NeuroImage **14,** 7–20 (2001)
doi:10.1006/nimg.2001.0785, available online at http://www.idealibrary.com on IDEAL®

Reorganization of Frontal Systems Used by Alcoholics for Spatial Working Memory: An fMRI Study

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Received July 19, 2000; published online May 15, 2001

Chronic alcoholism is associated with impairment in sustained attention and visual working memory. Thus, alcoholics have reduced ability, but not necessarily inability, to perform these executive tasks, assumed to be subserved by regions of prefrontal cortex. To identify neural substrates associated with this impairment, we used functional MRI (fMRI) to determine whether alcoholics invoke the same or different brain systems as controls when engaged in working memory tasks that the two groups were able to perform at equivalent levels. The fMRI spatial working memory paradigm instructed subjects to respond with a button press when a target position was either in the center of the field (match to center) or matched the spatial position of one presented two items previously (match 2-back) or to rest. Using whole-brain fMRI, alcoholics showed diminished activation frontal cortical systems compared to controls (bilateral dorsolateral prefrontal cortex) when responding 2-back vs rest. In the center vs rest contrast, the control group compared with the alcoholic group activated a large expanse of prefrontal cortex (including Brodmann areas 9, 10, and 45), whereas there was significantly greater activation by the alcoholic group relative to the control group localized more posteriorly and inferiorly in the frontal cortex (area 47). Examination of within group activation patterns revealed two different patterns of activation: the control group exhibited activation of the dorsal ("Where?") stream for visual spatial working memory processing, whereas the alcoholic group exhibited activation of the ventral ("What?") stream and declarative memory systems to accomplish the spatial working memory task. The differences in the pattern of brain activations exhibited by the alcoholic and control groups, despite equivalence in behavioral performance, is consistent with a functional reorganization of the brain systems invoked by alcoholic individuals or invocation of an inappropriate brain system when engaged in a visual spatial task requiring working memory.

INTRODUCTION

Chronic alcoholism carries with it a life-long burden of cognitive and motor compromise. Despite significant recovery of brain structure (Pfefferbaum *et al.,* 1998, 1995; Shear *et al.,* 1994) and function (Brandt *et al.,* 1983; Sullivan *et al.,* 2000) with prolonged alcohol abstinence, full restitution typically does not occur, and mild to moderate impairment in selective functions persists. Postmortem (Courville, 1955; Harper and Kril, 1989) and *in vivo* neuroimaging (Pfefferbaum *et al.,* 1997) studies have shown that frontal lobe systems are especially vulnerable to the untoward effects of alcohol abuse. Although neuropsychological studies have revealed enduring deficits in spatial working memory, problem solving, and cognitive flexibility, all considered to be executive or frontal lobe functions (Nixon *et al.,* 1995; Oscar-Berman and Hutner, 1993; Sullivan *et al.,* 1993), attempts to establish direct links between circumscribed frontal lobe structures and specific functions in alcoholics have been largely unsuccessful [for review, (Sullivan, 2000)]. Exceptions are from two resting-state FDG PET studies done in detoxified alcoholics. The first reported a selective relationship between medial frontal hypometabolism and concepts attained on the Wisconsin Card Sorting Test (WCST) (Adams *et al.,* 1993). The second reported correlations in older alcoholics between performance on the Halstead Category Test, which assesses concept formation, and regional glucose metabolism rate in the cingulate, dorsolateral frontal, and orbitomedial frontal cortices, whereas the WCST performance correlated with glucose metabolism in the cingulate cortex only (Adams *et al.,* 1995). In neither study were the cognitive tests performed as part of a PET activation paradigm.

1053-8119/01 $35.00

The "lesion" associated with alcoholism can be considered "incomplete" in that it can represent shrinkage or disruption of neuronal processes (Harper, 1998) and not necessarily cell loss (Badsberg-Jensen and Pakkenberg, 1993). This conceptualization follows from the clinical observations and systematic lesion studies of Sherrington and colleagues, who demonstrated the importance of remaining fibers to recovery of movement in lesion and deafferentation experiments (Mott and Sherrington, 1895). Therefore, the resulting cognitive deficits in abstinent alcoholics may reflect more a compromised or distorted function than a lost function, possibly attributable to reduced or diffuse activation of task-appropriate brain regions or, alternatively, activation of task-inappropriate brain regions. We tested these two possibilities by examining group differences in regional activation observed in an fMRI experiment requiring spatial working memory. Heretofore, such alcohol-related impairments have not been investigated with fMRI paradigms.

MATERIALS AND METHODS

Subjects

The subject groups comprised 10 control men and 7 chronically alcoholic men. All subjects underwent screening with structured medical and psychiatric questionnaires and were excluded for history of major medical or psychiatric conditions. Six men in the alcoholic group were free of any lifetime comorbidity for nonalcohol drug dependence and one man had been codependent for cocaine in the past. The controls were recruited from the local community, and the alcoholics were recruited from local rehabilitation facilities. The groups did not differ in age (mean ± SD) (controls = 60.2 ± 12.8, alcoholics = 58.1 ± 8.9 years; $t(15) = 0.366$, n.s.), education (controls = 16.2 ± 2.6, alcoholics = 15.6 ± 3.4 years; $t(15) = 0.434$, n.s.), or estimated premorbid intelligence as assessed by the National Adult Reading Test (control IQ = 114.4 ± 7.9, alcoholic IQ = 106.9 ± 10.2; $t(15) = 1.718$, n.s.). Lifetime alcohol consumption was, as expected, far greater in the alcoholics than controls (controls = 154.3 ± 131.7, alcoholics = 1635.4 ± 1122.4 kg; $t(14) = 3.964$, $P < 0.002$). The alcoholics had refrained from drinking 31 to 5957 days (median = 129 days).

Task procedures. The fMRI paradigm comprised three conditions run in a blocked design and balanced across subjects within each group for the two active tasks. The blocks were run as follows: rest (36 s), three alternations of 2-back and match-to-center (36 s), rest (36 s), three alternations of 2-back and match-to-center (36 s), and a final rest (54 s). All instructions and stimuli were created through and driven by Psyscope V1.1 (http://psyscope.psy.cmu.edu) run on an Apple Macintosh Power PC and displayed visually with a magnet-compatible projector. Prior to testing in the fMRI environment, subjects were given at least three practice trials of each of the two active conditions; additional practice was given until subjects were able to perform the 2-back task with a maximum of two errors and the match-to-center task without any errors. On average, the controls completed (mean ± SD) 4.9 ± 1.99 practice trials and the alcoholics completed 5.6 ± 1.51 practice trials; this difference was not significant ($t(15) = 0.757$, n.s.).

2-Back task. At the start of each block, the instruction "2 BACK" was presented for 2 s. After another 2-s interval, a series of 16 letter "0"s were presented, one every 2 s, in one of nine spatial locations in a rectangular box. A center position was surrounded by eight additional positions equally spaced in oval formation. When a newly presented stimulus had appeared two items ago, subjects responded by pressing a button with the index finger of the preferred hand. The choice of positions was determined pseudorandomly, ensuring that across the six blocks of the 2-back task each position was equally distributed and that 30% of answers (30 of 96) were correct. The order of the stimuli within each block was fixed across subjects.

Match-to-center task. The start of each block began with the instruction "MATCH TO CENTER." The stimulus presentation of the match-to-center task and proportion of correct answers were the same as for the 2-back task. Subjects responded by pressing a button with the index finger of the preferred hand whenever a stimulus appeared in the center position.

Rest. The word "REST" appeared for 2 s followed by a stimulus-free interval during which time the subjects performed no task. Each subject was given three rest conditions: the first and second were 36 s in duration and the third was 54 s.

