mg)	V400	None	C1.5, Z200	V400	V800, PH 200, PB90	
Wechsler adult intelligence scale-revised						
Verbal IQ	97	123	86	112	79	
Performance IQ	91	91	84	98	88	
Full IQ	94	110	84	106	81	
WMS-R						
Verbal memory	82	104	86	74	105	
Visual memory	87	106	95	99	106	
General memory	82	105	88	77	106	
Delayed recall	71	99	80	93	110	
Attention/concentration	112	113	115	113	108	

Note: V, sodium valproate; C, clonazepam; Z, zonisamide; PH, phenytoin; PB, phenobarbital.

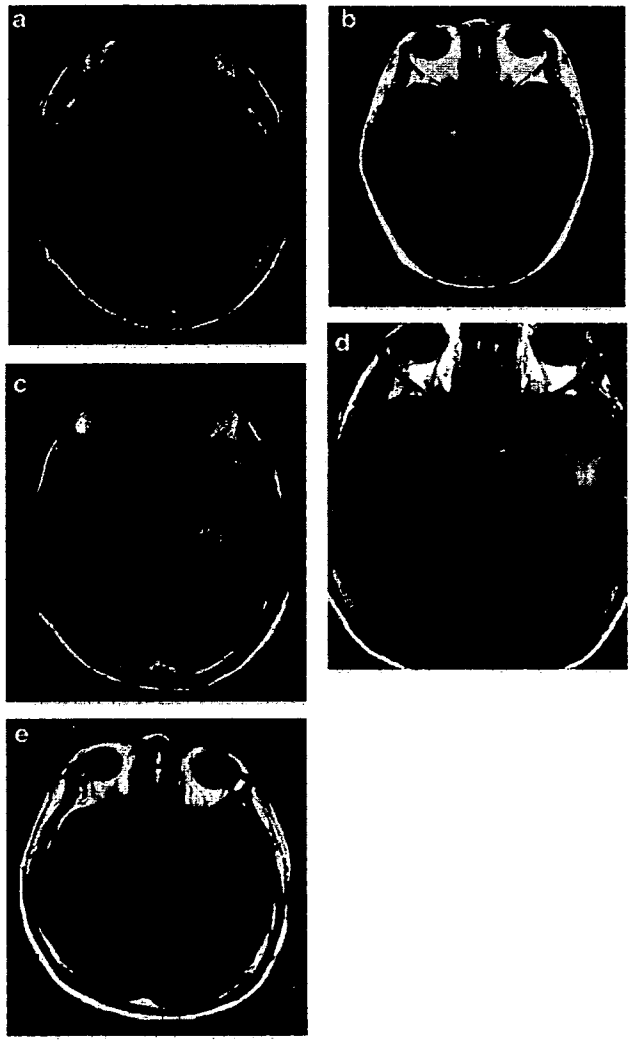

Figure 1. MRI of cases 1–5 (*a–e*, respectively), each depicting a lesion in the unilateral (cases 1 and 2, right; cases 3–5, left) amygdala.

[ANOVAs] revealed no interaction of order on cue-type or congruency, nor a 3-way interaction, in both cases [all Fs < 1].) Within each block, cue-target SOAs (100, 300, 700 ms), cue-target relations (congruent, incongruent, neutral), and target locations (right, left) were randomly selected with equal probability to make up a nonpredictive, spatially cued, target detection test. Ten catch trials where no target followed the cue were randomly dispersed within each block.

Procedure

Participants sat 45 cm from the monitor. Subjects were instructed to maintain fixation throughout each trial, and upon target detection, to press the spacebar on the keyboard with their dominant index finger. The nature of the cue stimuli (e.g., the resemblance thereof to eyes or arrows) was never mentioned, nor was the probability in relation to cue-target congruency. Fifteen practice trials were given before each block. The RT from the onset of the target, to the pressing of the key was recorded. Time out was set at 1500 ms, with an interstimulus interval of 3000 ms. A total of 190 trials comprised one block, which took approximately 15 min to complete. Subjects were given a minimum of 10 min between blocks to rest. Eye movements were not monitored for the control subjects, for it has been confirmed in a number of studies that normal subjects reliably do not move their eyes on similar experiments (Posner 1980; Friesen and Kingstone 2003; Friesen et al. 2004). Amygdala subjects were monitored for eye movements by direct viewing of the experimenter, and all were able to maintain fixation almost all the time.

