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The Human Basal Forebrain Integrates the Old and the New

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Summary

Acquisition of new learning is challenged by the phenomenon of proactive interference (PI), which occurs when previous learning disrupts later learning. Whereas human neuroimaging studies have focused on the cortical contributions to interference resolution, animal studies demonstrate that efficient resolution of PI depends on cholinergic modulation from basal forebrain (BF). Whether the BF promotes PI resolution in humans is unknown. Here, we adapted a PI paradigm from animal studies for use in a functional MRI experiment. During PI resolution, neurologically intact subjects recruited a BF network that included afferent anterior and posterior cortical sites associated with efficient memory acquisition and perceptual processing. Despite normal performance, nonamnesic patients with alcoholism, which is known to disrupt BF function, did not activate a BF network but instead invoked anterior cortical sites traditionally associated with executive function. These results provide evidence for parallel neural systems, each with the potential to resolve interference in the face of competing information.

Introduction

When past learning impairs the acquisition of new related information, proactive interference (PI) occurs. Classic observations of human memory established that, following the initial impairing influence of PI, information associated with the interfering stimuli can effectively coexist in memory (McGeoch, 1942). Electrophysiological, pharmacological, and immunotoxic lesion evidence from nonhuman animal studies suggests that the neurochemical acetylcholine from the cholinergic basal forebrain projection system (BF) provides a specialized mechanism that allows contextually associated information to exist independently and concurrently in memory with minimal interference (De Rosa and Hasselmo, 2000; De Rosa et al., 2001; Hasselmo and Bower, 1993). The pharmacological and lesion studies demonstrated that reduced cholinergic modulation from the BF results in a selective increase in the magnitude of PI, while leaving the learning of completely new paired associations intact (De Rosa and Hasselmo, 2000; De Rosa et al., 2001). It is unknown, however, whether the BF plays a similar role in human memory by promoting the integration of new information with similar existing memory traces while minimizing interference.

Previous functional magnetic resonance imaging (fMRI) studies of PI have implicated a lateral prefrontal and anterior cingulate cortical network in resolving PI during executive processing tasks where incongruent stimulus features compete within or across trials (e.g., Eriksen Flanker and Sternberg memory scanning). Activation of these brain regions has been proposed to reflect executive processes involved in resolving competing task demands via conflict monitoring and cognitive control (D'Esposito et al., 1999; MacDonald et al., 2000; van Veen et al., 2001). To limit executive task demands and enable direct comparisons between human and animal studies, we modified a simultaneous discrimination paired-associate learning paradigm used in a rat model of BF function (De Rosa and Hasselmo, 2000) for use in the fMRI environment with humans (Figure 1). Standard paired-associate methods for studying PI in the human verbal learning tradition involve learning novel associations that compete with pre-existing associations. Similarly, the paired-associate PI stimuli used in the present simultaneous discrimination task shared elements with, but were configurally distinct from, the initially learned stimuli; therefore, the subjects were required to learn a new response in a similar stimulus setting. With this paradigm, we tested the hypothesis that, independent of an executive function network, the human BF would be selectively activated when resolving PI. We further hypothesized that signal from the BF nuclei would be modified by learning and would be associated with a reduction of behavioral PI.

The BF projection system has a complex organization and neurochemical composition but is customarily defined by the magnocellular cholinergic neurons (Insausti et al., 1987; Mesulam et al., 1983; Rye et al., 1984). These cholinergic neurons are colocalized with a substantial population of noncholinergic neurons that share similar projection patterns (Zaborszky et al., 1999); γ-aminobutyric acid (GABAergic) neurons represent the main population of noncholinergic neurons in the BF. The BF, the gross structure of which is identifiable on T1-weighted magnetic resonance images (MRI), comprises three basic nuclei that send projections to distinct brain regions: (1) the medial septum (MS) projects primarily to the hippocampus via the entorhinal cortex (Ghashghaei and Barbas, 2001; Insausti et al., 1987; Rye et al., 1984); (2) the diagonal band of Broca (DB) projects primarily to the medial prefrontal, orbitofrontal, and cingulate cortices (Ghashghaei and Barbas, 2001; Mesulam et al., 1983) and secondarily to the olfactory bulb and piriform cortex (Mesulam et al., 1983); and (3) the nucleus basalis of Meynert or magnocellularis (NBM) projects primarily to the neocortex and the amygdala (Rye et al., 1984). Thus,

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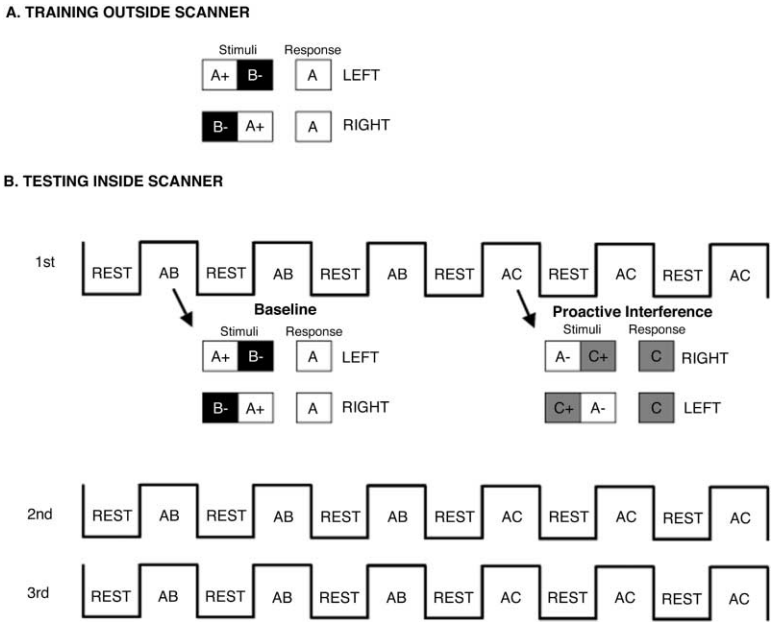

Figure 1. Simultaneous Discrimination Paired-Associate Paradigm

The paired-associate color stimuli were displayed (650 ms) simultaneously and the subject was to report on which side the target was presented while the stimuli were on the computer screen.

(A) Training on baseline task outside of scanner.

(B) Experimental block design for proactive interference test inside of scanner. The baseline condition required subjects to respond with a button press to color A in the context of color B, and then, in the PI condition, to respond with a button press to color C in the context of color A.

this intricate architecture allows the BF to modulate information processing in functionally distinct brain areas.

Consistent with its neuromodulatory role, in vivo and in vitro animal studies have shown that the BF influences memory formation through orchestrating changes in information processing at muscarinic cholinergic synapses in its target cortical structures (Ashe et al., 1989; Hasselmo and Schnell, 1994; Miasnikov et al., 2001) by enhancing physiological signal-to-noise ratio (SNR). Our fMRI task sought evidence of similar neuromodulatory function of the human BF. Consonant with its proposed neuromodulatory role, we expected that BF nuclei along with their afferent target cortical structures would increase the blood oxygen level-dependent (BOLD) signal when resolving PI with this simple color discrimination paradigm. This hypothesis was posed in the light of prior findings showing that cholinergic modulation from BF afferents during perceptual learning enhances SNR for individual neurons in sensory cortex as indexed by increased firing rates (Miasnikov et al., 2001) and that such increases in neural activity during perceptual learning are manifested in increased BOLD signal (Schwartz et al., 2002). Thus, we predicted that BOLD signal would increase in perceptual and mnemonic target regions of the BF nuclei, reflecting the increased salience (i.e., SNR) of these events, and would be associated with dissipation of behavioral PI.