Response accuracy and reaction time. The response key permitted collection of behavioral data concurrent with collection of the fMRI data. Measures yielded were reaction time, hits, misses, correct rejects, and false alarms and afforded the opportunity to calculate d' and β for each active test condition.

MRI Data Acquisition

All MRI data were acquired on a GE 1.5T whole-body scanner equipped with a standard head coil. To minimize head movement within the scanning session, each subject was fitted with a customized bite bar made from dental impression compound; the bite bar apparatus was affixed to the head coil (Menon *et al.*, 1997).

Structural MRI protocols. Three structural studies were collected in the following order. The first was a coronal localizer scan required for graphical prescription for the second scan, which was a 3-D spoiled gradient recovery (SPGR) scan (TE = 5 ms; TR = 24 ms; flip = 40°; voxel size = 1.5 mm × 1.5 mm × 0.975 mm;

TABLE 1

Performance on the Match-to-Center and 2-Back Tasks: Mean and Standard Deviation

Group	Hits median RT (ms)	Performance in percentage					
		Hits	Misses	False alarms	Correct rejects	d'	β
Match-to-Center							
Control	419.0	99.7	0.3	1.6	98.4	5.36	0.67
$N = 10$	[52.7]	[1.0]	[1.0]	[1.3]	[1.3]	[0.59]	[0.73]
Alcoholic	507.1	91.0	9.0	1.7	98.3	4.72	3.89
$N = 7$	[165.9]	[18.4]	[18.4]	[2.0]	[2.0]	[1.53]	[6.22]
2-Back							
Control	604.2	72.7	27.3	11.7	88.3	1.93	1.58
$N = 10$	[116.4]	[15.7]	[15.7]	[4.7]	[4.7]	[0.81]	[0.46]
Alcoholic	709.6	61.9	38.1	12.6	87.4	1.57	1.72
$N = 7$	[340.2]	[26.4]	[26.4]	[8.5]	[8.5]	[1.00]	[0.62]

124 sagittal slices; 256 × 192 matrix; FOV = 24 cm; 1 NEX; acquisition time = 9:53 min). For display purposes, group activations were superimposed onto averaged 3-D images of the 10 controls. The third scan was a T2-weighted coronal fast spin-echo protocol (TE = 85; TR = 3000 ms; echo train length = 8; thickness = 6 mm, 29 slices; 256 × 192 matrix; FOV = 24 cm; 1 NEX; acquisition time = 2:36 min) acquired to be spatially registered with the fMRI data.

fMRI protocol. Whole-brain fMRI data were collected last and acquired with a T2*-weighted gradient echo spiral pulse sequence, which is relatively insensitive to cardiac pulsatility motion artifact (Glover and Lai, 1998) (TE = 40 ms; TR = 3000 ms; flip = 89°; inplane resolution = 3.75 mm; slice thickness = 6 mm; 29 coronal slices; FOV = 24 cm; 1 NEX; acquisition time = 9:24 min). The start of the scan was triggered automatically from the onset of the Psyscope-driven stimulus presentation from the Macintosh computer. Prior to the onset of this protocol, the examiner spoke to the subjects via the scanner's intercom system to review the test instructions and to announce that the test was about to begin.

Imaging Data Analysis

Image preprocessing and statistical analyses were performed using the SPM96 software package (Wellcome Department of Cognitive Neurology) (Friston *et al.,* 1995). Motion-correction was used to reduce motion-related artifacts. To examine the amount of the motion correction required, we calculated the average three-dimensional rotational and translational vector length of displacement (i.e., image misregistration) before application of motion correction; comparison of the amount misregistration indicated no group difference ($t(15) = 0.834$, $P = 0.42$). After smoothing the volumes with a Gaussian kernel of 5 mm (FWHM), individual statistics were computed using a general linear model approach (Friston *et al.,* 1995) as implemented in SPM96. A reference waveform corresponding to the alternating experimental and control conditions was constructed and convolved with an estimate of the hemodynamic response function. Low frequency signal changes that were not significantly correlated with the reference function were modeled as confounding covariates and eliminated. Contrasts between conditions were tested at each voxel with a t value, with appropriate adjustment in the effective degrees of freedom due to temporal autocorrelations in the fMRI timeseries. This procedure identifies voxels, timeseries of which correlates significantly with the hemodynamically filtered waveform. These voxels were identified as a color-coded functional map that was superimposed on high-quality structural images. Corrections for multiple voxel comparisons were accomplished using a cluster-size method of Friston *et al.* (1994).

To perform random effects analysis, one image per condition was computed for each subject. In computing these averaged images, the data were subjected to a high pass filter and intensity values were globally scaled to a common mean value. To put these averages into a common coordinate system, these images were then normalized to the SPM96 template using a nine-parameter affine normalization (x, y, z translation, rotations, and scaling). Subsequent adjustment of the SPM96 coordinates to Talairach space (Talairach and Tournoux, 1988) was performed using the method described by Desmond and Lim (Desmond and Lim, 1997).

Given our hypotheses regarding differences in activation patterns between controls and alcoholics, contrasts were formed to show how activation differences between conditions differed between the two groups. Specifically, we examined three alcohol vs control group contrasts: 2-back vs center match, 2-back vs rest, and center match vs rest. Significance threshold was $P = 0.025$ (two-tailed) for the contrasts and $P = 0.05$ (two-tailed) for spatial clusters. In all cases, corrections

TABLE 2

Maximum Talairach & Tournoux Location of Significant Clusters for Each Contrast with the Control Group

	Hemisphere	Brain region[a]	Brodmann area	*x*	*y*	*z*
2-Back vs Match-to-center						
Activation: 2-back > center						
	Left	**GFm**	**46**	**−32.2**	**27.7**	**24.3**
	Left	GFi	44	−47.4	16.0	25.7
	Left	GFi	45	−34.5	35.3	12.4
	Left	GFi	45	−35.7	28.3	17.2
	Left	**LPs**	**7**	**−30.2**	**−50.4**	**48.8**
	Left	LPs	7	−31.6	−68.7	45.1
	Left	LPs	7	−7.7	−61.2	63.9
	Left	LPs	7	−15.3	−59.8	61.5
	Left	PCu	7	−14.6	−67.8	49.2
	Right	PCu	7	8.0	−44.0	49.5
	Left	**GFm**	**6**	**−36.5**	**−0.1**	**44.6**
	Left	GFm	8	−36.5	12.6	38.9
	Left	GFm	6	−32.9	7.8	45.1
	Left	GFm	6	−20.0	11.7	55.3
	Left	GFs	6	11.7	55.3	3.2
	Right	**GC**	**32**	**3.7**	**26.0**	**35.1**
	Right	**LPi**	**7**	**39.4**	**−63.0**	**40.8**
	Right	LPi	40	39.0	−54.2	46.1
	Right	LPi	40	50.2	−41.7	49.5
	Right	LPs	7	11.6	−61.5	61.5
	Right	LPs	5	30.4	−45.4	62.9
	Right	**GFi**	**45**	**46.5**	**22.1**	**22.4**
	Right	GFm	8	24.6	21.2	40.4
	Right	GFm	46	50.2	32.0	22.6
	Right	GFm	6	28.4	6.7	46.6
	Right	GFi	45	54.3	20.0	21.5
	Right	GFm	9	50.1	19.5	29.9
	Right	**GO**	**19**	**43.9**	**−68.4**	**−11.3**
Deactivation: 2-back < center						
	Left	**GFs**	**8**	**−14.1**	**44.6**	**41.1**
	Left	GFs	9	−7.7	60.7	21.4
2-Back vs rest						
Activation: 2-back > rest						
	Left	**cerebellum**	**—**	**−36.0**	**−51.2**	**−23.1**
	Left	**GFi**	**45**	**−38.7**	**23.1**	**6.1**
	Left	GFi	45	−27.0	18.8	15.6
	Left	**Pu**	**—**	**−24.5**	**−0.2**	**11.0**
	Left	NC	—	−16.0	13.5	−3.2
	Left	NL	—	−18.1	4.3	2.4
	Left	**cerebellum**	**—**	**−2.2**	**−44.4**	**−20.6**
	Right	**GPrC**	**6**	**33.3**	**0.6**	**58.5**
	Left	GFi	45	−39.4	37.1	15.8
	Right	GFm	6	29.4	8.1	55.0
	Right	GFi	9	60.3	12.9	35.3
	Right	**LPs**	**7**	**24.5**	**−63.0**	**55.3**
	Right	LPi	7	38.8	−61.9	49.7
	Right	**GTm**	**21**	**43.4**	**−50.1**	**−9.2**
Deactivation: 2-back < rest						
	Left	**GFd**	**10**	**−7.0**	**66.6**	**−2.1**
	Left	GF	10	−1.4	56.7	10.1
	Right	GO	10	7.6	64.7	−13.3
	Right	GFi	10	9	66.9	−1.4
	Right	GFi	10	17.2	68.3	−5.3
	Right	**GC**	**29**	**−7.7**	**−45**	**9.7**
	Right	PCu	31	−3.7	−58.1	16.3
	Right		30	−4.2	−50.7	23.1
	Right	GC	23	−12.2	−54.5	25.4
	Right	GC	31	17.5	−53.2	30.8
	Right	PCu	7	11.6	−59.3	31.6
	Right	**GFd**	**4**	**5.9**	**−26.5**	**55.9**
	Right	Sc	4	1.6	−35.0	65.4
	Left	GFd	4	−6.1	−22.7	54.6

