Cerebral Cortex July 2007;17:1650–1663
doi:10.1093/cercor/bhl076
Advance Access publication September 12, 2006

Two Distinct Functional Networks for Successful Resolution of Proactive Interference

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In proactive interference (PI) paradigms, previous learning impairs the acquisition of new, related information. In rats, efficient resolution of PI relies on cholinergic modulation from the basal forebrain (BF). To test whether humans resolve PI using a functional network dependent on the medial septum/diagonal band of Broca (MS/DB) nuclei of the BF, we analyzed functional magnetic resonance imaging signal recorded while human participants learned to respond to baseline color paired associates and then additional pairs that interfered with the baseline pairs. Multivariate, partial least-squares analysis supported a MS/DB-dependent functional network: MS/DB activity covaried with activity in areas important to selective attention, including intraparietal sulcus, and memory that are direct cholinergic efferents of the MS/DB, including the hippocampus, as well as the ventrolateral prefrontal cortex, implicated in PI resolution. This network was associated with effective PI-resolution behavior. A second network also correlated with PI resolution but appearing not to be driven by the MS/DB, included the lateral orbitofrontal cortex. Patients with compromised BF function did not engage the MS/DB-dependent network reliably; instead their PI-resolution behavior was well explained by the second network. Thus, 2 functional networks may underly a single cognitive function; when the MS/DB-dependent attention/memory integration network is compromised, an alternate network is available to maintain normal levels of performance.

Keywords: acetylcholine, basal forebrain, fMRI, learning and memory, proactive interference

Introduction

In many learning situations, to-be-learned associations conflict with one another. Based on electrophysiology and computational modeling, Hasselmo and Bower (1993) proposed that the rodent brain resolves such interference via cholinergic (ACh) modulation from the basal forebrain (BF) by increasing the responsiveness of the modulated brain region to its inputs while suppressing recurrent connections, thus reducing the potentially interfering influence of prior learning (for further elaboration of this model, see Hasselmo and McGaughy 2004). De Rosa and Hasselmo (2000) and De Rosa and others (2001) tested this model with a proactive interference (PI) paradigm, wherein prior learning interferes with new learning. Systemic pharmacology and cholinergic immunotoxic lesions showed that efficient resolution of PI relied on cholinergic modulation from the BF. These findings have been corroborated with human systemic pharmacology (Atri and others 2004). The BF may play a similar role in human resolution of PI; De Rosa and others (2004) found blood oxygen level–dependent functional magnetic resonance imaging (BOLD-fMRI) activity in a set of regions important to mnemonic processing along with the medial septum/diagonal band of Broca (MS/DB) nuclei of the BF. The MS/DB nuclei provide cholinergic innervation primarily to the hippocampus as well as medial prefrontal, orbitofrontal, and cingulate cortices (Mesulam and others 1983; Rye and others 1984; Insausti and others 1987; Ghashghaei and Barbas 2001). This confirmed one prediction of the BF-dependent functional network hypothesis—namely, coactivation of the MS/DB and afferent regions. However, coactive regions do not necessarily interact. If regions interact, their activity should covary. Thus, a stronger prediction is that activity in these regions should covary with activity in the MS/DB.

Our aims were 3-fold. First, we asked whether the distributed activity patterns found in the De Rosa and others (2004) study could withstand more stringent tests of the functional network hypothesis. We aimed to identify functional networks involved in resolution of PI and determine whether they were dependent on or independent of the MS/DB as well as whether they were related to behavior (reaction times). We were also interested in whether functional networks would differ between early and late resolution of PI. In the initial region of interest (ROI) analysis of the MS/DB (De Rosa and others 2004), the MS/DB signal peaked when PI was behaviorally resolved, suggesting that peak MS/DB activity allowed PI performance to improve. We therefore predicted that the MS/DB-dependent functional network would be most present when PI was resolved, namely, in the late PI condition. We examined the correlations, that is, functional connections, between voxel activity and the signal in the MS/DB as well as with response time (RT), a measure of performance. We use the seed partial least-squares (PLS) method (McIntosh and others 1996; Schreurs and others 1997; McIntosh and Lobaugh 2004), a multivariate decomposition of the correlation, across participants, between brain activity at all voxels and activity of a ROI ("seed region") as a function of task condition. Our chief hypothesis was that MS/DB activity would covary with mnemonic and sensory processing regions and this network's activity would in turn covary with PI resolution as measured by speeded RTs.

A second aim was to observe what happens in a population with compromised BF function but preserved declarative memory. We include data from the De Rosa and others (2004) study from nonamnesic patients with chronic alcoholism because although ethanol exposure has widespread effects on the brain, it reduces cholinergic function at the muscarinic receptors (De Rosa and Sullivan 2003; De Rosa and others 2004). Even though the patients did not differ from controls in performance (Fig. 1), their average brain activity differed from controls during PI resolution. In contrast to controls, alcoholics activated brain regions associated with executive functions rather than mnemonic and sensory regions. Moreover, the