Table 2
Performance on conventional attentional and visuomotor tests

	Amygdala group					Control group
	Case 1	2	3	4	5	(N = 15)
Age	48	40	59	28	42	42.3 ± 5.6
Cancellation Test (%)						
"3"	100	100	99.1	99.1	100	99.6 ± 0.6
"ka"	98.2	99.1	97.4	97.4	99.1	97.6 ± 2.4
Tapping Span Test						
Forward	6	6	8	7	7	6.3 ± 1.3
Backward	7	6	7	5	6	5.9 ± 1.4
SDMT (% achieved)	55.5	61.8	54.5	60.0	60.9	58.4 ± 8.3

Note: This control group is different from the experimental control group.

(In the retesting session mentioned in previous section, eye movements of Cases 1 and 3 were monitored using an infrared pupil-corneal reflection eye movement monitoring system [Eyemark Recorder 8B model ST-650, nac Image Technology Inc., Tokyo, Japan]. Case 1 demonstrated only one eye movement in the Eyes block. Case 3 demonstrated eye movements in 7, 5, and 8 trials for Eyes, Faces, and Arrows, respectively, comprising 3.3% of the entire experiment. All eye movements were detected in the target display. There was no fixation failure in the fixation display, or in the cue display.)

Results

Errors, defined as anticipations (RTs < 100 ms), RTs longer than 1000 ms, time outs (no response), and incorrect responses (pressing a key other than the correct spacebar), were first discarded from further analysis, which eliminated less than 1% of both amygdala and normal data. The mean RTs and standard deviations (SDs) of all trials for both groups are presented in Table 3. The mean RTs as a function of congruency and SOA are shown for each cue-type, for each group in Figure 3.

Raw RTs were then submitted to ANOVA with a between-subject variable of group (amygdala, normal), and within-subject variables of cue-type (Arrows, Eyes, Faces), cue-target congruency (congruent, incongruent, neutral), and SOA (100, 300 and 700 ms). The main effects of congruency ($F_{2,18}$ = 9.49, P < 0.001) and SOA ($F_{2,18}$ = 12.43, P < 0.001) were significant. The main effect of group approached significance ($F_{1,18}$ = 3.51, P = 0.077). The critical group × cue-type × congruency interaction was significant ($F_{4,18}$ = 3.18, P = 0.018). Post hoc analysis of this interaction revealed that the congruency effect was significant for all cue-types for the controls (Arrows; $F_{2,14}$ = 9.58, P < 0.001, Eyes; $F_{2,14}$ = 8.01, P < 0.001, Faces; $F_{2,14}$ = 5.25, P = 0.007), whereas the amygdala group showed a significant congruency effect only for Arrows ($F_{2,4}$ = 7.24, P = 0.001), and not for the 2 gaze cues (Eyes; $F_{2,4}$ = 0.29, P = 0.751, Faces; $F_{2,4}$ = 1.16, P = 0.319). To illustrate the critical interaction more clearly, the benefits of congruent cues over incongruent/ neutral cues were determined for each cue-type as RT differences (RT incongruent - RT congruent, and RT neutral - RT congruent) and were calculated for each individual. They were averaged within groups and are illustrated in Figure 4. In sum, unilateral amygdala-damaged subjects demonstrated a distinctive difference from the normal subjects in that their response is differentially facilitated by congruent arrow cues but not by congruent gaze cues. Other significant interactions were cue-type × congruency ($F_{4,18}$ = 4.45, P = 0.003) (diminished congruency effect for Faces), and cue-type × SOA ($F_{4,18}$ = 3.78, P = 0.008) (less SOA effect for Faces).