TABLE 2—*Continued*

	Hemisphere	Brain region[a]	Brodmann area	*x*	*y*	*z*
Center vs rest						
Activation: center > rest						
	Left	GFi	9	−55.8	17.3	30.7
	Left	**Pu**	**—**	**−15.9**	**13.2**	**−5.2**
	Left	Pu	—	−24.4	1.4	8.7
	Left	Pu	—	−16.3	−6.7	8.5
	Left	NC	—	−7.8	7.0	−5.7
	Right	**GC**	**32**	**5.6**	**34.3**	**−1.8**
	Right	GC	32	11.2	41.3	3.3
	Right	GFi	11	30.7	28.8	−21.9
	Right	Pu	—	12.3	9.0	−7.1
	Right	GFi	11	24.2	28.5	−12.0
Deactivation: center < rest						
	Right	**PCu**	**7**	**5.3**	**−64.2**	**38.2**
	Right	PCu	7	11.5	−58.9	33.5
	Right	PCu	31	10.5	−58.9	11.1
	Left	PCu	31	−11.8	−61.8	18.6
	Left	GL	17	−7.0	−66.5	3.5
	Left	LPi	40	−26.9	−54.2	38.9

[a] Cu, cuneus; GFs, superior frontal gyrus; GO, orbital gyrus; GOs, superior occipital gyrus; GTs, superior temporal gyrus; GTm, middle temporal gyrus; GC, cingulate gyrus; GPrC, precentral gyrus; GF, fusiform gyrus; GFd, medial aspect of middle frontal gyrus; GFm, middle frontal gyrus; GFi, inferior frontal gyrus; GL, lingual gyrus; LPi, inferior parietal lobe; LPs, superior parietal lobe; NC, caudate nucleus; NL, lenticular nucleus; PCu, precuneus; Pu, puramen; Sc, central sulcus; bold font, cluster maximum location.

for multiple comparisons were performed so that the overall Type I error was $P < 0.05$.

Behavioral data analysis. Group performance levels were expressed as percentage hits, misses, correct rejects, and false alarms and as median reaction time for hits and were tested with *t* tests. Group-by-condition differences in d' and β were tested with analysis of variance (ANOVA).

RESULTS

Group Differences in Behavioral Performance

The two groups did not differ significantly from each other on any of the five measures of performance (i.e., median reaction time for hits and percentage of hits, misses, correct rejects, and false alarms) on either the 2-back task or the match-to-center task (Table 1). The ANOVA for d' failed to yield a group effect ($F(1,15) = 1.445$, n.s.) or interaction ($F(1,15) = 0.313$, n.s.) but did yield a significant task effect ($F(1,15) = 180.394$, $P = 0.0001$), indicating better performance by both groups in the match-to-center condition than the 2-back condition. The ANOVA for β revealed a trend in the alcoholic group for a bias to withhold responses ($F(1,15) = 3.28$, $P = 0.0902$), but neither a task effect ($F(1,15) = 0.122$, n.s.) nor a group-by-task interaction ($F(1,15) = 2.169$, n.s.).

Within-Group Brain Activation Patterns

Controls (Table 2). In the 2-back vs match-to-center contrast (Fig. 1), the unilateral areas in the controls showing significantly greater activation in the 2-back relative to the match-to-center condition were the right occipital gyrus (area 19), inferior parietal cortex (areas 7, 40, and 5), cingulate gyrus (area 32), and middle frontal gyri (area 9). The areas activated bilaterally were the precuneous and superior parietal cortex (7), premotor cortex (area 6), and inferior and middle frontal gyri (areas 46, 45, and 8). The left superior frontal gyrus (areas 8 and 9) had greater activation in the match-to-center relative to the 2-back condition.

In the 2-back vs rest contrast, only unilateral areas were significantly activated. In the right hemisphere, these areas included the inferior and superior parietal cortex (area 7), middle temporal gyrus (area 21), premotor (area 6), and inferior frontal gyrus (area 9). In the left hemisphere, these areas included the cerebellum, putamen, caudate nucleus, lenticular nuclei, and inferior frontal gyrus (area 45). The following areas were significantly deactivated bilaterally: left and right inferior and frontal pole (area 10) and precentral gyrus (area 4). Unilateral deactivations were present in the right precuneous (areas 7 and 31), cingulate gyrus (areas 23, 29, and 31), and area 30.

For the match-to-center vs rest contrast, significant activation occurred on the right in the cingulate gyrus (area 32) and inferior frontal gyrus (area 11) and on the left in the inferior frontal gyrus (area 9) and caudate nucleus. Bilateral activation was present in the caudate nucleus. Significant deactivation was present in the right precuneous at area 7, the left precuneous at areas 7 and 31, area 17, and inferior parietal cortex (area 40).

TABLE 3

Maximum Talairach & Tournoux Location of Significant Clusters for Each Contrast with the Alcoholic Group