As an additional test of these hypotheses, we examined BOLD response in nonamnesic alcoholic patients with presumed compromised BF system to provide convergent evidence for the critical role of the BF in normal memory formation. Empirical evidence suggests that chronic ethanol consumption exerts neurotoxic effects on and reduces markers of muscarinic BF cholinergic function in both rats and humans (Arendt, 1994; Arendt et al., 1988; Casamenti et al., 1993; Nordberg et al., 1982, 1983; Rothberg and Hunter, 1991). Even though chronic ethanol exposure has widespread effects on the brain, there is evidence that it induces selective effects on BF nuclei. In BF nuclei, such as the MS, ethanol reduces cholinergic function at muscarinic receptors (Arendt, 1994; Arendt et al., 1988; Miller et al., 2002; Nordberg et al., 1982, 1983; Rothberg and Hunter, 1991) and potentiates the effects of GABA at $GABA_A$ receptors (Matthews et al., 2000; White et al., 2000); both of these actions of ethanol would suppress cellular activity in the BF and decrease its ability to sustain cholinergic neurotransmission. The behavioral correlates of this dysfunction includes exacerbated susceptibility to PI as evidenced in alcoholic Korsakoff syndrome (Cermak and Butters, 1972; Oscar-Berman and Zola-Morgan, 1980). In conjunction with in vitro and postmortem evidence that chronic alcohol exposure disrupts but does not delete BF cholinergic function, alcoholism serves as a viable model to test damped function in this system. Thus, we expected that BF activation would be diminished in alcoholics relative to controls. Consistent with its proposed neuromodulatory influence, we further hypothesized that, due to compromised BF function, afferent target cortical structures would not be involved in the management of PI. Further, in its absence alcoholics may invoke alternative compensatory neural systems in an attempt to resolve PI.

The test of these hypotheses was accomplished using a paired-associate color discrimination task (Figure 1). Subjects were presented with a two-colored screen (e.g., half purple, half green) and were asked to respond to the side of the screen where one of the two colors appeared (e.g., respond purple)—the baseline condition. Subjects were then asked to perform the same task on a new color pair. This new color pair retained the old response color (e.g., half purple, half gray), but now the subjects were asked to respond to the new color component (e.g., respond gray)—the PI condition—and we saw a substantial behavioral decrement in performance relative to learning of the initial color pair.

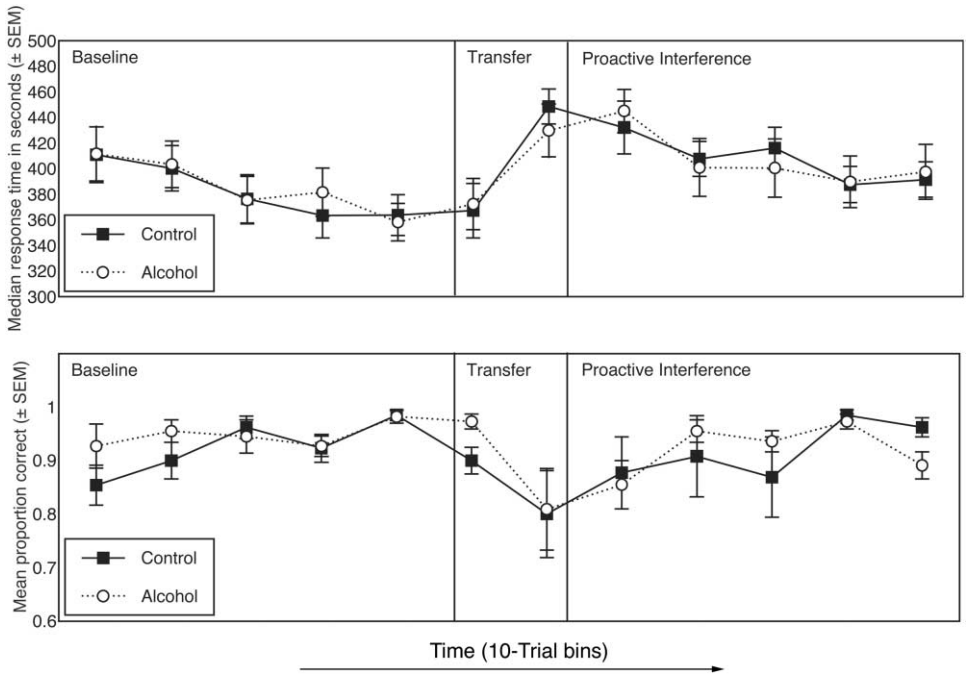

Figure 2. Mean Profile of Baseline and Proactive Interference Performance as Median Response Time in Milliseconds and Mean Proportion of Correct Responses

Acquisition of the baseline color pairs (A+B−) and then the proactive interference color pairs (A−C+). Behavioral analyses were performed on the point of transfer, where PI was expected to be maximal. Each data point represents a 10-trial bin. The two groups performed equivalently at all points.

Results

Neurologically Intact Adults: Proactive Interference

We tested the hypothesis that neurologically intact individuals would show activation of a BF network thought to contribute to integration of new with old related learning. Thus, the BF nuclei and their corresponding target cortical structures, including medial orbitofrontal and entorhinal cortices, were predicted to be active when the PI condition was contrasted with the baseline condition. The PI condition corresponds to the trials where subjects acquired the interfering stimuli, and the baseline condition corresponds to the trials where subjects responded to stimuli learned prior to entering the scanner (Figure 1). Figure 2 depicts the acquisition profile of the PI stimuli consistent with successful evocation of PI in this simultaneous color discrimination paradigm.

Accompanying behavioral PI, a cluster of activation along the right ventromedial wall of the anterior horn of the lateral ventricle, spatially located within the MS/DB (x,y,z in Talairach coordinates, 8, 7, −7), was significantly active [$t(12) = 4.37$, $p < 0.0009$] when the PI condition was contrasted with baseline, pooled across the entire experiment (Figure 3) and endured with small volume correction $p < 0.006$, consistent with our a priori hypothesis. There were also bilateral activations in medial entorhinal cortex [20, 8, −29, $t(12) = 4.29$, $p < 0.001$ and −26, 3, −24, $t(12) = 3.51$, $p < .004$] as well as activations in the ventromedial portion of the orbitofrontal cortex under these conditions with maximum intensity voxels located at (1) the gyrus rectus [−10, 48, −12, $t(12) = 5.59$, $p < 0.0001$]; (2) the triangular part of the inferior frontal gyrus [−44, 21, 27, $t(12) = 5.01$, $p < 0.0003$]; (3) the medial orbital gyrus [20, 26, −23, $t(12) = 4.81$, $p < 0.0004$]; and (4) the posterior orbital gyrus [32, 26, −16, $t(12) = 4.75$, $p < 0.0005$]. Furthermore, this comparison yielded significant activations in the pons [6, −31, −39, $t(12) = 5.01$, $p < 0.0001$] and areas associated with later as well as the earliest stages of visual processing, i.e., the intraparietal sulcus bilaterally [−32, −76, 39, $t(12) = 7.41$, $p < 0.0001$ and 34, −25, 40, $t(12) = 3.86$, $p < 0.002$], the lingual gyrus [−14, −54, −1, $t(12) = 7.77$, $p < 0.0001$], the lateral geniculate nucleus [26, −27, −4, $t(12) = 4.60$, $p < 0.0006$], and pulvinar [6, −29, 9, $t(12) = 4.17$, $p < 0.001$] of the thalamus.