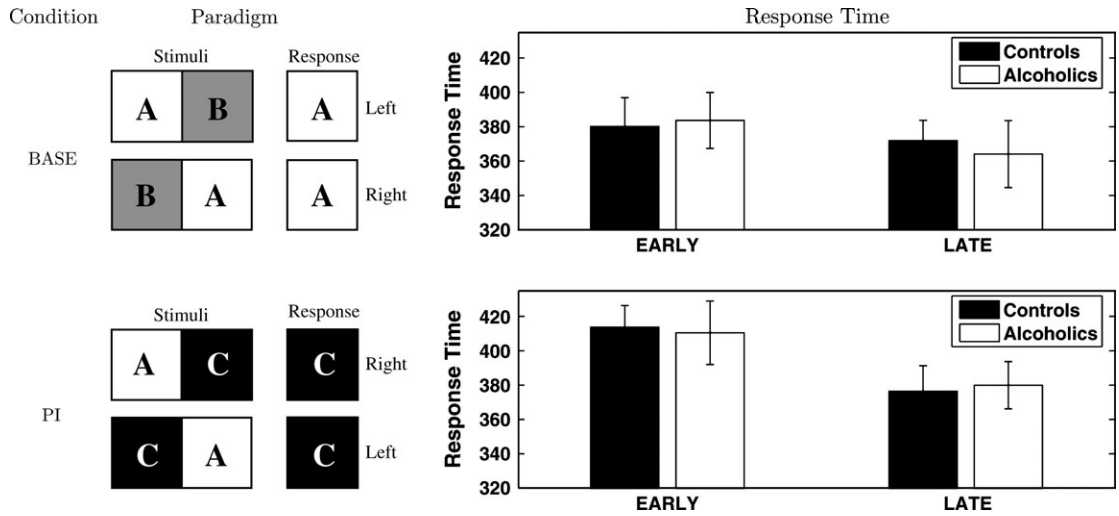

Figure 1. Task and performance. In baseline blocks, participants learned to respond to A colors given color patches A and B. Boxes with letters represent color-patch stimuli. Responses speed up from early to late trials. In PI blocks, participants had to respond to C when presented with color patches A and C, overcoming the interfering, prepotent response to A. Responses were slower early in PI trials and recovered to baseline levels in late trials. Control and alcoholic participants did not differ significantly in their performance. Error bars denote standard error of the mean across participants.

MS/DB was not reliably active, suggesting that the cholinergic modulation found in controls may not be present in alcoholics. This difference in the neural substrates, that is, the lateral orbitofrontal and anterior cingulate cortices, for resolving PI may reflect alternate strategies that might rely on executive areas associated with more cognitively demanding interference tasks (D'Esposito and others 1999; Postle and others 2001, 2004; Henson and others 2002).

Finally, it is reasonable to assume that the hippocampus should be involved, given the associative nature of the task (Rudy and Sutherland 1989, 1995), as well as its innervation from the MS/DB (Mesulam and others 1983; Ghashghaei and Barbas 2001). Further, the cholinergic modulation model, although regarded as a general-purpose mechanism throughout the cortex (Hasselmo and McGaughy 2004), was proposed to operate in the present type of task specifically in the hippocampus (Hasselmo and Schnell 1994). However, the previous univariate analysis of fMRI data failed to find reliable activation of the hippocampus. One possible explanation of this null finding is that the hippocampus is not involved in this specific task. An alternative possibility is that, if the hippocampus forms a functional network with the MS/DB and other regions, then its activity level might be quite variable (making it difficult to assess mean differences across conditions) but this variability, far from being noise, should be tightly coupled to the activity of the MS/DB. Thus, by analyzing the correlation between MS/DB activity and activity in the rest of the brain, hippocampal involvement in PI resolution might be more evident. Furthermore, in the alcoholic population, compromised MS/DB function should result in less effective modulation of the hippocampus; thus the involvement of the hippocampus should be specific to control participants.

Materials and Methods

The data presented here were previously analyzed with univariate methods by De Rosa and colleagues. Thus, the basic methods are identical and are summarized here followed by the detailed seed/behavior PLS analytic methods used in this study.

Participants

Demographic data are summarized in Table 1. To establish eligibility for the study, all participants underwent medical and psychiatric screening that included a structured alcohol history (Pfefferbaum and others 1988) and a structured clinical interview (American Psychiatric Association 1994). Twenty-four 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. Participants 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 Diagnostic and Statistical Manual of Mental Disorders (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 participants met the DSM-IV criteria for alcohol dependence and were tested well after any acute physiological withdrawal had subsided. No participant from either group presented a profile of clinically or operationally defined amnesia or dementia (Mattis 1998). Upon arrival to the laboratory, all participants underwent an alcohol breath analyzer test and scored 0.0.

Behavioral Task

The entire experiment was created and implemented with PsyScope 1.2.5 (http://psyscope.psy.cmu.edu). Participants had to learn to discriminate pairs of color patches. The participants were informed that 2 colors were to be targets. They were then presented with pairs of colors, one was always a target and the other was always a nontarget stimulus, and were trained always to choose the target-color stimuli targets. Color-patch pairs were presented simultaneously for 650 ms; each color filled half of the computer screen. Two versions of the color assignments were used, counterbalanced across participants (see Table 2). The participants reported the side on which one of the target colors appeared, using one of 2 specified keys on the keyboard during training or the custom finger-switch response system in the scanner (Fig. 1). The participants were instructed to respond as quickly and as accurately as possible while the colors were still on the computer screen. Each stimulus was followed by a fixation point that appeared in the middle of the computer screen during a 220-ms interstimulus interval. The participants received 360 practice trials. During training, the participants received auditory feedback (tone indicating correctness) from the computer on every trial. In the scanner, the participants did not receive auditory feedback but the experimenters were able to monitor online participant compliance with task instructions.

Both the sides on which each stimulus was presented across trials and the color pairs used in these conditions were counterbalanced within and across groups. Counterbalancing the color pairs for the PI stimuli necessitated 2 different versions of the test 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 2 versions of the test.

Experimental Block Design

For the baseline blocks, the participants were required to discriminate color pairs on which they had been trained prior to the scan. For the PI blocks, the participants learned a new color component for each color pair. The block design during scanning is depicted in Figure 2. The participants received 3, 20-s blocks of baseline stimuli each interspersed with a 20-s block of rest, followed by 3, 20-s blocks of PI stimuli each interspersed with 20-s blocks of rest. This entire design was repeated 3 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. The participants 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 affect the 2 conditions. The rest blocks served 2 purposes: 1) allowed the participants to rest so that the experiment was not too taxing and 2) allowed the hemodynamic response to go back to baseline levels (Fig. 1).

Table 1
Participant demographics

Measure	Alcoholics (n = 11)	Controls (n = 13)	t-test (df = 22)
Age (years)	50.1 (8.1)	55.6 (11.3)	1.4
Education (years)	15.6 (2.1)	17.8 (2.4)	2.4
NART[a]	109.6 (7.7)	115.2 (5.9)	2.0
General memory index	107.7 (11.3)	119.8 (13.9)	1.9
Dementia rating scaling	139.8 (2.8)	140.1 (2.4)	1.2
Total lifetime consumption (kg)	1202 (1211)	155 (162)	9.6
Median length of sobriety (days)	100 (range 20–790)	—	—

Note: Standard deviations are reported in parentheses.
[a]NART, premorbid estimation of IQ, measured by National Adult Reading Test; general memory index, measured by Wechsler Memory Scale-Revised. $P < 0.05$.