	Hemisphere	Brain region[a]	Brodmann Area	*x*	*y*	*z*
2-Back vs match-to-center						
Activation: 2-back > center	n.s.					
Deactivation: 2-back < center	n.s.					
2-Back vs rest						
Activation: 2-back > rest						
	Left	**Cu**	**17**	**−14.9**	**−87.9**	**8.9**
	Left	GOi	19	−36.8	−79.2	2.2
	Left	GOm	19	−50.4	−72.9	−7.7
	Left	**GFm/GFi**	**47**	**−22.3**	**33.4**	**−5.1**
	Left	GFm	10	−18.8	46.7	0.9
	Left	NC	—	−10.5	19.0	4.2
	Left	GFi	47	−22.5	20.7	3.3
	Right	**GFi**	**45**	**45.5**	**27.4**	**3.5**
	Right	GFi	47	34.7	15.5	−17.3
	Right	GFi	45	48.0	23.7	−5.9
	Right	GFi	47	27.7	32.3	−2.4
	Right	GFi	44	51.7	13.4	4.3
	Right	**LPi**	**39**	**40.0**	**−64.1**	**25.7**
	Right	LPs	19	33.6	−70.7	34.7
	Right	LPs	7	33.3	−73.2	43.3
	Right	**GFm**	**6**	**35.5**	**7.8**	**53.3**
	Right	GFm	8	36.5	13.8	29.9
	Right	GFm	9	46.2	18.6	33.6
	Right	GFm	9	40.8	24.3	20.1
Deactivation: 2-back < rest						
	Left	GPrC	4	−67.2	−4.0	25.8
	Left	LPs	19	−34.4	−73.5	33.8
	Left	LPi	7	−38.8	−62.3	39.7
	Left	**GFm**	**9**	**−29.5**	**34.0**	**20.9**
	Left	GFd	10	−11.5	58.8	11.3
	Left	GFs	8	−28.3	42.4	33.7
	Right	GFm	10	32.8	54.6	8.1
	Right	GFd	10	6.4	61.4	13.7
	Right	**GC**	**31**	**8.9**	**−39.8**	**38.1**
	Left	Sc	4	−16.6	−34.6	68.4
	Left	Sc	4	−27.1	−15.6	72.7
	Left	GOs	19	13.3	−79.1	45.4
	Right	GC	23	1.4	−49.3	31.3
	Right	GPrC	4	23.6	−19.6	59.6
	Left	**GFs**	**6**	**−14.2**	**9.9**	**44.3**
	Left	GFs	6	−16.1	22.9	37.8
	Left	GFm	6	−24.0	16.5	36.5
	Left	GFm	6	−25.9	8.6	37.8
	Left	GC	32	−15.7	27.1	26.9
	Left	GFd	6	−10.3	2.4	47.9
	Right	**GL**	**17**	**22.8**	**−78.7**	**13.2**
	Right	GOs	19	19.9	−83.1	34.2
	Right	LPi	40	47.2	−57.6	39.2
	Right	GOm	19	42.7	−74.4	13.5
	Right	LPi	40	55.0	−39.4	38.3
	Right	**GTm**	**21**	**62.9**	**−46.3**	**−0.7**
	Right	GTm	21	55.4	−51.8	−8.2
Center vs rest						
Activation: center > rest						
	Left	**GTm**	**21**	**−63.6**	**−48.0**	**7.5**
	Left	GTm	21	−45.1	−56.9	1.9
	Left	GTs	22	−37.7	−49.1	11.0
	Left	**Cu**	**18**	**−14.9**	**−87.9**	**8.9**
	Left	RO	—	−32.7	−58.5	−7.4
	Left	GOi	18	−50.4	−72.9	−7.7
	Left	GOi	19	−34.8	−79.1	2.3

TABLE 3—*Continued*

	Hemisphere	Brain region[a]	Brodmann Area	*x*	*y*	*z*
	Left	GF	19	−32.9	−63.3	−0.4
	Left	**GL**	**17**	**−19.3**	**−73.2**	**12.2**
	Left	GOm	18	−31.5	−86.1	20.0
	Left	GOm	19	−40.1	−80.2	30.7
	Left	GOm	19	−31.6	−76.2	18.2
	Left	**U**	**—**	**−25.0**	**9.8**	**−23.4**
	Left	GFi	11	−20.4	28.3	0.0
	Left	NL	—	−15.6	−10.8	−2.9
	Left	GFi	45	−33.1	24.6	14.3
	Left	GFi	46	−43.8	29.7	−13.6
	Left	GFm	46	−22.8	39.2	4.0
	Left	**GFm**	**10**	**−11.8**	**69.7**	**15.4**
	Right	LPi	39	39.9	−63.8	27.7
	Right	GTs	22	58.0	−33.4	15.0
	Right	NC	—	15.7	−27.1	17.9
	Right	**GL**	**18**	**3.4**	**−77.2**	**−0.2**
	Right	**GFi**	**45**	**45.5**	**27.4**	**3.5**
	Right	GFi	47	48.0	23.7	−5.9
	Right	internal capsule	—	11.7	9.1	5.1
	Right	GFi	47	34.7	15.5	−17.3
	Right	GFi	45	39.8	22.3	−2.0
	Right	GFi	47	27.7	32.3	−2.4
	Right	**Thalamus**	**—**	**14.6**	**−18.9**	**−4.0**
	Right	NL	—	26.6	−7.2	−7.5
	Right	INS	—	40.3	−4.3	−3.3
	Right	INS	—	32.3	−12.0	−0.3
	Right	**GFm**	**9**	**38.3**	**18.1**	**31.2**
	Right	GFm	6	35.5	7.8	53.3
	Right	GFm	6	44.0	5.9	41.9
	Right	GFm	8	29.4	19.6	50.9
	Right	GFm	9	44.5	21.5	26.9
	Right	GFm	8	46.3	10.7	35.0
Deactivation: center < rest						
	Left	**LPs**	**7**	**−40.5**	**−63.4**	**33.8**
	Left	LPi	39	−38.1	−64.7	26.0
	Left	LPs	7	−34.4	−73.5	33.8
	Right	**GFm**	**8**	**22.0**	**22.9**	**35.7**
	Left	GFm	9	−29.5	34.0	20.9
	Left	GFm	10	32.8	54.6	8.1
	Right	GFm	10	4.3	61.8	15.6
	Right	GFm	10	−43.6	43.6	18.5
	Right	GFm	10	41.5	57.8	−8.3
	Right	**GC**	**23**	**1.4**	**−49.2**	**31.3**
	Left	PCu	7	−2.9	−55.8	40.4
	Right	PCu	7	13.2	−59.8	39.9
	Right	**GOs**	**19**	**22.7**	**−78.7**	**13.2**
	Right		17	26.3	−63.5	18.8
	Right	GOs	19	20.4	−79.3	21.4
	Right	GF	19	32.9	−63.9	5.0

[a] Cu, cuneus; GC, cingulate gyrus; GF, fusiform gyrus; GFm, middle frontal gyrus; GFi, inferior frontal gyrus; GFs, superior frontal gyrus; GL, lingual gyrus; GOi, inferior occipital gyrus; GOm, middle occipital gyrus; GOs, superior occipital gyrus; GPrC, precentral gyrus; GTs, superior temporal gyrus; GTm, middle temporal gyrus; INS, insula; LPi, inferior parietal lobe; LPs, superior parietal lobe; NC, caudate nucleus; NL, lenticular nucleus; PCu, precuneus; Pu, putamen; U, uncus; RO, optic radiation; Sc, central sulcus; bold font signifies cluster maximum location.

Alcoholics (Table 3). No areas were significantly activated or deactivated in the 2-back vs match-to-center contrast in the alcoholic patients.