Subsequently, within-group analyses of laterality effects were conducted for the amygdala group. The simple effect of lesion

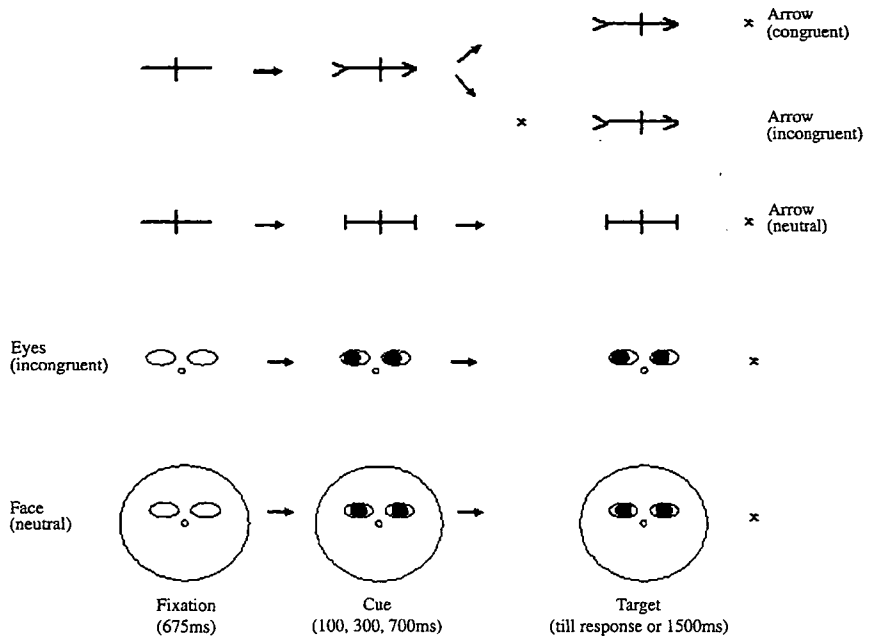

Figure 2. Illustration of the trial sequence in the experiment. A fixation display was presented for 675 ms, followed by a cue display, which was either arrow or gaze (Eyes, Face) direction. The cue was displayed for 100, 300, or 700 ms, then a target was presented, either to the right or left of the cue, and irrespective of cue direction.

side (right, left) proved to be nonsignificant using ANOVA ($F_{1,3} = 1.77$, $P = 0.276$). Then all performance was regrouped in reference to lesion side. First, an ANOVA was conducted with cue-side (in reference to lesion; ipsilesional, contralesional) and congruency (congruent, incongruent) as the variables, which revealed neither a significant main effect of cue-side ($F_{1,4} = 0.36$, $P = 0.583$) nor a significant interaction ($F_{1,4} = 1.22$, $P = 0.332$) (note that neutral cues were not included in this analysis because they would automatically predict neutral trials). Second, an ANOVA was conducted with target-side (in reference to lesion; ipsilesional, contralesional) and congruency (congruent, incongruent, neutral) as the variable, which also revealed neither a significant main effect of target-side ($F_{1,4} = 1.18$, $P = 0.339$) nor a significant interaction ($F_{2,4} = 0.24$, $P = 0.791$). In sum, based on the very limited number of unilateral amygdala cases in this study, no laterality effect was delineated.

Finally, in an attempt to investigate whether the extent of amygdala lesion might correlate with the behavioral benefit derived from congruent cues, MRIs of amygdala cases were reviewed by 2 independent radiologists with close scrutiny, and the lesions were consistently ranked from the least extensive (1), to the most extensive (5). When both benefit differences (RT incongruent - RT congruent and RT neutral - RT congruent) for all blocks were grouped together, we observed a Spearman's rank correlation coefficient of -0.274 ($P = 0.143$), which might be tentatively suggestive of a very weak trend for a negative correlation between the extent of amygdala damage and benefit. Nevertheless, when regrouped according to benefit types (benefit over *incongruent* or *neutral* trials), or according to blocks (Arrows, Eyes, Faces), the correlation did not approach significance.