Table 2
PI color counterbalancing

Baseline pairs A+ B−	PI pairs C+ A−
Version 1	
Pink:orange	Brown:pink
Purple:green	Gray:purple
Version 2	
Pink:brown	Orange:pink
Purple:gray	Green:purple

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 participant responses and RTs. The start of the scan was triggered automatically from the onset of the PsyScope-driven stimulus presentation from a Macintosh computer.

Functional MRI Data Acquisition

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 participant'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 T_2*-weighted gradient echo spiral pulse sequence (Glover and Lai 1998) (TE = 30ms; TR = 2000 ms; 75° flip angle; 24-cm^2 field of view; 64 × 64 data acquisition matrix, in-plane voxel size = 2 mm) in 6-mm-thick slices, each subtending 2 of the slice locations used for the higher resolution anatomical images. The T_2*-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 participant (Friston and others 1995). The anatomical volume was segmented into gray matter, white matter, and cerebrospinal fluid 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^3 size. The spatial transformations derived from normalizing the structural volume taken in the functional acquisition plane were applied to the realigned T_2*-weighted volumes. The volumes were then spatially smoothed with a 5-mm full width at half-maximum Gaussian smoothing kernel. Finally, to reduce computational overhead of the PLS analyses, voxels were resampled to 4 × 4 × 4 mm^3 size.

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.

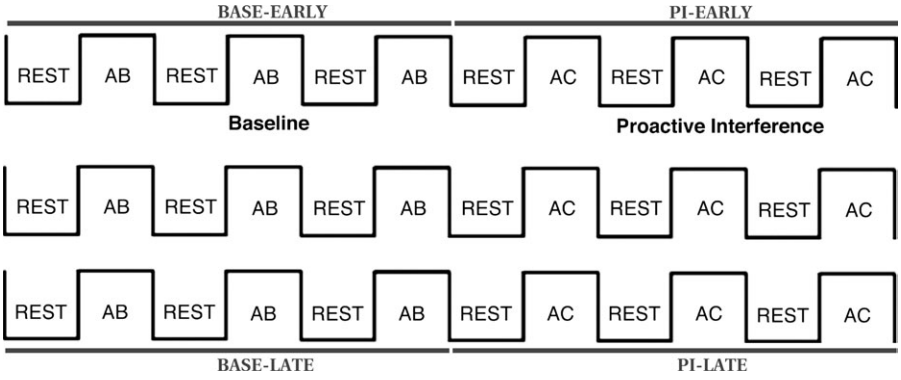

Figure 2. Scanning paradigm. After being pretrained outside the scanner on the baseline (AB) pairs, participants were scanned while they performed blocks of the task (baseline or PI pairs) interspersed with rest. This was repeated a total of 3 times to assess PI resolution.

Multiblock PLS Analysis

Overview

The motivation of this multivariate analysis was to uncover functional networks and characterize their dependence on MS/DB activity and relationship to behavior measured by reaction times. We were also interested in whether these functional networks would distinguish between our participant populations, as well as PI resolution over time. A single multivariate analysis includes all these factors, enabling us to concisely summarize multiple functional networks. The PLS approach simply decomposes a correlation matrix that describes brain–behavior (covariance between voxel activity and measures of behavior across participants), brain–brain (covariance between activity in one voxel and activity in another voxel), and brain–task (changes in voxel activity as a function of task conditions) relationships. PLS is a multivariate technique that describes the relationship between the input, task design, and output measures, voxel activity in the whole brain or brain-activity–seed correlations (McIntosh and others 1996; Schreurs and others 1997; McIntosh, Cabeza, and others 1998). A "task PLS" analyzes mean changes in brain activity as a function of conditions to assess changes in the presence of distributed patterns of brain activity in each condition. In a complementary approach, "seed PLS" analyzes the correlation between brain activity and seed measures to identify distributed patterns of brain activity that covary with the seeds. Seeds can be activated in seed voxels for functional connectivity or performance measures for behavioral relevance. The PLS applied here, a "multiblock PLS" (McIntosh, Lobaugh, and others 1998), combines both a task PLS and a seed PLS into a single analysis. This enables us to identify distributed patterns of brain activity and simultaneously assess how they change in presence or absence across conditions and how they covary in functional connectivity and relevance to behavior.

Task PLS Block

To compare performance of baseline pairs with performance of interference pairs and to look for effects of learning, we analyzed 4 conditions, as marked in Figure 2: the first and last blocks of baseline pairs (BASE-EARLY and BASE-LATE, respectively) and first and last blocks of interference pairs (PI-EARLY and PI-LATE, respectively). The PI-EARLY condition is when participants are first faced with interfering pairs and performance consequently worsens, whereas during PI-LATE, participants have successfully resolved PI as evident in their performance returning to baseline levels. All 4 conditions were included in the task PLS block.

The voxel values (including seed voxels) were calculated from each 10-TR block as the average over TRs 4–9 minus a reference signal taken from the first TR of the block. The analysis window started well after block onset to capture the slowly rising hemodynamic response function, and the baseline was subtracted in order to remove signal drift across the testing session.

The voxel activity in each condition (BASE-EARLY, BASE-LATE, PI-EARLY, or PI-LATE) became a row of the task PLS submatrix; thus, the submatrix has size 4 conditions × 2 participant groups rows and n columns, where n is the number of voxels.

Seed PLS Block

For the seed block, only the PI conditions were included. We were interested in the relationship between brain activity throughout the brain and 2 covariates: 1) Activity in the MS/DB (MNI [X, Y, Z] = [8, 8, –8] mm), identified as peak-voxel in the MS/DB cluster from prior univariate analyses (De Rosa and others 2004) and 2) RT, a measure of performance. For RT, we wanted to isolate effects of interference and interference resolution rather than identifying individual variability in overall response speed. Thus, for condition PI-EARLY, the RT seed was the difference between the RT for PI-EARLY and its baseline control (BASE-EARLY), which assesses the hit taken to RT due to PI. For condition PI-LATE, the RT seed was the difference between the RT for PI-LATE and its control (BASE-LATE), which assesses the degree to which a participant had successfully resolved PI. In both cases, only correct-response RTs were included. Thus, the input to the seed-PLS block consists of the correlations across participants between voxel activity and both MS/DB activity and RT for each condition and separately for each participant group.