These brain data alone cannot discern whether the BF supports successful integration of newly associated information with old. In support of this interpretation, baseline behavior in the scanner remained constant and did not decrease with acquisition of newly associated information [$F_{RT}(2,24) = 0.51$, $p < 0.61$; $F_{accuracy}(2,24) = 1.39$, $p < 0.27$], even though each baseline measure was interspersed with a block of PI learning (Figure 4A). By contrast, consistent with PI, there was an initial decrement in performance in response time (RT) and accuracy in the PI task. Then, with subsequent exposure to the interfering stimuli, RT and accuracy improved with learning, thereby demonstrating dissipation of PI [$F_{RT}(2,24) = 10.36$, $p < 0.0006$; $F_{accuracy}(2,24) = 3.44$, $p < 0.05$]. Stable baseline performance and comparable performance on both the baseline and PI stimuli at the end of the experi-

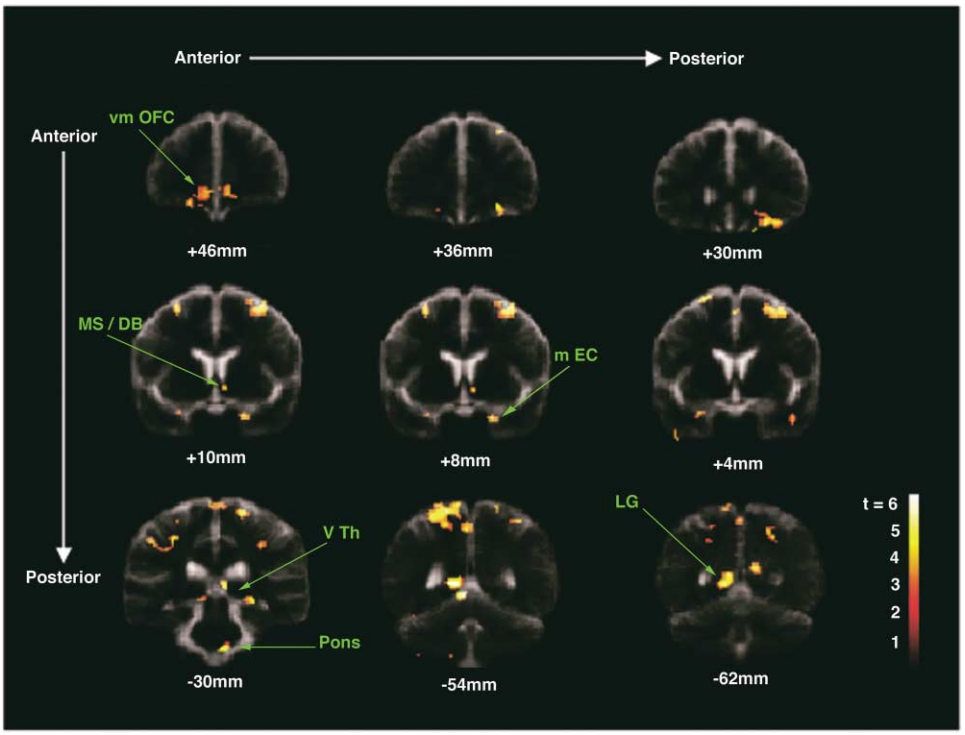

Figure 3. Controls: Proactive Interference versus Baseline

The results from the group random effects analysis across control subjects with a height threshold of $p < 0.005$ and an extent threshold of 15 contiguous voxels superimposed on the mean anatomical image for all 13 subjects. The first panel depicts the ventromedial orbitofrontal (vmOFC) activations; the second panel depicts the medial septum/diagonal band nuclei (MS/DB) activation and medial entorhinal cortex (mEC) activations; and the third panel depicts activations in the pons and areas associated with early visual processing [i.e., lateral geniculate and pulvinar nuclei of the thalamus (VTh), and lingual gyrus (LG)]. The y values for each coronal section are provided under each frame.

ment suggest successful integration of the PI stimuli into memory without disrupting the representation of the baseline stimuli.

As a test of the integration interpretation of the behavioral data, we examined how signal from the MS/DB changed during the acquisition of interfering stimuli. As Figure 4B depicts, there was a striking dissociation in the temporal profiles of signal in the MS/DB associated with new and old learning. Signal from the MS/DB region of interest (ROI) increased with the successful acquisition of new information, and commensurately decreased while recalling information learned outside of the scanner. This significant task condition $\times$ repetition interaction from the ROI analysis, $F(2,24) = 4.58$, $p < 0.02$, indicated that the MS/DB signal was modified as PI dissipated. The temporal divergence in response is further illustrated in how the MS/DB signal did not discriminate between baseline and PI conditions at the first learning experience [$F_{\text{baseline v PI first}}(1,24) = 0.27$, $p < 0.61$], but did so most robustly at the end of acquisition [$F_{\text{baseline v PI last}}(1,20) = 12.53$, $p < 0.002$]. These results demonstrate a graded change in the MS/DB signal with repetition of the baseline and PI stimuli, with the maximum difference occurring at the end of acquisition when both the baseline and PI stimuli are behaviorally comparable. Thus, the MS/DB signal was associated with the dissipation of PI and may play an important role in integrating the PI stimuli into memory in healthy adults.

Neurologically Intact Adults: Baseline versus Rest

To examine whether management of PI resulted in a distinct neural network from baseline learning or greater activation of a common network, we examined which brain regions were more activated to baseline relative to rest. Significant activations were found in structures associated with visuomotor learning, i.e., bilateral precentral gyrus, left postcentral gyrus, bilateral putamen, bilateral lingual gyrus, bilateral cerebellar hemispheres, and bilateral cuneus. Thus, management of PI reflects recruitment of distinct regions from baseline learning. In conjunction with the divergent ROI profile of PI and baseline conditions, these results further suggest that the MS/DB activation does not simply reflect the process of learning, but rather the integration of new information with preexisting memory traces. This interpretation is consistent with the rat data that demonstrated intact learning of novel paired associates unrelated to prior training under conditions of weakened cholinergic modulation (De Rosa and Hasselmo, 2000; De Rosa et al., 2001).

Alcoholics: Proactive Interference

Evidence from controls suggests that the BF acts in a neuromodulatory capacity to influence processing in brain regions that may increase mnemonic and perceptual salience during learning. If the BF plays such a neuromodulatory role during learning, then alcoholics

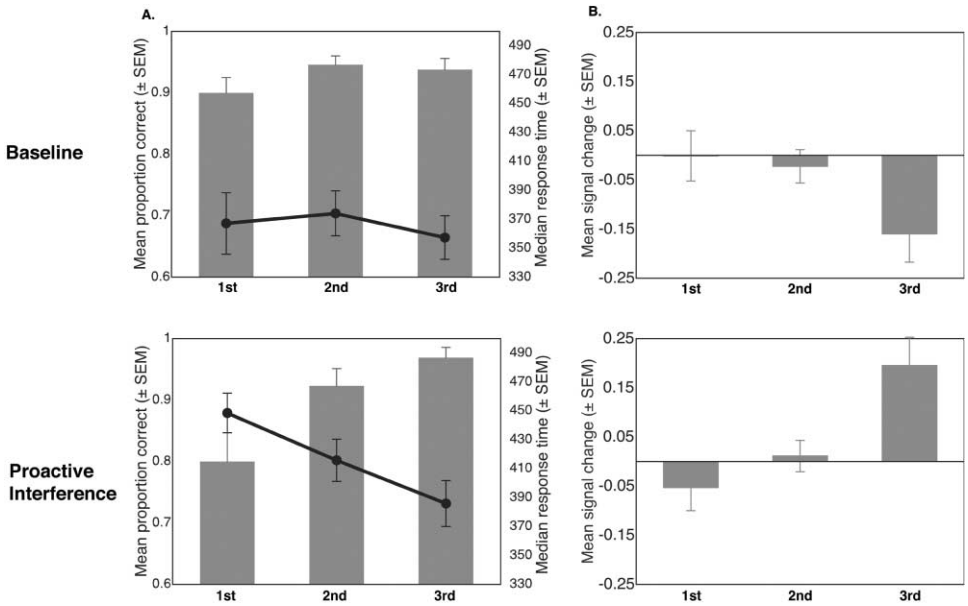

Figure 4. Behavioral and fMRI Signal Data from Neurologically Intact Adults

The first data point represents the first learning exposure, the second data point represents the second learning exposure, and the third data point represents the third learning exposure. The upper row depicts the baseline data and the lower row depicts the proactive interference data.

(A) Behavioral proactive interference. The bar graph depicts mean proportion correct, and the line graph represents the median response time data.