For the 2-back vs rest contrast (Fig. 2), significant areas of activation were the right inferior (areas 19 and 9) and superior (area 7) parietal cortex, precentral (area 6), and inferior frontal gyrus (areas 44, 45, and 47) and the left cuneous (area 17), inferior and middle occipital gyri (area 19), and inferior and middle frontal gyri (areas 47 and 10). Significant deactivation was present bilaterally in the precentral gyri (area 4), cingulate gyrus (area 32),and prefrontal cortex (area 10);

TABLE 4

Maximum Talairach & Tournoux Location of Significant Clusters for Each Contrast[a] between the Two Groups

	Hemisphere	Brain region[b]	Brodmann area	*x*	*y*	*z*
Match-to-center vs rest						
Control	**Left**	**GPrC**	**4**	**−58.3**	**−3.1**	**18.3**
	Left	GPrC	6	−55.2	−2.3	33.7
	Left	GFd	9	−7.4	41.1	21.5
	Left	GFm	46	−28.2	32.6	18.5
	Left	GFm	10	−22.3	39.4	12.4
	Right	**GFi**	**45**	**24.0**	**29.4**	**9.7**
	Right	GFm	10	35.2	54.7	7.4
	Right	GFs	9	11.8	50.3	17.3
Alcoholic	**Right**	**GFi**	**45**	**41.6**	**24.7**	**4.5**
	Right	GFi	47	45.9	23.0	−5.2
	Right	GFi	47	36.9	23.0	−16.0
2-Back vs rest						
Control	**Left**	**GPrC**	**6**	**−57.3**	**4.0**	**35.9**
	Left	GPrC	4	−64.1	−4.8	20.0
	Left	GPrC	4	−32.8	−27.4	56.5
	Left	GPrC	4	−17.6	−13.8	54.9
	Left	**LPi**	**40**	**−52.9**	**−32.9**	**37.6**
	Left	LPi	40	−51.9	−29.6	56.0
	Left	**GOs**	**19**	**−37.0**	**−60.8**	**34.8**
	Left	GOs	19	−31.5	−63.6	40.8
	Left	LPi	39	−36.6	−67.7	29.2
	Left	**GFm**	**46**	**−35.3**	**39.6**	**3.2**
	Left	GFm	46	−28.2	32.6	18.5
	Left	GFs	9	−26.8	40.1	27.6
	Left	GFm	9	−36.6	20.2	37.5
	Left	GFs	9	−19.3	37.0	31.9
	Left	GFm	10	−37.6	37.2	12.1
	Right	**GFm**	**10**	**35.2**	**54.7**	**7.4**
	Right	GFm	10	27.4	55.1	10.4
	Right	GFm	10	27.6	61.8	4.1
	Right	GFs	9	11.8	48.4	17.7
	Right	GFm	8	20.6	31.0	40.2
	Right	GFi	46	27.9	40.3	4.5
	Right	**LPi**	**40**	**42.7**	**−44.4**	**46.2**
	Right	LPi	40	41.1	−38.0	38.1
	Right	GFm	9	52.9	−37.1	31.7
Alcoholic	n.s.					

[a] 2-Back vs match-to-center contrast yielded no areas of significant activation between the groups. Bold font signifies cluster maximum location.

[b] GPrC, precentral gyrus; GFd, medial aspect of middle frontal gyrus; GFm, middle frontal gyrus; GFi-inferior frontal gyrus; GFs, superior frontal gyrus; LPi, inferior parietal lobe; GOs, superior occipital gyrus.

right occipital pole (area 17), superior occiput (area 19), cingulate gyrus (area 31), inferior parietal lobe (area 40), and middle temporal gyrus (area 21); left inferior parietal gyrus (area 7), motor cortex (area 6), and superior (area 8) and middle (area 9) frontal gyri.

For the match-to-center vs rest contrast (Fig. 3), the alcoholics showed significant activation in right occipital cortex (area 18), inferior parietal cortex (area 39), superior temporal gyrus (area 22), motor cortex (area 6), and inferior and middle frontal gyri (areas 45 and 47) as well as subcortical regions, including thalamus, lenticular nuclei, and insula. Regions activated in the left hemisphere were visual cortex (areas 17, 18, 19), middle (area 21) and superior (area 22) temporal gyri, inferior and middle frontal gyri (areas 10, 45, and 46), lenticular nuclei, and uncus. Regions of deactivation were the right occiput (areas 17 and 19), cingulate gyrus (area 23), and middle frontal gyrus (areas 8 and 0), the left inferior parietal region (area 39), and bilateral precuneous (area 7).

Group Differences in Brain Activation Patterns

Table 4 present the maximum standard location of significant clusters for each contrast between the two groups. For the match-to-center vs rest contrast (Fig. 4), activation of control group was greater than that of alcoholic group in anterior medial and superior prefrontal cortex, where a large region of activation included Brodmann areas 9, 10, 45, and 46 bilaterally,

although more widespread in the right than left hemisphere; the left motor cortex (areas 4 and 6) was also significantly more activated. By contrast, activation of alcoholic group was greater than that of control group in the right prefrontal cortex (areas 45 and 47), positioned more inferiorly and posteriorly than prefrontal regions significant in the controls. The differences in activations between the groups were due to greater activation in one group rather than deactivation in the other group.

For the 2-back vs rest contrast (Fig. 5), the control group showed significantly greater activations than the alcoholic group in several bilateral cortical regions, namely, middle and inferior frontal gyri (areas 9, 10, and 46) and inferior parietal lobe (area 40). Significant unilateral activations involved left dorsolateral prefrontal cortex (area 45), left motor cortex (areas 4 and 6), left angular gyrus (area 39), left extrastriate cortex (area 19), and right middle frontal gyrus (area 8). Inspection of this contrast within each group revealed that these increases in activation between groups were due to significantly greater activations in the 2-back condition relative to rest for the controls rather than decreases in this contrast for alcoholics. The alcoholics did not significantly activate any unique areas relative to controls for this contrast.

In the 2-back vs match-to-center contrast, neither group produced statistically significantly greater activations than the other.

DISCUSSION

This study set out to examine whether the often-reported mild deficits of visuospatial working memory in alcoholics could be accounted for by activation of inappropriate brain regions or by abnormally diffuse activation. In the current study, despite equivalent group performance on the two behavioral tasks, the brain activation patterns differed substantially between the alcoholic and control groups. The results of the center-rest comparison provide support for the contention that detoxified alcoholic men activated different brain regions from those activated by age-matched controls. In the right hemisphere, the controls activated a large expanse of prefrontal cortex (including Brodmann areas 9, 10, and 45), whereas significantly greater activation of the alcoholics relative to controls was localized more posteriorly and inferiorly in the frontal cortex (area 47). In the left hemisphere, the controls showed greater activation than the alcoholics in the left prefrontal cortex (areas 9, 10, and 46) and also in the motor cortex (areas 4 and 6), which may reflect that controls pressed the response button slightly (~8%), albeit insignificantly, more than did the alcoholics. The abnormal patterns of brain activation displayed by the alcoholic group may reflect either strategy differences in the approach taken to perform the task, or alternatively, default (or nearest neighbor) brain systems engaged when the optimal ones are compromised. This type of shift in activation locus was noted in patients with Parkinson's disease who invoked alternative cortical motor regions to those invoked by healthy age-matched controls when performing a motor task (Sabatini *et al.*, 2000).

Within-group analyses revealed an important complement to the group difference data. The control group pattern indicated activation of the dorsal visual spatial ("Where?") stream in the right hemisphere involving visual cortex in area 19, precuneous and inferior and superior parietal cortex in areas 7 and 40, anterior cingulate cortex, and prefrontal areas 9, 46, and 45. In addition to the unilateral activations observed in this spatial working memory system, the controls showed bilateral activation in a subset of these regions. This bilateral distribution of activation is consistent with a recent speculation about processing requirements in normal aging. In particular, for a given task, older healthy individuals tend to recruit systems of the nondominant hemisphere in regions homologous to the task-appropriate hemisphere (Cabeza, in press), possibly reflecting age-related increase in effort required to accomplish a task.

In contrast to the control pattern, the pattern observed within the alcoholic group indicated activation of nodes of the ventral ("What?") stream (inferior and ventral reaches of prefrontal and temporal gyri), components of the declarative memory system (uncus and thalamus), and widespread bilateral recruitment in both the 2-back vs rest and center vs rest contrasts. One interpretation of this abnormal activation pattern for a visuospatial working memory task is that both of the active tasks (i.e., 2-back and match-to-center) were equivalently demanding for the alcoholic patients; this possibility was supported by the critical comparison of the 2-back vs match-to-center contrast, which failed to yield any significant activations within the alcoholics. Further, in an attempt at best performance, these subjects may have invoked verbal and nonverbal processes as well as declarative and contextual processes to accomplish the tasks at hand. In light of the deficiencies in visuospatial processing characteristic of alcoholism, it may have been resourceful for these alcoholic subjects to call upon the presumably less impaired verbal system in a best attempt effort to execute the tasks.