Each correlation map (unwrapped into a vector) became a row of the submatrix for MS/DB and RT seeds, respectively; thus, the matrix had a number of rows equal to 2 PI conditions × 2 groups × 2 seeds and n columns.

PLS Input

The input to the analysis was the column wise concatenation of the task PLS and both seed PLS blocks. These correlation matrices were concatenated together column wise. Each block was normalized separately and the columns of the task PLS block were mean centered.

PLS Procedure

The 3 submatrices were concatenated column wise. A singular value decomposition was applied to this matrix to compute an optimal *least-squares* fit. This produces asset of mutually orthogonal latent variables (LVs), each consisting of 2 parts: a singular image ("brain LV," or the brain portion of the LV) and a singular profile ("design/seed/behavior LV," or the seed/behavior portion of the LV), connected by a singular value (the square root of the eigenvalue). The singular value indicates how much of the covariance of the input matrix is accounted for by its respective LV. This is not an index of the total variance accounted for and is only a measure of the relative importance of an LV with respect to all other LVs. Brain LVs consist of a weighted linear combination of voxels that as a whole covary with each seed's activity across participants. The numerical weights within the brain LV are called "voxel saliences" and can be positive or negative, indicating the degree to which each voxel is related to the design/seed/behavior LV. The design/seed/behavior LV can be broken into 2 parts. First, the design LV (relating to the task PLS block) reveals how the brain LV changes its activity across conditions in each group, analogous to a contrast. The seed/behavior LV (relating to the seed PLS block) characterizes the brain–seed covariance, and in particular, how this covariance varies across task conditions. The seed/behavior LV thus characterizes the functional connectivity of the brain LV with the MS/DB seed and with PI behavior.

Interpretation of Saliences

The interpretation of voxel saliences depends on the brain LV's relationship to the design, behavior, and seed saliences: 1) *Design*: If a particular voxel has a positive voxel salience, this indicates that the portion of the voxel's activity that is contributing to the LV is greater in conditions with more positive design saliences when compared with conditions with more negative design saliences. A negative voxel-salience region has the reverse relationship. Thus, the design LV explains how the mean activity level of the brain LV varies across task conditions. 2) *Behavior*: If a voxel has a positive voxel salience, then the subset of voxel activity variability contributing to the LV covaries positively with positive-salience behavioral measures and inversely with negative-salience behavioral measures (high performance for accuracy, poor performance for RT for which longer RTs reflect lower performance). A negative voxel-salience region has the reverse relationship. Thus, the behavior LV explains how the activity of the brain LV covaries with performance in each condition. 3) *Seed*: Analogous to the behavior LV, if a voxel has a positive voxel salience, then the subset of voxel activity variability contributing to the LV covaries positively with the seed in positive seed-salience conditions and negatively with the seed in negative seed-salience conditions. A negative voxel-salience region has the reverse relationship. Both positive and negative covariance with the seed constitute functional connectivity. Thus, the seed LV reveals the functional connectivity between the brain LV regions and the seed region (here, MS/DB) in each condition.

Assessing Reliability

The significance of each LV was assessed with a permutation test (500 iterations) in which task condition labels were shuffled across all participants resulting in random assignment of both tasks and group membership. This resulted in a distribution of singular values from shuffled data sets, from which the cumulative 95th percentile was taken as the significance threshold. The reliability of each voxel's contribution to the LV is assessed by a bootstrap estimation of standard errors for the voxel salience (100 iterations) by resampling participants with

replacement while preserving the total amount of data in each bootstrap set (a minimum of 50% of resampled participants had to be different in each bootstrap). Each voxel salience can be expressed as a bootstrap ratio, or the probability that each voxel salience is nonzero. Thus, the bootstrap assessment of voxel saliences evaluates how stable the brain LV maps are across participants. We also used the results of the bootstrap to similarly compute standard errors on seed-brain LV correlations to identify task conditions for each seed that have a reliably nonzero seed activity–brain activity relationship.

Finally, cluster reports were used to identify significant regions involved in the LVs. Clusters were considered significant if 15 contiguous voxels exhibited a single-voxel bootstrap ratio of 2.58 (roughly equivalent to a z score with probability 0.01), with a minimum of 10 mm between peaks. All anatomical localizations were determined by reference to the Duvernoy (1991) atlas as well as to structural MRIs.

Results

Overview

The multiblock PLS method analyzes the correlation between the seeds (MS/DB ROI and RT) and activity in all voxels in the brain as a function of PI condition and group, as well as mean voxel activity in each of the 4 conditions. This results in a set of LVs that parsimoniously explain the task design–brain seed–brain correlations. Each LV has a brain portion ("brain LV"), a design portion ("design LV"), and a seed/behavior portion ("seed/behavior LV"). The brain LV is a distributed pattern of activity over voxels. The design LV indicates how this distributed pattern changes in presence across the 4 conditions: BASE-EARLY and BASE-LATE, first and last blocks of baseline pairs, and PI-EARLY and PI-LATE, first and last blocks of PI pairs. The seed/behavior LV indicates how this distributed pattern covaries with the seeds and across the PI conditions, PI-EARLY and PI-LATE.

Figure 1 plots RT as a function of group (control vs. alcoholic), time (early vs. late), and pair (BASE vs. PI). An ANOVA on PAIR[2] × TIME[2] × GROUP[2] yielded a significant interaction of PAIR × TIME ($F_{1,22} = 11.97$, $P < 0.005$) but the 3-way interaction PAIR × TIME × GROUP was not significant ($F_{1,22} = 0.04$, $P > 0.5$). Thus, as evident in the figure, although no group differences were found, RTs were slow during PI-EARLY, indicating the presence of unresolved PI, but recovered to baseline levels during PI-LATE, suggesting that this interference was satisfactorily resolved. The RT seeds used in the PLS for PI-EARLY and PI-LATE are relative to their respective baseline RTs (BASE-EARLY and BASE-LATE), so they represent the degree of slowing due to the PI challenge (for PI-EARLY) and the degree to which PI is resolved (for PI-LATE).