(B) Medial septum/diagonal band nuclei region of interest (ROI) signal. The bar graph depicts the ROI signal transformed to standardized units.

with presumed compromised BF function may call upon a different network of regions to manage behavioral PI. When the PI condition was contrasted with baseline, unlike control subjects, the alcoholics did not activate the MS/DB nuclei of the BF.

Postmortem studies in alcoholics and in vivo studies in animals have documented a loss in the number and function of muscarinic receptors, resulting in decreased cholinergic function in the MS/DB. Accordingly, decreased MS/DB signal in alcoholics may have been due to shrinkage or loss of gray matter in this region. To examine this possibility, we manually outlined the MS/DB region on individual high-resolution anatomical images and observed that the control and alcoholic groups had comparable MS/DB gray matter volumes, $t(20) = 0.607$ ($M_{control} = 694.33\ mm^3$, $SD = 151.92$ and $M_{alcoholic} = 651.95\ mm^3$, $SD = 174.57$). Thus, the group difference in fMRI activation patterns indicated functional alterations within the existing architecture of the MS/DB region despite an absence of group difference volume.

To examine whether this absence of BF activation was a result of diminished signal, we analyzed the signal intensity from the normalized T2*-weighted images from each individual in the critical MS/DB area relative to nonbrain areas in the bounding box. This comparison tested the adequacy of the signal acquired in the BF region in each group. There was significantly higher signal intensity in the MS/DB relative to nonbrain regions, $F(1,22) = 52.93$, $p = 0.0001$, effect size $r = 0.71$. By contrast, there was no significant difference in the degree of signal intensity between the two groups, $F(1,22) = 0.36$, $p = 0.56$, effect size $r = 0.02$. Thus, we were able to measure reliable signal in the MS/DB in both groups.

Instead of a BF-centered network, alcoholics showed significant activations in a distributed network of brain regions traditionally associated with executive functioning (Figure 5). Specifically, the alcoholics activated (1) the lateral prefrontal cortex bilaterally and in particular the orbital region of the inferior frontal gyrus [$-44, 41, -4$, $t(10) = 4.91$, $p < 0.0006$ and $48, 35, -7$, $t(10) = 3.72$, $p < 0.004$]; (2) the anterior cingulate cortex [$-8, 20, 17$, $t(10) = 5.18$, $p < 0.0004$ and $-6, 30, 17$, $t(10) = 4.04$, $p < 0.002$]; and (3) the ventral striatum [$14, -2, -2$, $t(10) = 5.24$, $p < 0.0004$]. The ventral striatum—residing posterior and lateral to the MS/DB activation in controls—receives efferent connections from the lateral prefrontal cortex (Eblen and Graybiel, 1995; Tekin and Cummings, 2002). Figure 6 is a magnified depiction of the two subcortical activations—MS/DB activated in controls and ventral striatum activated in alcoholics—plotted on the averaged anatomy image of all 24 subjects.

Because alcoholics did not show activation in the MS/DB, we plotted the ROI defined in controls onto the mean alcoholic brain to ensure that the centroid of activation fell within MS/DB gray matter. Given that the ROI fell within MS/DB gray matter, we analyzed the signal change in this region in alcoholics as PI dissipated. As Figure 7B depicts, unlike the change in activation observed in controls, the MS/DB ROI signal did not significantly change in alcoholics during the acquisition of new information or while recalling the information learned outside of the scanner. In alcoholics, the task condition $\times$ repetition interaction was not significant, $F(2,20) < 1$. So in alcoholic patients, the signal in the MS/DB ROI was not significantly modified with learning and showed no significant difference between base-

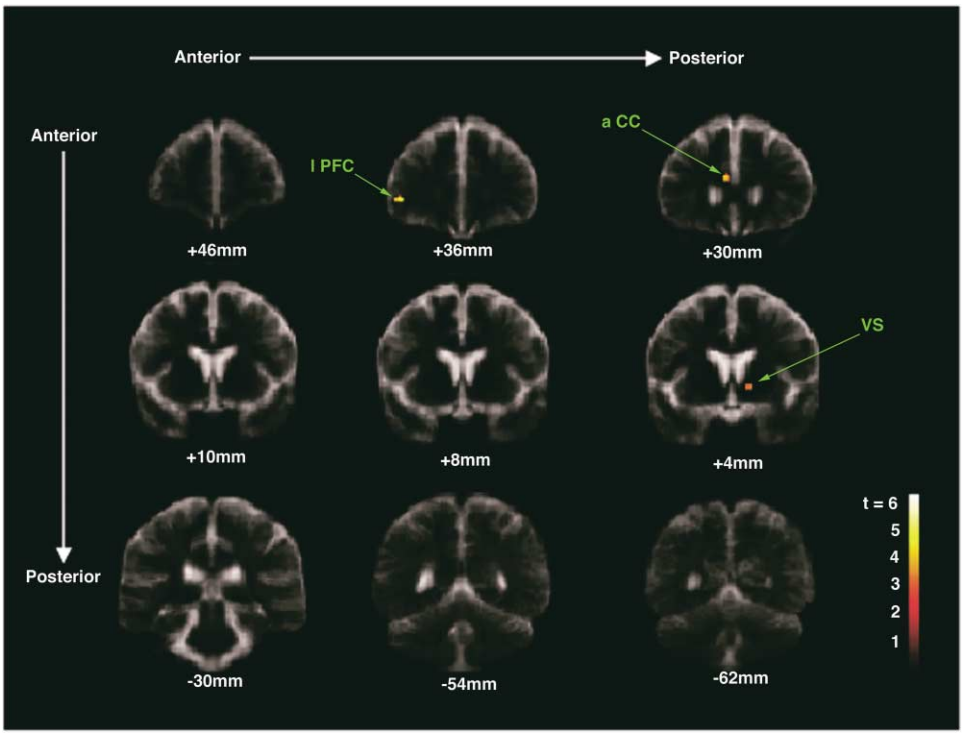

Figure 5. Alcoholics: Proactive Interference versus Baseline

The results from the group random effects analysis across alcoholic subjects with a height threshold of $p < 0.005$ and an extent threshold of 5 contiguous voxels superimposed on the mean anatomical image for all 11 subjects. The first panel depicts the lateral prefrontal (lPFC) and anterior cingulate (aCC) activations; the second panel depicts the ventral striatum (VS) activation. The y values for each coronal section are provided under each frame.

line and PI at any time point [$F_{\text{baseline v PI first}}(1,20) = 0.14$; $F_{\text{baseline v PI second}}(1,20) < 1$; $F_{\text{baseline v PI last}}(1,20) < 1$].

The control group tended to be older and have higher general memory function and intelligence than the alcoholic group. So the whole-brain voxel-wise data, which contrasted PI with baseline, were submitted to separate analyses of covariance for each demographic measure—age, education, GMI score, and NART IQ score (Table 1)—within each group. Whole-brain data did not covary with any of the demographic measures; thus, the whole-brain analysis did not alter the pattern of results observed with the targeted analyses.

Alcoholics: Baseline versus Rest

To ensure that the MS/DB was not hyperactive in alcoholics in the experimental conditions, analyses contrasting baseline versus rest were executed. The MS/DB was not significantly active in either the baseline or PI contrasts with rest; thus, the lack of MS/DB activation in the alcoholics was not due to a hyperactive MS/DB during baseline or PI. Both groups had significant activations in a network of structures associated with visuomotor learning, i.e., bilateral precentral gyrus, left postcentral gyrus, bilateral putamen, bilateral lingual gyrus, bilateral cerebellar hemispheres, and bilateral cuneus.