The initial design of this paradigm sought to distinguish attentional components from working memory components by comparing match-to-center vs 2-back; however, the 2-back vs center contrast did not reveal group differences in activation, perhaps due to considerable task difficulty. Nonetheless, the regions of maximal activation evident in the match-to-center vs rest contrast invoked those commonly activated when young adults perform tasks that either involve working memory for spatial location or have task demands re-

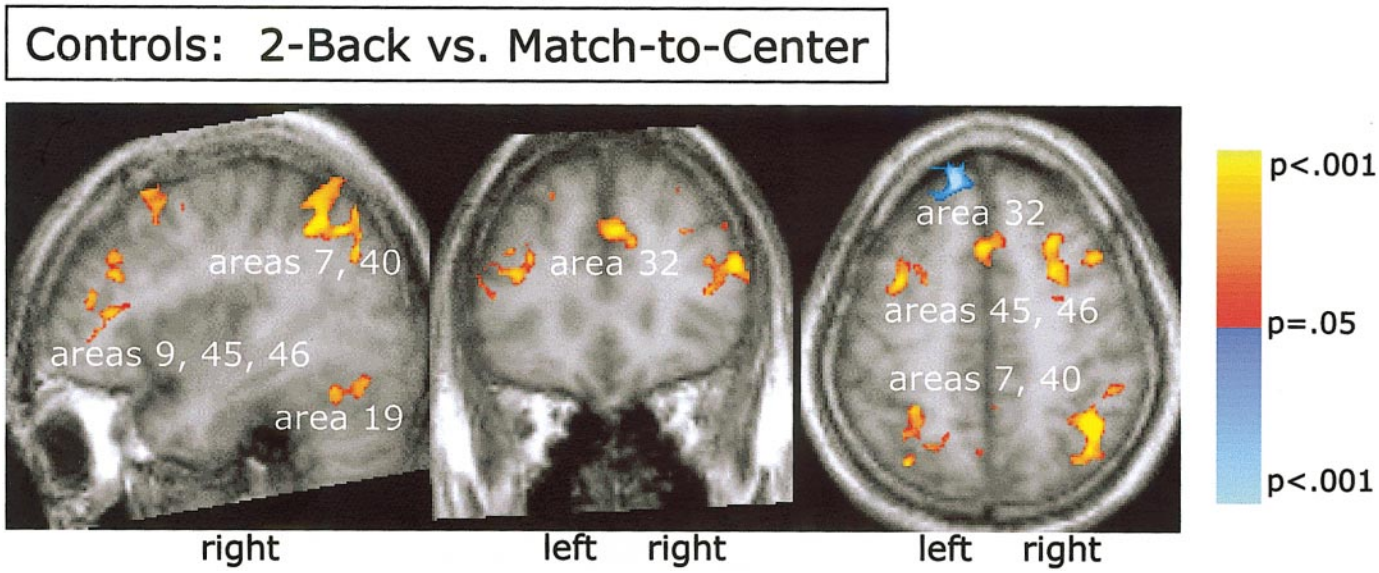

FIG. 1. Significant regions of activation in the 2-back vs match-to-center contrast observed in controls. Activation significantly greater in the 2-back than match-to-center condition is in the red to yellow tones. The pattern of activations indicates recruitment of the right hemisphere dorsal stream in performance of the visual spatial working memory task. Areas where match-to-center shows greater activation than the 2-back task are in blue tones.

quiring information maintenance or temporal order (Owen *et al.*, 1996). These observations are indicative of a working memory component in the attentional demands of the task. One scenario to consider is that even this relatively simple spatial task, as executed in the fMRI environment, posed a substantially greater challenge for the middle age to elderly men who participated in this experiment than it would have posed for college age students typically recruited for such studies. Stimulus presentation was fast and relentless, the two active conditions were visually identical and provided no contextual reminders during stimulus presentation as to which task was current, the scanning environment was noisy and unnatural, and task demands continually changed throughout a test session, thus requiring subjects to mentally keep track of which

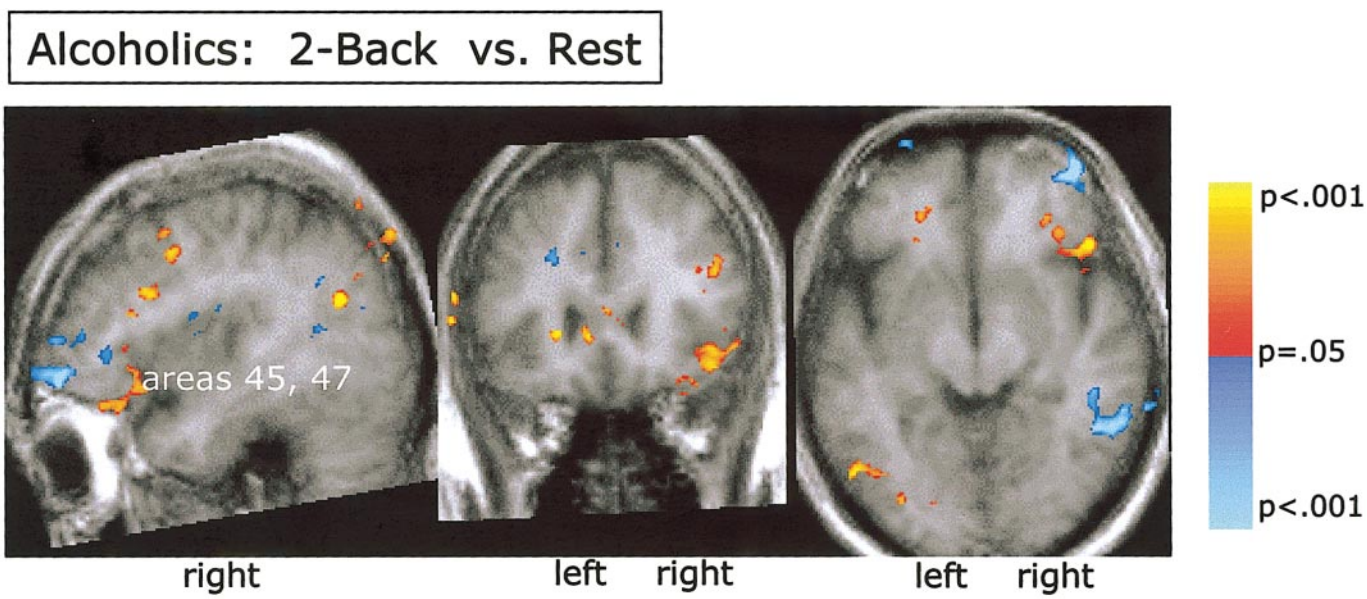

FIG. 2. Significant regions of activation in the 2-back vs rest contrast observed in alcoholics. Activation significantly greater in the 2-back than rest condition is in the red to yellow tones. The alcoholics activated areas of right prefrontal cortex that were more ventral and posterior than those activated by the controls in the working memory task. Areas where match-to-center shows greater activation than the 2-back task are in blue tones.