Interpretation of the PLS findings could be complicated if there were structural changes due to chronic alcohol use in the patient group. However, as reported in the univariate analyses (De Rosa and others 2004), no morphometric differences were found between the 2 groups (gray matter outlined manually: $t(20) = 0.61$, not significant). In addition, the univariate analyses of MS/DB demonstrated that the activity of the MS/DB was modulated by learning in controls but showed no change in alcoholics. Thus, functional differences were found without any structural differences.

The seed/behavior PLS identified 2 significant LVs ($P < 0.05$ by permutation test). Both LVs differed in average activity between early and late conditions. The first LV is MS/DB-dependent and describes primarily control participants' data, whereas the second LV, which does not appear to implicate cholinergic modulation from the MS/DB in PI resolution, describes both participant groups to comparable degrees. We now report both LVs in detail.

Latent Variable #1

The first LV identified by the PLS confirms the existence of a MS/DB-dependent functional network associated with the resolution of PI, supporting the principle hypothesis we put forward based on data from computational modeling, pharmacology, and immunotoxic lesions. As we shall see, this network is prominently present in controls and only weakly present in alcoholics, consistent with the notion that it relies on a cholinergically intact BF. We now report the characteristics of this LV in detail. The first LV accounted for 13% of the cross-block covariance. We first analyze the relationship of the distributed pattern of brain activity to the task conditions and seeds, followed by a breakdown of the regions involved in the brain LV.

The design LV (Fig. 3*a*) reveals that the brain LV on average showed greater activity in LATE compared with EARLY conditions. This pattern is pronounced for controls and consistent, although much smaller in magnitude, for alcoholics, already suggesting that LV 1 describes controls more than the alcoholics.

The seed/behavior LV (Fig. 3*b*) tells us how the brain LV activity covaried (around its mean) with MS/DB and RT seeds. Overall, this brain LV covaried substantially with controls' MS/DB and RT, suggesting that this network is responsible, along with the MS/DB, for successful resolution of PI but was far less reliably correlated with MS/DB activity and RT for alcoholics. We focus on saliences that are reliably nonzero by bootstrap test (i.e., confidence intervals not including zero). For controls in condition PI-EARLY, increasing activation of the brain LV was correlated reliably with both MS/DB activity and slow RTs. Recall that this RT measure reflects the magnitude of the PI effect. This suggests that brain LV 1 is invoked, along with MS/DB, in proportion to the degree of PI for a given participant. Later, in condition PI-LATE the brain LV still correlates with MS/DB activity but correlates *inversely* with RT. Because the RT measure used for this condition reflects the degree to which PI has been successfully resolved, this suggests that activation of the positive-salience regions of brain LV 1, along with the MS/DB, is responsible for successful resolution of PI.

For alcoholics, brain LV 1 did not reliably correlate with either MS/DB or RT in condition PI-EARLY, and in condition PI-LATE, the correlations pointed in the same direction as for controls but with greater variability. Thus, for alcoholics, brain LV 1 not only did not vary substantially from early to late conditions but was irrelevant to MS/DB and RT early in PI exposure. Its subsequent coupling with the MS/DB was weaker and it did not reliably predict resolution of PI behavior.

The regions in the brain LV (summarized in Table 3 and plotted in Fig. 3*c* superimposed on the average anatomical scans from all 24 participants) with positive saliences included areas previously found to be active during PI conditions in controls, like medial orbitofrontal cortex, areas that were previously active in alcoholics, like anterior cingulate cortex, as well as areas specific to this multivariate analysis, like the hippocampus. The hippocampal activation is noteworthy because it was hypothesized to be positively correlated with MS/DB activity as it is a direct cholinergic target of the MS/DB (Mesulam and others 1983; Ghashghaei and Barbas 2001), so this functional connection is consistent with a known anatomical/neuromodulatory