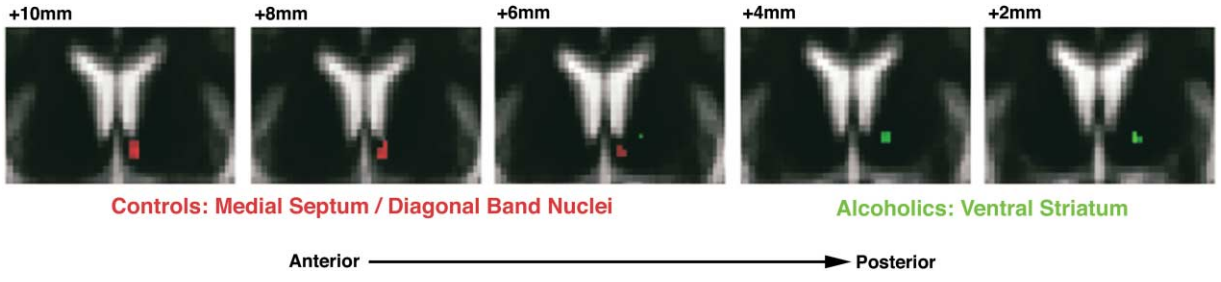

Figure 6. Subcortical Activations

The subcortical activations when proactive interference condition was contrasted with baseline superimposed on the mean anatomical image for all 24 subjects. The control medial septum/diagonal band activation is depicted in red and the alcoholic ventral striatum activation is depicted in green. The y values for each coronal section are provided above each frame.

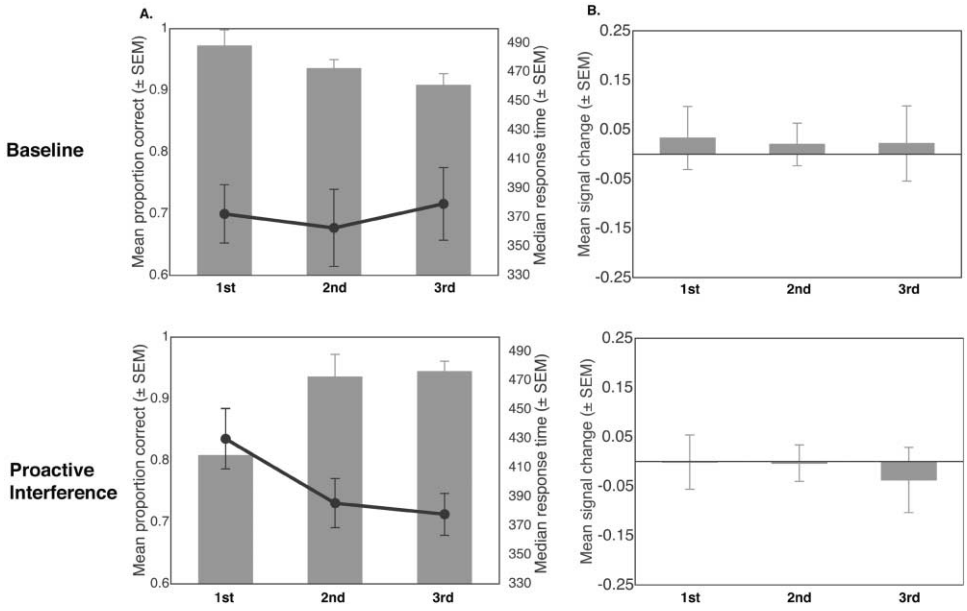

Figure 7. Behavioral and fMRI Signal Data from Nonamnesic Alcoholic Patients

The first data point represents the first learning exposure, the second data point represents the second learning exposure, and the third data point represents the third learning exposure. The upper row depicts the baseline data and the lower row depicts the proactive interference data.

(A) Behavioral proactive interference. The bar graph depicts mean proportion correct and the line graph represents the median response time data.

(B) Medial septum/diagonal band nuclei region of interest (ROI) signal. The bar graph depicts the ROI signal transformed to standardized units.

Unlike PI conditions where entirely distinct networks were activated in controls and alcoholics, the network of structures were commonly activated in controls and alcoholics during baseline performance relative to rest.

Direct Comparisons between Controls and Alcoholics

To examine whether the alcoholics activated the BF and its target structures at subthreshold levels, we tested whether the BF network was more active in controls than alcoholics; and conversely, whether the frontally based executive network active in alcoholics was more active in alcoholics than controls. All brain areas described in the corresponding BF network and the ventral striatum network survived direct comparisons performed with two group t tests. When controls were contrasted with alcoholics, local maxima were found in the MS/DB [4, 13, −11, $t(22) = 2.98$, $p < 0.002$], the bilateral medial entorhinal cortex [24, −3, −30, $t(22) = 3.09$, $p < 0.002$ and −28, 3, −25, $t(22) = 4.87$, $p < 0.00002$], and the ventromedial orbitofrontal cortex—including the gyrus rectus [−20, 46, −19, $t(22) = 3.98$, $p < 0.0003$], the triangular part of the inferior frontal gyrus [−44, 22, 28, $t(22) = 3.70$, $p < 0.0003$], the medial orbital gyrus [16, 28, −28, $t(22) = 3.21$, $p < 0.001$], and the posterior orbital gyrus [30, 26, −17, $t(22) = 3.14$, $p < 0.001$]. Once again, significant activations were present in the pons [2, −29, −34, $t(22) = 3.90$, $p < 0.0008$], intraparietal sulcus [−34, −77, 44, $t(22) = 2.91$, $p < 0.002$ and 34, −29, 40, $t(22) = 2.62$, $p < 0.004$], the lingual gyrus [−8, −68, −2, $t(22) = 3.12$, $p < 0.002$], the lateral geniculate nucleus [26, −29 −2, $t(22) = 2.71$, $p < 0.003$], and pulvinar [10, −29, −4, $t(22) = 3.34$, $p < 0.001$] of the thalamus. When alcoholics were contrasted with controls, local maxima were observed in the ventral striatum [16, 8, −2, $t(22) = 2.71$, $p < 0.003$], orbital region of the

Table 1. Subject Characteristics and Alcohol History

	Alcoholics (n = 11)	Controls (n = 13)	Comparison
Age in years	50.1 (8.1)	55.6 (11.3)	$t(22) = 1.4$, $p = 0.19$
Education	15.6 (2.1)	17.8 (2.4)	$t(22) = 2.4$, $p = 0.03$[a]
NART	109.6 (7.7)	115.2 (5.9)	$t(22) = 2.0$, $p = 0.06$
General memory index	107.7 (11.3)	119.8 (13.9)	$t(22) = 1.9$, $p = 0.07$
Dementia rating scale	139.8 (2.8)	140.1 (2.4)	$t(22) = 1.2$, $p = 0.25$
Median length of sobriety in days	100 (range 20–790)	-	-
Total lifetime consumption in kg	1202.0 (1211.36)	155.4 (161.5)	$t(22) = 9.6$, $p = 0.005$[a]

Data shown are mean (standard deviation) values. NART, premorbid estimation of IQ, measured by National Adult Reading Test; general memory index, measured by Wechsler Memory Scale-Revised.

[a] $p < 0.05$

inferior frontal gyrus [−48, 36, −2, t(22) = 2.78, p < 0.003], and anterior cingulate cortex [−12, 21, 27, t(22) = 2.72, p < 0.003 and −12, 34, 11, t(22) = 2.90, p < 0.002].

To ensure that this group difference in the pattern of activation was not due to duty cycle effects, related to differential time spent on task, we compared the controls and the alcoholics on performance in the associative learning task. Both groups showed equivalent RTs and accuracy [$F_{RT}(1,22) < 1$; $F_{accuracy}(1,22) < 1$]; thus, the differential activation pattern could not be attributable to differences in time on task. The performance of both groups significantly improved over the experiment, i.e., accuracy increased and RT decreased with repetition, $F_{RT}(2,44) = 8.23$, $p < 0.001$; $F_{accuracy}(2,44) = 6.19$, $p < 0.004$. The absence of a task condition × repetition × group interaction [$F_{RT}(2,44) < 1$; $F_{accuracy}(2,44) < 1$] indicated that effect of task and repetition was similar across groups.