Table 3
Results

Condition	Amygdala group		Normal group	
	RT	SD	RT	SD
Arrows				
SOA 100 ms				
Congruent	414	93	366	78
Incongruent	414	78	372	69
Neutral	432	91	379	69
SOA 300 ms				
Congruent	379	84	323	65
Incongruent	392	73	355	77
Neutral	395	76	350	72
SOA 700 ms				
Congruent	366	61	338	75
Incongruent	373	62	355	78
Neutral	378	79	356	85
Eyes				
SOA 100 ms				
Congruent	415	81	350	60
Incongruent	413	84	371	78
Neutral	416	87	362	65
SOA 300 ms				
Congruent	384	87	321	56
Incongruent	393	75	340	67
Neutral	384	81	343	71
SOA 700 ms				
Congruent	383	69	335	75
Incongruent	387	68	350	70
Neutral	386	68	348	76
Faces				
SOA 100 ms				
Congruent	420	89	345	73
Incongruent	420	95	352	63
Neutral	408	85	353	72
SOA 300 ms				
Congruent	395	74	320	73
Incongruent	396	87	332	68
Neutral	400	98	341	83
SOA 700 ms				
Congruent	394	83	328	65
Incongruent	402	97	343	81
Neutral	386	78	348	77

Discussion

In this report, we have demonstrated in a group of unilateral amygdala-damaged subjects, a robust deficit in attentional

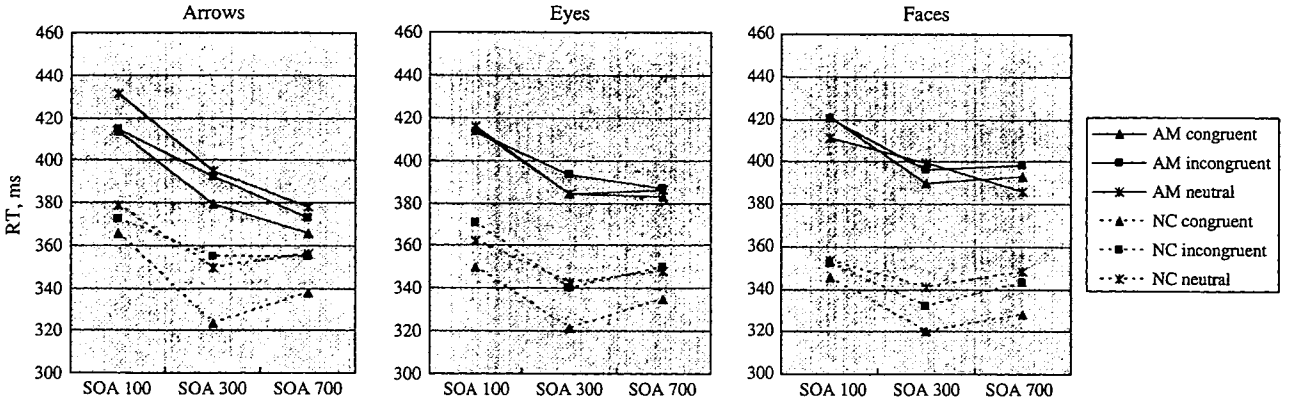

Figure 3. Results of the experiment. The mean RTs of the amygdala group (AM; lines) and normal controls (NC; dotted lines) for each cue-type, as a function of cue-target congruency and SOA length.

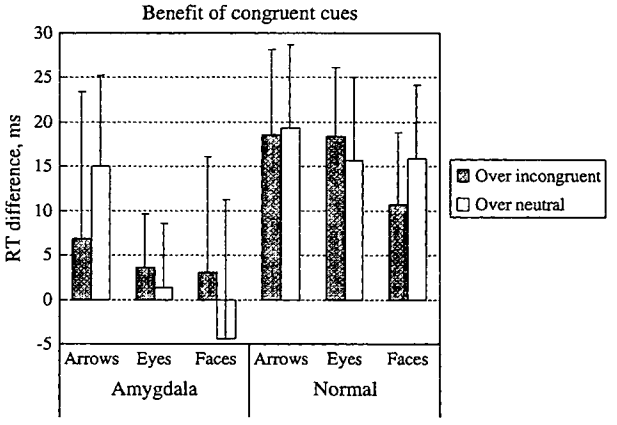

Figure 4. The benefits of congruent over incongruent cues (calculated as RT incongruent – RT congruent), and over neutral cues (RT neutral – RT congruent) are shown for each cue-type, averaged within each group. Error bars indicate the 95% confidence interval.