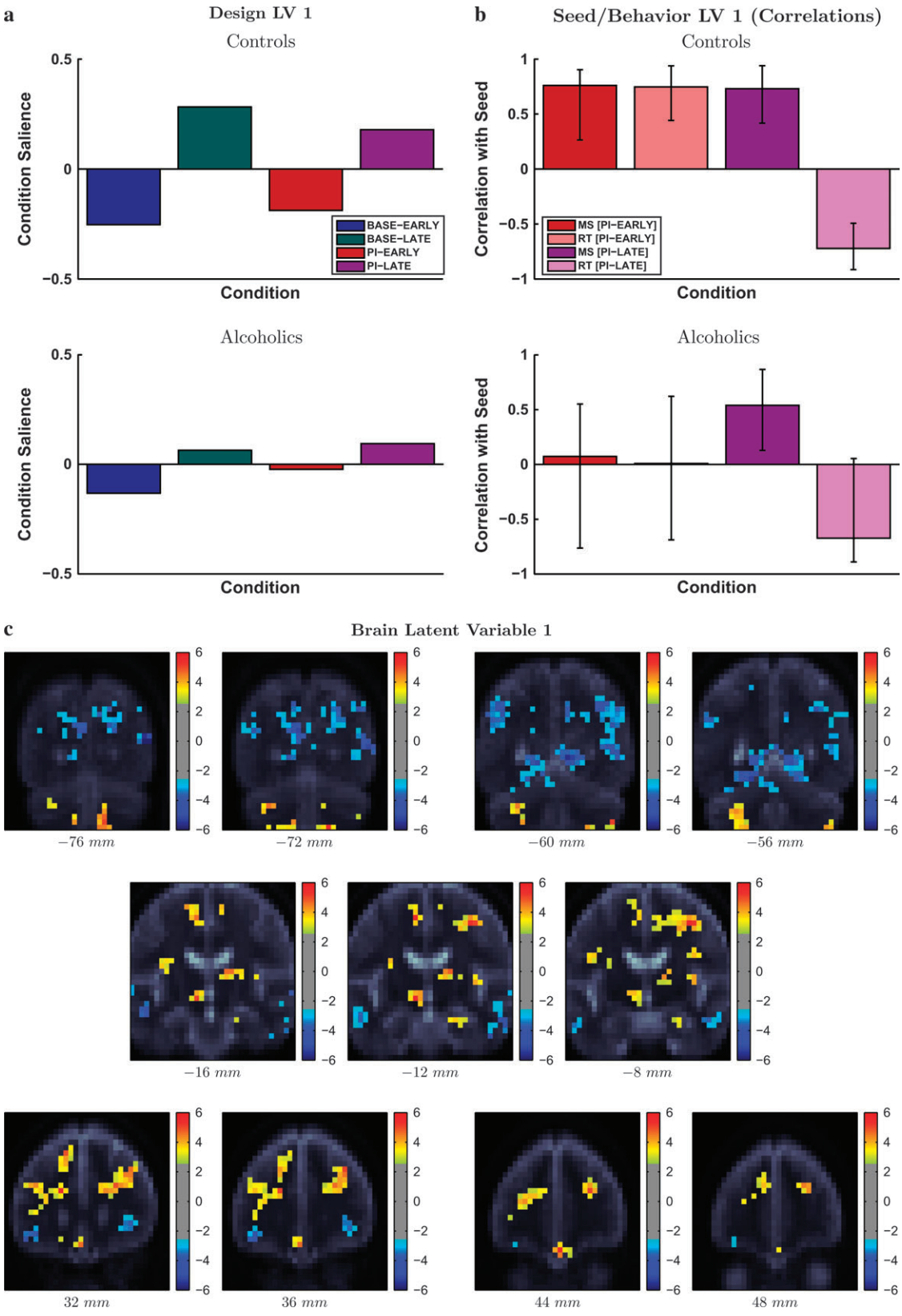

Figure 3. Latent variable #1. (*a*) Design LV 1. Saliences reflect differences in the pattern activity of the brain LV as a function of condition. (*b*) Behavior/seed LV 1. Each bar plots the correlation with MS/DB (left bar of each pair) and RT (right bar of each pair) as a function of PI condition and participant group. Error bars denote 95% confidence intervals based on the permutation test. (*c*) Brain LV 1. Voxels meeting the cluster-analysis criteria (single-voxel bootstrap ratio ⩾2.58 min cluster size = 15 voxels) are plotted superimposed on the average anatomical scans from all 24 participants. The color scale denotes the bootstrap ratio in the range –6 (cool colors) to +6 (hot colors).

Table 3
Significant clusters identified for LV 1

Cluster region	X	Y	Z	Size	Bootstrap
LV 1	Positive salience				
1 L insula/mid-ventrolateral prefrontal cortex	−32	16	8	347	6.9
2 R anterior cingulate	8	0	48	185	6.4
3 R insula	48	12	16	333	6.3
4 R posterior cingulate	20	−32	56	54	6.2
5 L cerebellum	−20	−68	−52	20	5.9
6 L posterior cingulate	−12	−12	52	55	5.6
7 R collateral sulcus	40	0	−36	23	5.3
8 Medial orbitofrontal	0	44	−24	18	5.2
9 R cerebellum	16	−72	−52	38	5.1
10 R cerebellum	44	−60	−48	21	4.8
11 L superior frontal gyrus	−16	32	48	32	4.6
12 L superior temporal gyrus	−52	8	−32	16	4.5
13 L cerebellum	−24	−40	−32	79	4.5
14 R hippocampus	24	0	−32	18	3.6
	Negative salience				
15 R angular gyrus	44	−76	12	202	6.3
16 L intraparietal sulcus	−44	−64	36	345	6.2
17 L parahippocampal gyrus	−16	−36	−12	124	5.5
18 L precuneus	−16	−44	36	41	5.3
19 R middle temporal gyrus	48	−12	−36	28	4.9
20 L middle temporal gyrus	−52	−16	−16	23	4.9
21 L inferior frontal gyrus/pars orbitalis	−44	28	−16	28	4.7
22 R precuneus	16	−68	32	73	4.4
23 L superior temporal sulcus	−68	−16	−4	16	4.4
24 R Inferior frontal gyrus/pars orbitalis	36	32	−4	23	3.8
25 L cerebellum	−8	−52	−24	24	3.4

Note: *X*, *Y*, and *Z* coordinates are in millimeters according to the MNI standard. "Size" denotes cluster size in number of voxels. "Bootstrap" refers to the bootstrap ratio, which indicates robustness across participants.

connection. Thus, these regions were invoked, along with the MS/DB, in proportion to PI and were associated with good PI resolution.

Regions with negative saliences included regions previously found to be active in controls during PI: intraparietal sulcus, associated with early stages of visual processing, the triangular part of the inferior frontal gyrus, and precuneus (De Rosa and others 2004). Another negative-salience region was right parahippocampal gyrus, a direct cholinergic target of the MS/DB (Mesulam and others 1983; Woolf 1996; Ghashghaei and Barbas 2001). The negative correlation with this region indicates that the right parahippocampal gyrus increases in activation, the MS/DB tends to decrease its activity. Thus, it seems unlikely that the involvement of this region relies on cholinergic modulation from the MS/DB. Activation of regions with negative salience early in PI trials may help participants handle PI, improving performance in PI-EARLY. However, a participant who activates these regions when PI should already be resolved (PI-LATE) would still show elevated RT.

We examined whether participants were activating the brain LV in PI-EARLY and deactivating it in PI-LATE, or vice versa. If this were the case, then the brain scores (projection of the brain LV onto individual participants' brain activity in each condition) should be negatively correlated between PI-EARLY and PI-LATE when the correlation is computed across participants. However, this correlation was positive (alcoholics: $r(10) = 0.60$, $P = 0.051$; controls: $r(12) = 0.75$, $P < 0.005$). This suggests that each participant only invoked one network and used this network exclusively to resolve PI. Namely, if a participant activated the positive-salience regions, then they deactivated the negative-salience regions throughout learning. Thus, the positive and negative saliences may reflect a variability in strategy.