Discussion

Pharmacological and cholinergic immunotoxic lesion studies in nonhuman animals demonstrate that management of PI from past learning experiences is regulated by neurochemical modulation originating from BF nuclei (De Rosa and Hasselmo, 2000; De Rosa et al., 2001). Although not a direct measure of cholinergic activity, fMRI permitted investigation of underlying cholinergic brain systems involved in PI resolution in vivo. The present study provides evidence that this BF contribution to memory is conserved in humans. This paradigm, similar to one originally designed for use in rodents (De Rosa and Hasselmo, 2000), was able to induce PI in human subjects. Like classic observations of PI in the human verbal learning tradition, our subjects also encoded two different learning situations appropriately without explicit access to conditional rule information (Wickens, 1970), despite understanding the rule at some computational or implicit level. With diminished executive task demands, the present study demonstrated that, instead of an executive network, a subcortically orchestrated BF projection system was sufficient to resolve PI in neurologically intact individuals.

Consistent with postmortem studies that have established that chronic alcohol consumption reduces markers of BF muscarinic cholinergic function (Arendt, 1994; Nordberg et al., 1982, 1983), alcoholic patients did not demonstrate significant BF activation associated with managing PI. This decreased utilization of the BF in patients was not a simple matter of degree but had significant ramifications for the kind of processing invoked, indexed by the different neural systems recruited to manage interference. When the BF system was rendered compromised in nonamnesic alcoholic patients, a frontally based executive network involving the lateral prefrontal and anterior cingulate cortices was recruited to resolve PI. This dissociation suggests that parallel neural systems are able to accommodate mnemonic interference. Parallel systems, however, do not necessarily imply equipotentiality of function.

In vivo and in vitro animal evidence has demonstrated that acetylcholine, via BF afferents, acts in a neuromodulatory capacity to increase the SNR of afferent physiological activity in target sensory and mnemonic structures (Ashe et al., 1989; Hasselmo and Schnell, 1994; Miasnikov et al., 2001). In humans, learning-induced changes in sensory cortices have been shown to be dependent on cholinergic neuromodulation via the muscarinic receptors (Thiel et al., 2002). Indeed, in animal studies, extensive damage to the BF (both cholinergic and noncholinergic components) results in a broad array of attentional and mnemonic impairments (Baxter and Chiba, 1999; Everitt and Robbins, 1997; Sarter and Bruno, 1997). BF cholinergic neurons, via direct and indirect modulation, appear to play an important role in regulating cortical information processing and are likely to be involved in aspects of sensory processing and mnemonic plasticity.

Consistent with this neuromodulatory capacity, the medial entorhinal and orbitofrontal cortices were active along with BF during PI resolution in controls; both of these structures receive direct cholinergic afferents from the BF and are also strongly interconnected (Ghashghaei and Barbas, 2001; Insausti et al., 1987; Mesulam et al., 1983; Rye et al., 1984). In functional neuroimaging studies, both the medial entorhinal and orbitofrontal cortices are target structures associated with enhanced learning of novel information, particularly under conditions requiring novel response contingencies (Savage et al., 2001) that deviate from previous expectations (Nobre et al., 1999). The entorhinal cortex, in particular, plays a critical role in retrieval of recently acquired memories and memory consolidation (Bontempi et al., 1999; Haist et al., 2001), and the orbitofrontal cortex contributes to early selection of efficient learning strategies in new learning situations (Nobre et al., 1999; Savage et al., 2001; Schnider et al., 2000), especially when the demands on executive processes have been minimized (Frey and Petrides, 2000).

Under PI conditions, we observed in controls significant activations in regions associated with color processing, i.e., the lingual gyrus, and successful feature integration or binding, i.e., the intraparietal sulcus (Courtney and Ungerleider, 1997; Sakai et al., 1995; Shafritz et al., 2002; Toth and Assad, 2002). The BF projection system is topographically organized, where the anterior portion (MS/DB) projects to the ventromedial orbitofrontal and entorhinal cortices (Ghashghaei and Barbas, 2001) and the posterior portion (NBM) projects primarily to neocortex. Even though the present PI paradigm was not designed to disambiguate the functions of the MS/DB and the NBM, our results do not provide any evidence of NBM activation during PI resolution in the healthy brain. Yet posterior cortical regions (i.e., visual cortex and the intraparietal sulcus), which are more traditionally associated with NBM projections, were more active during PI relative to baseline conditions.

Under the same contrasting conditions, we also observed in controls significant activations in regions associated with the earliest stages of visual processing, i.e., the lateral geniculate and pulvinar nuclei of the thalamus. The visual thalamus is not innervated by either the MS/DB or the NBM. Both the thalamus and the BF receive ascending projections from cholinergic neurons in the mesopontine tegmental areas of the brainstem; these cholinergic projections innervate the MS/DB, lateral ge-

niculate and reticular thalamic nuclei, and cerebral cortex (Woolf and Butcher, 1986). Losier and Semba (1993) provide compelling evidence that these cholinergic brainstem neurons, through dual projections, can concurrently modulate activity of neurons in the thalamus and the MS/DB, and activation of these BF cholinergic neurons facilitates thalamocortical sensory transmission. Thus, the significant activation in the pons (in addition to the MS/DB, lateral geniculate, and reticular thalamic nuclei) and visual cortex observed in controls (Figure 3) may implicate the important neuromodulatory influence from the mesopontine cholinergic complex. The increased activations in these interconnected sensory regions may reflect the transient modulation of the neural pathways supporting the processing of perceptual properties of color targets. Modulation of these mnemonic and sensory regions comports with the concept of the BF as amplifying task-relevant information for integration into long-term memory. As a result, along with an independence from executive processing, this pattern of coactivation suggests that projections from the BF nuclei and mesopontine regions of the brainstem are involved in a bottom-up neuromodulatory capacity (Sarter et al., 2001), thereby influencing the efficiency of both mnemonic and sensory integration.

The selective recruitment of the BF network deviates from studies demonstrating the obligatory participation of frontal executive networks in interference resolution; it is thus important to consider how the present study may differ from prior studies. With the present task, subjects responded directly to one color element in many rapidly presented color pairs (every 650 ms). As with many perceptual discrimination tasks, the subject's performance improved and gained substantial perceptual and mnemonic fluency for these particular stimuli. Such progress is supported by the significant BOLD activations in the posterior brain and the increase in MS/DB signal as PI dissipated in controls. By contrast, previous functional neuroimaging studies induced PI by presenting incongruent events only in a minority of trials, which effectively discouraged improvement in perceptual or mnemonic performance. Additionally, these tasks were more cognitively challenging than the present simultaneous discrimination task. For example, the Sternberg paradigm (D'Esposito et al., 1999) required maintenance of items in working memory; interference was generated by repetition of irrelevant target events from prior trials. Similarly, variants of the Flanker paradigm (Botvinick et al., 1999; van Veen et al., 2001) required maintenance of a conditional rule, e.g., when you see red, press right, and when you see green, press left; interference was generated by presenting a target event flanked by irrelevant stimuli that have conflicting response mapping. Thus, the frontally based cortical network associated with higher-order functions, such as evaluation of conflict, response conflict resolution, and organizational strategy (D'Esposito et al., 1999; MacDonald et al., 2000; van Veen et al., 2001), may be necessary during more resource demanding tasks, which are not amenable to enhanced perceptual or mnemonic processing during the course of learning. Thus, a function of the frontal executive system may include generic support of cognitive flexibility, which is useful when stimulus-specific learning is not possible.

Consistent with this view, alcoholic patients with putative compromised BF function recruited a frontally based cortical network of the prefrontal and anterior cingulate cortices when resolving PI. Rather than taking advantage of the normally invoked BF system, alcoholics employed an alternative compensatory mechanism to resolve PI. Thus, it is possible that the alcoholics, in order to achieve normal performance, had to rely on a supervisory executive system more than controls to switch between contingencies throughout the experiment. Nevertheless, we speculate that use of this executive network puts these processes at risk by introducing capacity competition for other tasks that require this executive neural system. This strategy may serve to augment frontal executive dysfunction known to occur in alcoholics (Desmond et al., 2003; Pfefferbaum et al., 2001; Sullivan, 2003; Sullivan et al., 1993).