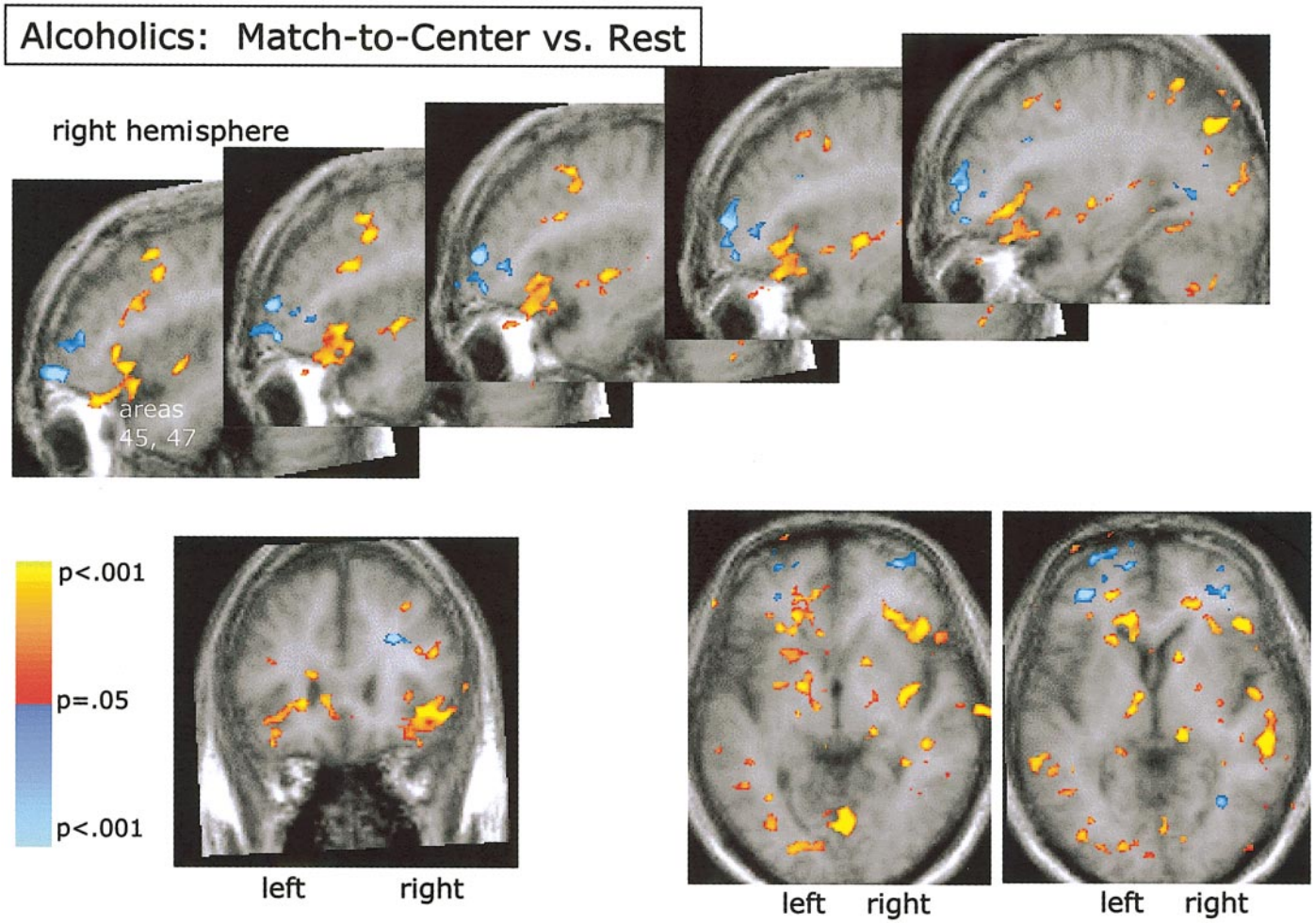

FIG. 3. Significant regions of activation in the match-to-center vs rest contrast observed in alcoholics. Activation significantly greater in the match-to-center than rest condition is in the red to yellow tones. The widespread pattern of activations indicates recruitment of the ventral stream in performance of the visual spatial working memory task with additional activation present in bilaterally and also in brain regions subserving declarative memory. Areas where match-to-center shows greater activation than the match-to-center task are in blue tones.

condition was current. This depiction of the spatial attentional task demands argues for an inherent, substantial working memory load in the match-to-center trials. The interleaving of the two different active conditions with alternating response instructions within the same paradigm exerted an additional memory burden to all trials in the paradigm. Our previous work using cognitive event-related potentials to examine simple vs complex tasks (Pfefferbaum *et al.*, 1986) suggests that the results may have been different had the match-to-center vs rest and 2-back vs rest conditions been presented as two separate experiments.

Both groups performed significantly worse on the 2-back than match-to-center condition, and no significant activation differences between the groups emerged when these two conditions were contrasted. However, in the 2-back versus rest condition, the control group showed robust regional activation not present in the alcoholic group, whereas the opposite group difference did not occur. Specific locations activated in the control group relevant to working memory performance were located bilaterally in the prefrontal cortex (areas 9, 10, and 46) (Belger *et al.*, 1998; McCarthy *et al.*, 1994; Ungerleider *et al.*, 1998). Relevant to visually presented stimuli, extrastriate (area 19), angular and supramarginal and angular gyri (areas 39 and 40), and possibly frontal eye fields (area 8) showed greater activation in the controls than alcoholics. Although these brain regions are known to be involved in the elementary to complex visuospatial processing used in spatial working memory tasks, in studies using younger subjects this dorsolateral prefrontal visual pathway is usually involved in object rather than spatial vision (Courtney *et al.*, 1998) or, alternatively, in maintenance rather than manipulation of working memory memoranda (Owen *et al.*, 1996). Discrepancies