In sum, LV 1 identified a network that primarily describes control participants. Regions included direct targets of the MS/DB, plus regions previously found to be active in control participants during PI conditions. The correlations with MS/DB and RT suggest that this network receives neuromodulatory functional connections from the MS/DB, either directly, for afferent targets, or indirectly, for other regions. Further, it is invoked early in PI in proportion to the amount of PI experienced, and is associated with better resolution of PI. Alcoholic participants, with presumed compromised BF function, activate the brain LV less overall, and the degree of activation of this LV is substantially decoupled from MS/DB activity and independent of performance measures, either of the magnitude of PI experienced or of the degree to which PI is resolved.

Latent Variable #2

The first LV tended to confirm our predictions, characterizing the control participants' brain–behavior and brain–seed pattern well. Complementing that LV, the second LV identified by the PLS describes both controls and alcoholics to a similar degree. Thus, this may be an alternate network that some control participants use and is also seed by alcoholics. Its relevance to alcoholics may explain why our alcoholic participants were able to maintain good performance levels despite evidently being less able to invoke the network identified in LV 1. We now describe this LV in detail. The second LV accounted for 12% of the cross-block covariance. The design LV (Fig. 4*a*) reveals that, like LV 1, brain LV 2 on average showed greater activity in LATE compared with EARLY conditions. Unlike LV 1, this pattern was comparable in magnitude for alcoholics as for controls. This suggests that LV 2 explains both alcoholics' and controls' brain activity to roughly similar degrees, with respect to changes in mean activity.

The seed/behavior LV (Fig. 4*b*) tells us how the brain LV activity covaried (around its mean) with MS/DB and RT seeds. Overall, the brain LV covaried with MS/DB and RT similarly for both groups and suggests that it represents an alternate strategy for PI resolution that does not ultimately rely on MS/DB function. For both groups, the brain LV correlated negatively with MS/DB activity in PI-EARLY and was independent of MS/DB in PI-LATE. Thus, the network was independent of MS/DB for PI resolution, and was related to reductions in MS/DB activity (positive-salience regions) or increases in MS/DB activity (negative-salience regions) while experiencing PI or greater RTs. Note that although a negative correlation represents a functional connection, the fact that the significant correlation between MS/DB and the second brain LV was confined to the PI-EARLY condition and covaried with long RTs suggests that MS/DB activation might index the degree of PI experienced behaviorally but that the MS/DB is not involved in the resolution of that interference in that LV.

In alcoholics only, the brain LV correlated positively with RT in PI-LATE and negatively with RT in PI-EARLY. Along with the design LV, this suggests that LV 2 is, on average, deactivated while the MS/DB is activated. In fact, the more the PI experienced, that is, the longer the RTs in PI-EARLY, the more LV 2 is deactivated. In PI-LATE, the brain LV network is activated on average. However, the less active it is, the better the PI has been resolved, as reflected in fast RTs.

For this brain LV, functional connectivity with the MS/DB indicates the initial level of PI present (during PI-EARLY) but is unrelated to the ultimate resolution of PI (during PI-LATE).