In the present study, chronic alcoholics did not show exacerbated PI. This is in contrast to evidence of exacerbated PI in alcoholic Korsakoff syndrome (Cermak and Butters, 1972; Oscar-Berman and Zola-Morgan, 1980) and the performance of rats under the influence of the systemic cholinergic antagonist scopolamine (De Rosa and Hasselmo, 2000). Compensatory frontal recruitment may not have been feasible in Korsakoff patients, who are considered to have severe conjoint BF and frontal dysfunction, or in the rat model of PI, where systemic cholinergic antagonists likely had widespread effects beyond the BF. The pattern of the alcoholic data is comparable to the data of rats after receiving selective cholinergic immunotoxic lesions of the BF nuclei (De Rosa et al., 2001). These immunotoxic lesion rats initially showed comparable PI to rats with sham lesions of the BF nuclei. However, when globally challenged with a small systemic administration of scopolamine, the immunotoxic lesioned rats could no longer compensate for the lack of a normal functioning BF and demonstrated exacerbated PI, whereas the sham lesioned rats performed normally under the same dose of scopolamine. We predict that if we had further challenged the resources available to nonamnesic alcoholic patients, for instance by providing the same global pharmacological challenge as in the rat model or by challenging executive resource availability, e.g., increasing the number of to-be-learned color pairs or having a distracting concurrent task, the PI performance of the alcoholics would have been exacerbated relative to controls.

The present study thus provides evidence for parallel systems with differing functional capacities for managing mnemonic interference. We propose that the BF system is involved in a relative accrual of bottom-up perceptual and mnemonic processing, reducing the need for participation of resource-limited executive processes. By contrast, these frontal executive systems, while being resource expensive, ensure behavioral flexibility across a variety of settings, in particular where the accrual of expertise may be unavailable. Complementing this view, functional neuroimaging studies have shown decreased dependence on frontally based executive processes and more reliance on posterior brain regions as a subject progresses from novice to expert status (Sakai et al., 1998). In the present study, activation of posterior brain regions and the pattern of MS/DB signal in controls suggest that the BF system is increas-

Table 2. Proactive Interference Target Color Balance

Proactive Interference Baseline (A+B−)	Proactive Interference Test (C+A−)
Version 1	
pink:orange	brown:pink
purple:green	grey:purple
Version 2	
pink:brown	orange:pink
purple:grey	green:purple

ingly recruited as learning to integrate old and new information proceeds, being most strongly activated during late learning. In striking contrast, alcoholics did not activate any posterior regions while managing PI. Therefore, a compromised BF function may not permit this qualitative change in how learning proceeds; rather, such compromise enforces maintenance of executive processes throughout learning, with the consequence that dependence on the executive system may impose inappropriate limits on cognitive processing capacity.

Consistent with the efficiency of the BF system, a prior study of healthy adults scanned under the influence of the cholinergic agonist physostigmine showed enhanced perceptual processing in extrastriate regions and a commensurate decrease in dependence on prefrontal executive processes during a face working memory task (Furey et al., 2000). This dynamic interaction between the prefrontal system and sensory cortices within subjects with and without physostigmine parallels the differences between alcoholics and controls described here. The cholinergic BF may dynamically alter the brain systems brought to bear on a given task and the resultant mode of processing information. This potential was demonstrated here by how recruitment of a BF network was associated with diminished prefrontal contributions and associated executive processes for successful integration of new with previously learned information into memory.

Experimental Procedures

Subjects

To establish eligibility for the study, all subjects underwent medical and psychiatric screening that included structured alcohol consumption history (Pfefferbaum et al., 1992) and clinical interview. All subjects (24 right-handed men) gave written informed consent to participate in this study, which was approved by the Institutional Review Board at Stanford University School of Medicine and SRI International. Subjects were given a modest stipend for their participation. The control group comprised 13 healthy men recruited as volunteers from the local community, screened and excluded for evidence of any DSM-IV Axis I disorder or substance abuse or dependence. The alcoholic group comprised 11 detoxified, nonamnesic alcoholic men recruited as volunteers from local rehabilitation facilities. All alcoholic subjects met DSM-IV criteria for alcohol dependence and were tested well after any acute physiological withdrawal had subsided. No subject from either group presented a profile of clinically or operationally defined amnesia or dementia. Clinical and demographic data as well as the alcohol consumption history of the subjects are summarized in Table 1. Upon arrival to the laboratory, all subjects underwent an alcohol breathalyzer test and scored 0.0.

Basic Simultaneous Discrimination Paired-Associate Paradigm

Whereas the original study used odor stimuli to take advantage of the fact that rats are highly olfactory animals, the present study used color stimuli. The entire experiment was created and implemented with PsyScope 1.2.5 (http://psyscope.psy.cmu.edu). The subjects were trained to discriminate two different color stimuli that were presented simultaneously for 650 ms; each color filled half of the computer screen. The subjects were instructed to respond as quickly and as accurately as possible while the colors were still on the computer screen. The subjects reported the side on which one of the target colors appeared, using one of two specified keys on the keyboard during training or the custom finger-switch response system in the scanner. Each stimulus was followed by a fixation point that appeared in the middle of the computer screen during a 220 ms interstimulus interval. The subjects received 360 practice trials. During training, the subjects received auditory feedback (correct or incorrect tone) from the computer on every trial. In the scanner the subjects did not receive auditory feedback, but the experimenters were able to monitor online subject compliance with task instructions.

We counterbalanced the side on which each stimulus was presented across trials as well as the color pairs used in these conditions within and across groups. Counterbalancing the color pairs for the PI stimuli necessitated two different versions of the test (Table 2) that were balanced within and across the groups. Statistical analyses revealed that the color pair balancing factor did not alter the difficulty of acquiring the PI task; thus, participants performed equally well across the two versions of the test.

Experimental Block Design

For the baseline blocks, the subjects were required to discriminate color pairs on which they had been trained prior to the scan. For the PI blocks, the subjects learned a new color component for each color pair (see Table 2). The subjects received three 20 s blocks of baseline stimuli each interspersed with a 20 s block of rest, followed by three 20 s blocks of PI stimuli each interspersed with 20 s blocks of rest (Figure 1). This entire design was repeated three times to measure learning in the scanner. PI conditions always followed baseline conditions because of the fundamental structure of the PI phenomenon. By definition, to measure PI the to-be-learned interfering stimuli must follow the learned baseline stimuli.

Due to concern about fatigue and attention effects associated with the rapid response format of the present study, the functional portion of the entire study was restricted to 12 min. Within this 12 min period, data were collected from 180 separate trials for each of the baseline and PI conditions. The subjects attended and responded to a color pair every 650 ms for a total of 20 s and then received 20 s of rest. This cycle repeated itself 18 times for a total of 12 min. In addition, blocks of rest preceded each baseline or PI block to ensure that attentional/fatigue effects did not differentially effect the two conditions. The rest blocks served two purposes: (1) allowed the subjects to rest so that the experiment was not too taxing and (2) allowed the hemodynamic response to go back to baseline levels.

Our task focused on PI and its resolution and could not be extended to include a new learning task because of fatigue effects, especially when testing neurologically compromised patients. Rather, we examined the time course of PI and the brain structures responsible for its resolution over time. The strength of our study was the ability to contrast directly old learning with the new related learning as they were being simultaneously integrated into memory. The simplicity of the design was that in the baseline and PI conditions, the subjects were doing the exact same task but the exposure history of color pairs was manipulated.