orienting triggered by gaze direction, in the face of a relatively normal orienting to arrow direction. This is evidence for the selective role that the amygdala plays in detecting and analyzing significant social stimuli, and orienting attention accordingly. Such function, when damaged, might underpin many of the intriguing impairments identified in a number of amygdala-damaged subjects. Namely, the aforementioned impairment in recognizing fearful faces (Adolphs et al. 1994, 1999), the difficulty in discriminating gaze direction (Young et al. 1995; Broks et al. 1998), the misjudgment of trustworthiness and approachability from unfavorable faces (Adolphs et al. 1998), and the impairment of making fixations on eyes (Adolphs et al. 2005) might all be attributed, at least in part, to a common fundamental deficit in exploring for a relevant social signal, allocating attention to it, extracting the critical feature, and guiding behavior accordingly. Our findings also converge with the neuroimaging data (Morris et al. 1998; Whalen et al. 1998; Morris et al. 2001; Vuilleumier et al. 2001) to implicate the involvement of the amygdala in covert attention allocated to significant social stimuli.

The current study answers in the affirmative to the outstanding question of whether the social (or biological) valence of a stimulus (e.g., eyes opposed to arrow signs) is critical for amygdala involvement. In close resemblance is the finding from a case with a lesion to the right superior temporal sulcus (STS) area, where biological motion processing is often implicated (Bonda et al. 1996; Puce et al. 1998; Pelphrey et al. 2003; Akiyama, Kato, Muramatsu, Saito, Nakachi, et al. 2006). This patient also demonstrated a deficit in gaze-triggered orienting in the face of an intact arrow-triggered orienting (Akiyama, Kato, Muramatsu, Saito, Umeda, et al. 2006). The similar findings from the 2 studies implicate that the amygdala and the STS might work in concert to selectively process significant social stimuli such as eyes. The amygdala, where very rapid, but coarse information enters (Morris et al. 1999; Vuilleumier et al. 2003), might be in the position to detect potential social stimulus, and crudely evaluate its significance. Through its reciprocal connections with the STS (Amaral et al. 1992; Freese and Amaral 2005), the amygdala might then relay potentially significant biological stimuli to the STS for finer analysis. Indeed, a recent study (Vuilleumier et al. 2004) reported that the extent of amygdala damage negatively correlated with the enhancement of fusiform and STS activation shown for fearful over neutral faces, suggesting the projection of activation from the amygdala in response to significant biological stimuli.

On the other hand, a considerable amount of literature suggests that the function of the amygdala might not be limited to a strictly social extent, but might extend to the detection of arousing, goal-relevant stimuli in general (Ochsner 2004; Sander et al. 2005). For example, learned predictive cues that guide goal-directed behavior have been shown to be dependent on the amygdala to be effectively utilized; rats with lesions to the central nucleus of the amygdala demonstrate decreased orienting responses toward cues (light), which reliably predict a significant event (food) (Holland and Gallagher 1999; Lee et al. 2005). Interestingly, attention to the target event (food) itself was uncompromised in these rats, implicating a specific deficit in attending to cues. Also in humans, there is growing evidence for the role of the amygdala, in conjunction with the prefrontal cortex, to compute the predictive value of a stimulus (Whalen et al. 2001; Kahn et al. 2002; Kim et al. 2003). Moreover, the human amygdala is considered to be critically involved in relevance detection, where not only social but motivational self-relevant stimuli are rapidly detected from the environment, allowing efficient orienting of processing resources toward salient events (Sander et al. 2005). In this line, there is a possibility that an arrow sign, which is inherently coupled

with the expectation for an important value or stimulus in its alignment might also "capture the amygdala's attention" to an extent. Although the results of the present study demonstrated no significant group differences in the congruency effect for Arrows, the amygdala group did show a nonsignificant reduction of congruency benefit for Arrows (Fig. 4). It could thus be tentatively suggested that unilateral amygdala damage preferentially hampers gaze-triggered orienting but might also affect arrow-triggered orienting very subtly.