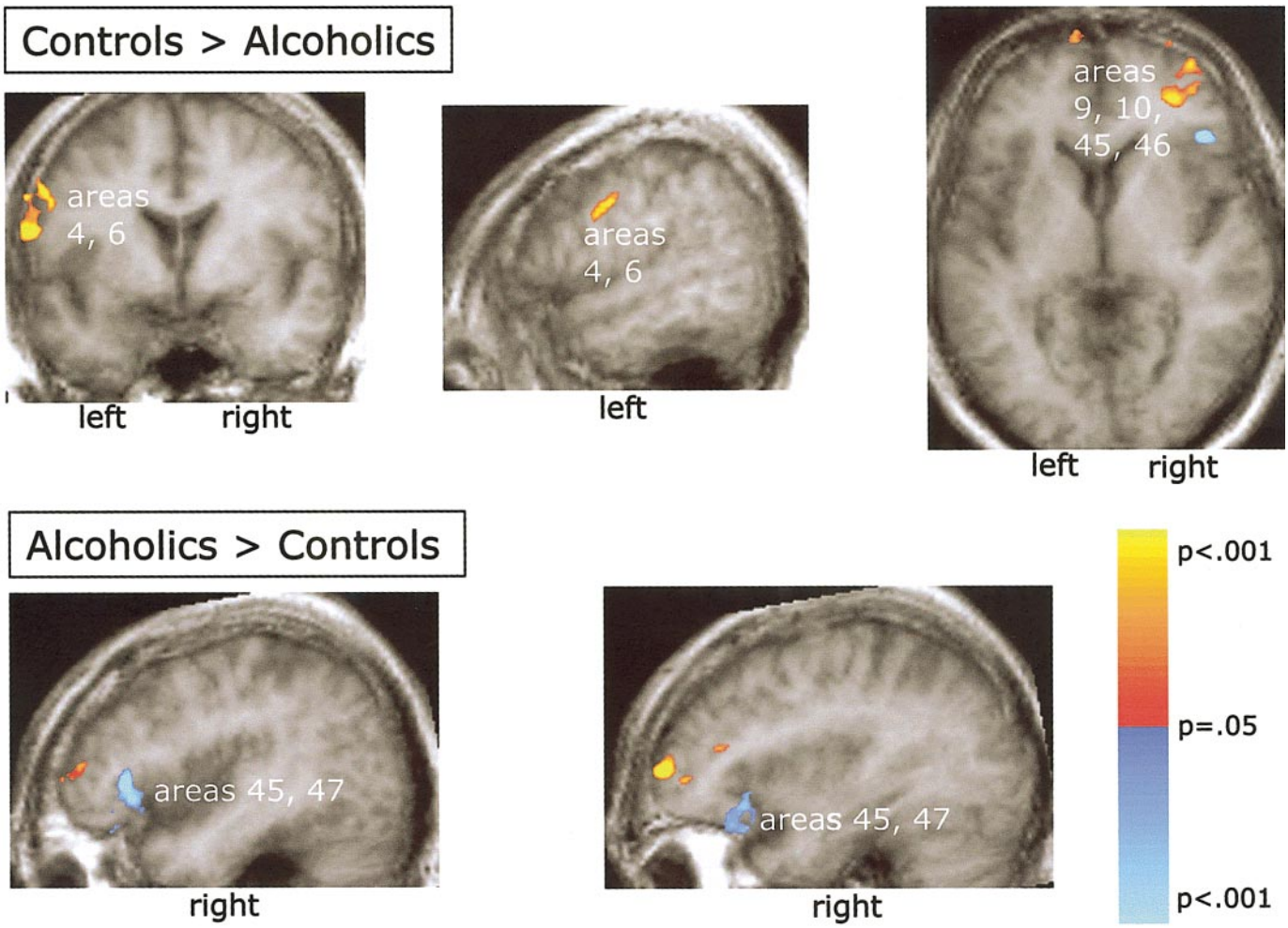

FIG. 4. Significant regions of group differences in activation in the match-to-center vs rest contrast. Loci where the activation of the control group was significantly greater than that of the alcoholic group are depicted in the red to yellow tones. Loci where the activation of the alcoholic group was significantly greater than that of the control group are depicted in the blue to purple tones.

such as this one in activation patterns have been reported between healthy young versus older controls and are consistent with an emerging thesis that larger and sometimes alternative brain regions are invoked in older than younger healthy subjects when performing the same task (Cabeza *et al.*, 1997). Alternatively, the greater activation of the right inferior frontal cortex by the alcoholic relative to the control group may indicate greater effort in invoking response inhibition by the alcoholics in suppressing stimulus information no longer needed as the working memory and attentional tasks proceeded (Garavan *et al.*, 1999).

These results suggest that even when performance deficits are not demonstrable, brain systems underlying performance can be different in older adult alcoholic men compared with age-matched controls but still be adequate for the task demands at hand. Displacement of ideal activational loci may characterize an age-related shift and the alcohol-related abnormality in the neural systems required to carry out the selective cognitive processes often deficient in alcoholics as well as healthy elderly individuals (Schacter *et al.*, 1996). We hypothesize that such a shift can occur, and may even be essential, when the ideal brain region or system is compromised by age or disease but not necessarily ablated or fully disconnected. This type of "incomplete lesion" could result in mild or only subclinical impairment or change in normal strategy in task performance that could go undetected unless elicited by competing task demands or without the advantage of concurrent visualization of brain activation, as with fMRI.

Thus, alcoholic individuals did not show the normal pattern of frontal systems activation required for attention and working memory for spatial information. The differences in the pattern of brain activations exhibited by the alcoholic and control groups, despite equivalence in behavioral performance, is consistent with a functional reorganization of the brain systems invoked by alcoholic individuals when engaged in a

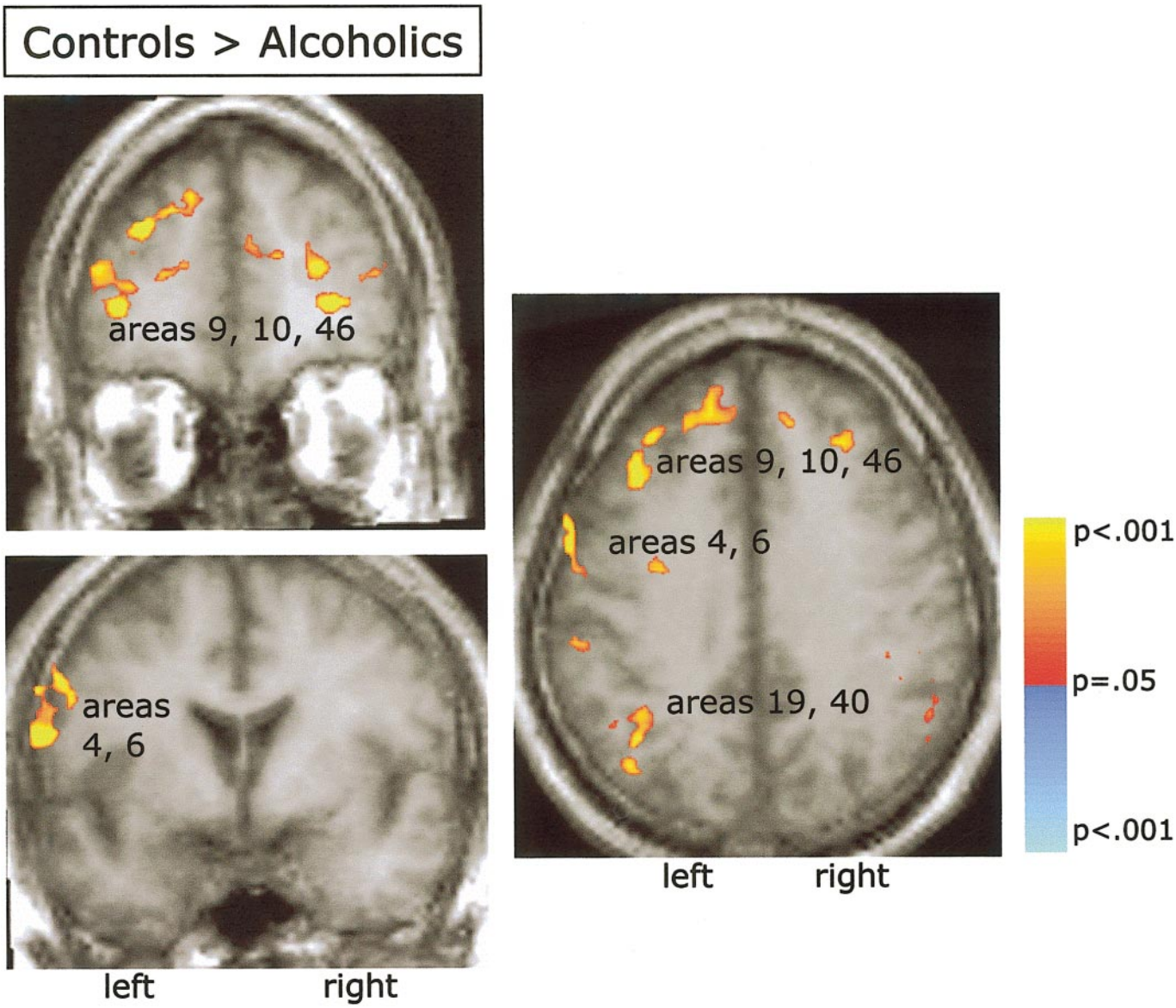

FIG. 5. Significant regions of group differences in activation in the 2-back vs rest contrast. Loci where the activation of the control group was significantly greater than that of the alocholic group are depicted in the red to yellow tones. In this contrast, none of the activation differences was in the direction of alcoholics greater than controls.

spatial task requiring working memory. The abnormal patterns of brain activation displayed by the alcoholic group may reflect either strategy differences in the approach taken to perform a task or, alternatively, default (or nearest neighbor) brain systems engaged when the optimal ones are compromised by disease or other disturbance.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (AA05965, AA10723, AG19717, and RR09784).

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