Scanning Procedure

The MRI session began with anatomical sequences followed by a 12 min functional scan for the simultaneous discrimination associative learning paradigm. In the scanner, the color pair stimuli were presented using a magnet-compatible back projector with a custom finger switch response system used for the acquisition of subject responses and response times (RT). The start of the scan was trig-

gered automatically from the onset of the PsyScope-driven stimulus presentation from a Macintosh computer.

fMRI Data Acquisition and Analysis

Whole-brain MRI data were acquired on a 3.0 Tesla MRI scanner (Signa; General Electric, Milwaukee, WI). Prior to functional imaging, dual-echo coronal fast spin echo anatomical images were acquired in 64 contiguous, 3 mm coronal slices [echo time (TE) TE1 = 17 ms; TE2 = 102 ms; repetition time (TR) = 6900 ms; echo train length = 8; number of excitations = 1; and 256 × 192 acquisition matrix]. Head motion was minimized by placing surgical tape across the subject's chin and attaching it to the head coil. An automated spiral shim procedure was run to improve analysis with B0 magnetic field homogeneity correction. Following this, functional images were acquired using T2*-weighted gradient echo spiral pulse sequence (Glover and Lai, 1998) [TE = 30 ms; TR = 2000 ms; 75° flip angle; 24 cm^2 field of view; 64 × 64 data acquisition matrix] in 6 mm thick slices, each subtending two of the slice locations used for the higher resolution anatomical images. The T2*-weighted gradient echo spiral pulse sequence is relatively insensitive to motion and flow artifacts (Glover and Law, 2001). These functional images were acquired continuously during task performance and contained BOLD contrast intensity values.

Image spatial preprocessing and statistical analysis were performed using SPM99 (Wellcome Department of Cognitive Neurology) for each subject (Friston et al., 1995). The anatomical volume was segmented into gray matter, white matter, and CSF for spatial normalization to the standard Montreal Neurological Institute (MNI) gray-matter template image. The voxels were resampled during normalization to a 2 × 2 × 2 mm size. The spatial transformations derived from normalizing the structural volume taken in the functional acquisition plane were applied to the realigned T2*-weighted volumes. The volumes were then spatially smoothed with a 5 mm full width at half-maximum Gaussian smoothing kernel.

Individual models were calculated for each subject using a general linear model. To remove low-frequency drifts in the BOLD signal, data were high-pass filtered using a period of 80 s. A reference waveform corresponding to alternating experimental and control conditions was constructed and convolved with a canonical hemodynamic response function, and a parameter estimate was generated for each voxel for each block type. No global or grand-mean scaling was performed during analysis. An anatomically defined gray matter mask was created for each individual and explicitly specified during analysis; this ensured that statistical analysis was performed in all brain regions, including those where signal may be low due to susceptibility artifacts. Group data, formed from contrast images from each subject's model, were submitted to random effects analyses (Holmes and Friston, 1998). In controls, areas of statistical significance were identified using a height threshold of $p < 0.005$ uncorrected and an extent threshold of 10 contiguous voxels (80 mm^3); a region was only considered significant if it passed this significance criterion and spatial extent criterion. Because we had an a priori hypothesis of BF activation, we also used small volume correction with a 3 mm sphere radius centered at ($x = 8$, $y = 7$, and $z = -7$) in Talairach coordinates to obtain corrected p values for this specific region. In alcoholics, areas of statistical significance were also identified using a height threshold of $p < 0.005$ uncorrected and an extent threshold of 10 contiguous voxels (80 mm^3). Direct comparisons of the control and alcoholic groups were executed, to protect against a type 1 error in the patient data, with the corresponding two group t tests using a height threshold of $p < 0.005$ uncorrected. Additionally, we submitted each demographic measure for each group—age, education, general memory index score, and NART IQ score—to a voxel-wise analysis of covariance with a height threshold of $p < 0.005$. All anatomical localizations were determined by reference to the Duvernoy (1991) and Mai et al. (1987) atlases as well as to structural MRIs.

We examined the signal intensity from the normalized T2*-weighted images in the MS/DB, whose location was defined from the control group database on the activation when PI contrasted with baseline (criterion $p < 0.005$) of each individual to ensure that we measured reliable signal in the BF area. The signal was transformed to standardized units and submitted to a 2 × 2 mixed ANOVA with one between-group factor and one within-group factor (location: MS/DB versus nonbrain bounding box). We also examined whether activation of the MS/DB was specifically related to the integration of new with old learning, as indexed by the dissipation of PI. An MS/DB functional ROI was defined from the control group database on the activation when PI contrasted with baseline (criterion $p < 0.005$) and was 216 mm^3. The signal change relative to the mean of the entire time series for the frames comprising a block was indexed by the fit of the data to a convolved reference waveform and extracted from this ROI for each individual. The signal was transformed to standardized units and submitted to a 2 × 2 × 2 mixed ANOVA with one between-group factor and two within-group factors (task condition and repetition). Additionally, we submitted each demographic measure for each group, i.e., age, education, general memory index score, and NART IQ score, to correlational analyses with the MS/DB signal extracted from the functional ROI.

MR Volume Quantification of Basal Forebrain Nuclei

Of the 24 subjects, 13 controls and 11 alcoholics had participated in another unrelated MRI study in our laboratory, including volumetric scanning for ROI quantification. On a 1.5 T MR scanner (Signa; General Electric, Milwaukee, WI), a 3-dimensional spoiled gradient recalled acquisition (SPGR) sequence was acquired to collect images of the entire brain in a single volumetric data set acquired in a coronal plane [TR = 26 ms; TE = 5 ms; 30° flip angle; 24 cm field of view; 256 × 196 data acquisition matrix; acquired resolution, 0.9 × 1.2 × 2.0 mm; reconstructed and resampled resolution, 1.0 × 1.0 × 1.0 mm]. Image analysis tools were developed within the laboratory by A.P. using Interactive Data Language software (Research Systems, Inc, Boulder, CO). Analysis first included a series of transformations for aligning the 3-dimensional data set into desired orientations, relating them to standardized coordinates, and then slicing 2-dimensional images in that orientation for delineation and measurement of the BF region. Once the images had been realigned and resliced, manual point placement was used for defining the BF nuclei. All images were coded to allow processing to be performed blind to subject identity and group. Volumes were determined by summation of each region on all slices measured for each individual. The borders of the BF nuclei were based on anatomical landmarks and manually outlined by E.D.R. with high intrarater reliability intraclass correlation coefficient, $r = 0.97$. The most anterior slice measured was the slice on which the optic chiasm appeared and on which the globus pallidus and anterior commissure first appeared bilaterally. The most posterior slice measured was the slice before the anterior commissure decussated. Pixel counts for the BF nuclei gray matter volumes were expressed in cubic millimeters to provide estimates of their absolute volume and submitted to a repeated-measures ANOVA.

Motion Parameters Analysis

To test that the group differences were not due to differences in subject motion in the scanner, we submitted the motion parameters (translation in the x, y, z directions and rotations corresponding to pitch, roll, and yaw) estimated at realignment to a repeated-measures 2 × 6 mixed analysis of variance (ANOVA) with one between-group factor and one within-group factor (motion parameters). This mixed ANOVA revealed no significant main effects or interactions and therefore no group differences in motion across the experiment. To investigate the motion associated with the different task conditions, we submitted a motion parameter composite (the mean of all six of the motion parameters) created for each individual to a repeated-measures 2 × 4 × 3 mixed ANOVA with one between-group factor and two within-group factors (block type and repetition). Again, the mixed ANOVA revealed no significant main effects or interactions; therefore, the two groups had comparable head rigidity in the scanner, and changes in motion did not correlate with a particular task condition.

Behavioral Statistical Analysis

The proportions of correct responses and the median RT for correct responses for each group were calculated and submitted to repeated-measures mixed ANOVA. A separate ANOVA was conducted on the behavioral data for each dependent measure. Analysis was

performed on the trials where PI was expected to be maximal, i.e., the last 10 trials of the third baseline block, and the first 10 trials of the first PI block, i.e., the initial transfer of the acquired response to a new learning situation. Each mixed 2 × 2 × 3 ANOVA included one between-group factor and two within-group factors (task condition and repetition).

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