In the field of functional neuroimaging, there is an on-going debate over the extent to which attentional factors modulate amygdala activation generated by fearful stimuli in the normal brain. On one hand, the amygdala seems to demonstrate automatic involvement to fearful faces, as evidenced by its activation even when the fearful face is outside the focus of attention (e.g., Morris et al. 1998, 2001; Vuilleumier et al. 2001; Anderson et al. 2003). On the other hand, there are also a number of studies that conflict with this view. Pessoa et al. (2002, 2005) have demonstrated that when competing tasks consume much of the attentional resources, the unattended fearful faces fail to activate the amygdala, thereby arguing against the automatic nature of amygdala involvement. Bishop et al. (2004) have reported that the state anxiety of individuals might be a determining factor of whether unattended fearful faces are captured by the amygdala; high-anxious subjects demonstrated left amygdala activation to both attended and unattended fearful faces, whereas subjects with low anxiety demonstrated differential activation in the left amygdala to attended, over unattended fearful faces. Although the primary purpose of this present report was not aimed at clarifying these discrepancies, it might nonetheless shed some light onto this interesting debate. Our results studying amygdala-damaged subjects, along with Adolphs et al.'s (2005) results, do suggest that bilaterally intact amygdala is essential in efficiently guiding attention according to the social stimuli it receives. It might thus be more correctly stated that *amygdala activation* modulates attention. In this view, amygdala activation might be reflective of the allocation of attention to significant, self-relevant stimuli.

The patient group of autism, whose lack in reciprocal gaze exchange is one of the cardinal manifestations (American Psychiatric Association 1994), and whose amygdala have been reported to be anatomically (Kemper and Bauman 1993, 1998; Courchesne 1997; Howard et al. 2000; Sparks et al. 2002) and functionally (Baron-Cohen et al. 1999; Pierce et al. 2001; Castelli et al. 2002) aberrant, have previously been studied with similar spatial cueing tasks. Senju et al. (2004) have reported that autistic children demonstrated a relatively normal gaze and arrow effect in a nonpredictive condition but their performance was quite aberrant when the condition was counterpredictive. Ristic et al. (2005) reported in a group of autistic children, a relatively normal gaze effect in a predictive condition but absent gaze effect in a nonpredictive condition. The 2 studies indicate a decrease in attentional orienting triggered by gaze in autistic children, similar to (but to a lesser extent than) the amygdala-damaged subjects in the current study. Taken together, properly functioning amygdala might be essential to normal attentional orienting triggered by gaze, and perhaps in a wider scope, to normal gaze behavior such as eye-contact and gaze-following.

In the present study, we have used 2 gaze stimuli; eyes with and without a facial outline. The 2 did not differentiate from one another in performance for both normal and amygdala groups; normal controls showed significant congruency effects for both gaze cues, and the amygdala subjects showed no such effect for either cue. This finding is in concordance with prior studies demonstrating that the mere eyes (or even eye-whites) of a frightened face is equally sufficient in activating the amygdala (Morris et al. 2002; Whalen et al. 2004) as the entire frightened face. Of note, the Face condition in our experiment was devoid of emotional expression, and so the present 2 gaze cues were essentially equivalent in their emotional valence. When taking into account the finding that gaze direction and facial expression interact when activating the amygdala (Adams et al. 2003; Holmes et al. 2006), and that facial expression modulates attentional orienting triggered by gaze cues (Holmes et al. 2006), future studies might also incorporate different emotional expressions in similar tasks to investigate if the modulation of expression on the gaze effect might differ between the 2 groups.

The major limitation of this study, which is the small number of amygdala cases leaves many unanswered questions to be addressed. Namely, the effect of bilateral amygdala lesions, the comparison of right versus left amygdala lesions with more cases, and the effect of gender on the performance of the amygdala group in similar tasks would be of importance. The comparison of early (congenital to perinatal) versus late amygdala lesion, and possibly a direct comparison with a group of autistic spectrum subjects might also afford fruitful insight into the function of the amygdala. Another limitation is the lack of accurate lesion volumetry in this study. The volumetric analysis of amygdala lesions, along with increased number of cases should yield further interesting findings in the future. The newly identified function of the amygdala, of directing one's "visual system to seek out, fixate, pay attention to and make use of" the sought information, as pointed out by Adolphs et al. (2005), might open new windows to our understanding of attentional, emotional, and social processes of the brain.

Notes

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