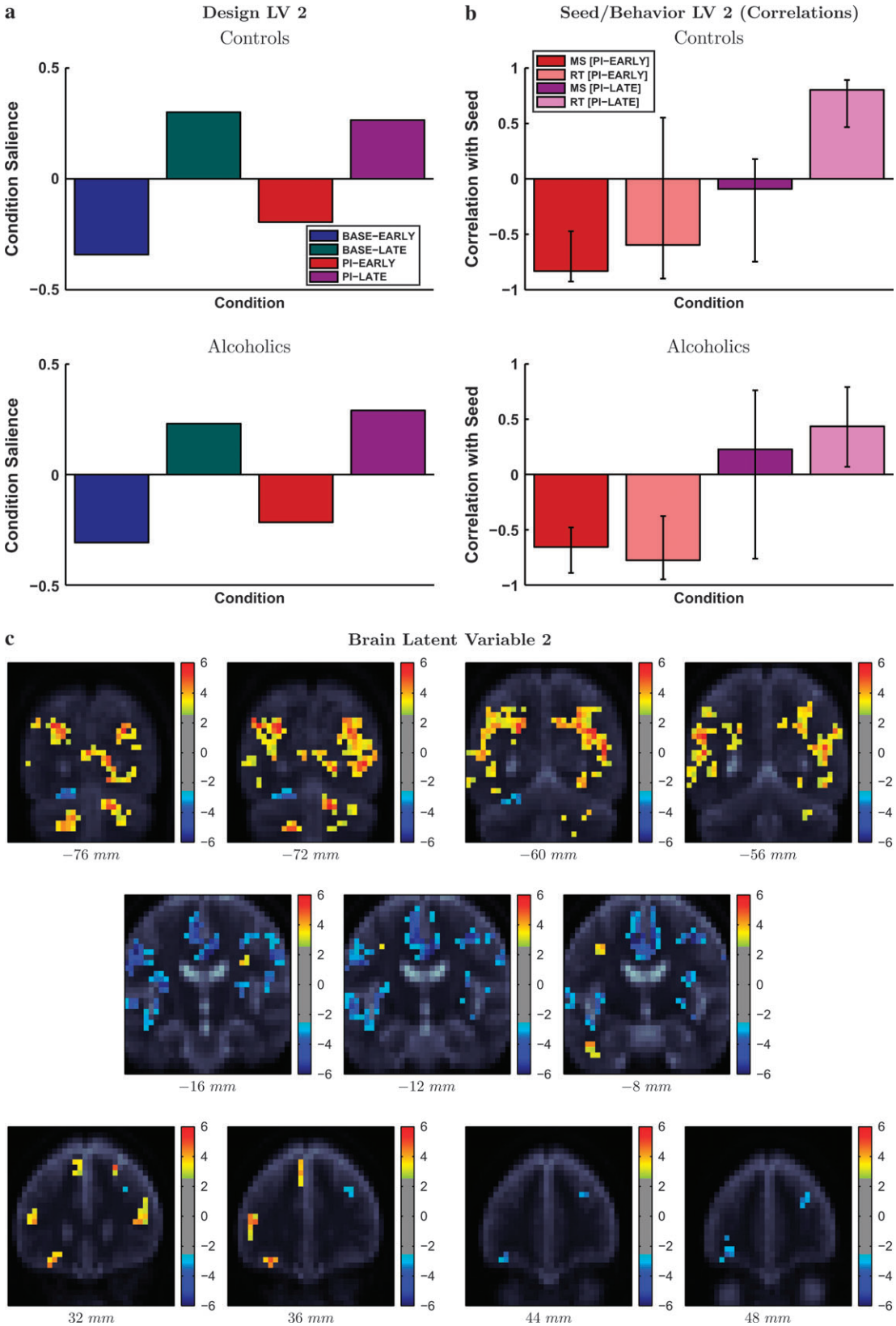

Figure 4. Latent variable #2. (*a*) Design LV 2. Saliences reflect differences in the pattern activity of the brain LV as a function of condition. (*b*) Behavior/seed LV 2. Each bar plots the correlation with MS/DB (left bar of each pair) and RT (right bar of each pair) as a function of PI condition and participant group. Error bars denote 95% confidence intervals based on the permutation test. (*c*) Brain LV 2. Voxels meeting the cluster-analysis criteria (single-voxel bootstrap ratio ⩾2.58 min cluster size = 15 voxels) are plotted superimposed on the average anatomical scans from all 24 participants. The color scale denotes the bootstrap ratio in the range –6 (cool colors) to +6 (hot colors).

The brain LV is summarized in Table 4 and plotted in Figure 4c superimposed on average anatomical scans from all 24 participants. Relative activation of those regions with negative salience was associated with better resolution of PI as evidenced by fast RTs during PI-LATE. The regions in the brain LV with negative saliences included areas previously found to be active during PI conditions in alcoholics, for example, anterior cingulate cortex and lateral orbitofrontal cortex, and the regions with positive saliences included areas previously found to be active during PI conditions in controls, for example, intraparietal sulcus and lingual gyrus. It has been shown that the anterior cingulate cortex is involved in more executive processes, like response selection (Turken and Swick 1999) and error monitoring (Carter and others 1998; Holroyd and others 2004).

As with LV 1, we asked whether participants were activating the brain LV in PI-EARLY and deactivating it in PI-LATE, or vice versa. However, the correlation between brain scores for PI-EARLY and PI-LATE was significantly positive (alcoholics: $r(10) = 0.80$, $P < 0.005$; controls: $r(12) = 0.80$, $P < 0.005$), again suggesting that participants invoke one strategy exclusively through PI resolution such that they either activate the positive-salience regions and deactivate the negative-salience regions during both PI-EARLY and PI-LATE, or deactivate the positive-salience areas while activating the negative-saliences areas during both PI-EARLY and PI-LATE. Thus, participants do not invert the activity of this brain LV pattern, but rather, its correlation with MS/DB and RT changes from early to late PI conditions.

In sum, LV 2 identified a distributed pattern of brain activity that describes both alcoholics and controls well, in contrast to the control-specific LV 1. The network is functionally coupled with the MS/DB early in exposure to PI pairs but becomes decoupled from the MS/DB when PI has been successfully resolved. Especially for alcoholics, the larger the magnitude of PI, the more the negative-salience portions of this network are initially activated (while positive-salience regions are reduced in activity) and the better the PI is ultimately resolved.

Negative-salience areas included additional executive control areas not present in LV 1, namely, left anterior cingulate and lateral orbitofrontal cortex. Thus, although alcoholics' compromised MS/DB seems to limit their ability to rely on the MS/DB-dependent LV 1 network, the LV 2 network (also implicated in controls) may serve as a critical alternate strategy.

Table 4
Significant clusters identified for LV 2

Cluster region	X	Y	Z	Size	Bootstrap
LV 2	Positive salience				
1 L inferior frontal sulcus	−28	20	32	202	8.0
2 R angular gyrus	44	−60	16	516	7.0
3 R inferior frontal sulcus	32	20	24	55	6.7
4 L supramarginal gyrus	−48	−40	32	360	6.2
5 R superior temporal gyrus	32	12	−28	48	5.9
6 L lateral orbital gyrus	−28	28	−24	39	5.8
7 R cerebellum	12	−72	−28	54	5.7
8 L anterior cingulate	−8	20	44	38	5.7
9 L cerebellum	−16	−68	−44	44	4.9
10 R middle frontal gyrus	20	32	48	36	4.7
11 L inferior occipital sulcus	−40	−64	−16	29	4.5
12 R supramarginal gyrus	40	−40	36	17	4.5
13 R central sulcus	28	−20	28	28	4.4
14 L intraparietal sulcus	−24	−100	4	34	4.4
15 L inferior temporal sulcus	−44	−8	−32	16	4.1
16 R cerebellum	28	−68	−44	16	3.9
17 L middle temporal gyrus	−60	−48	0	16	3.4
	Negative Salience				
18 R anterior cingulate	4	−4	48	214	8.3
19 R superior temporal gyrus	56	−36	24	98	6.5
20 L superior temporal gyrus	−60	−24	24	272	6.3
21 R insula	28	−20	4	47	6.0
22 R middle frontal gyrus	36	−8	48	31	6.0
23 R insula	40	4	−8	63	5.5
24 L cerebellum	−28	−40	−32	21	5.3
25 Superior colliculus	−8	−32	−16	33	5.3
26 R middle frontal gyrus	24	52	20	16	5.2
27 L lingual gyrus	−24	−76	−20	37	5.1
28 L lateral orbital sulcus	−20	64	0	56	4.8
29 Pons	−8	−36	−40	16	4.7

Note: *X*, *Y*, and *Z* coordinates are in millimeters according to the MNI standard. "Size" denotes cluster size in number of voxels. "Bootstrap" refers to the bootstrap ratio, which indicates robustness across participants.

Absolute RTs

We next investigated (and ruled out) a potential alternate explanation of the correlations with RT. The measures of RT were difference measures deliberately chosen to target those aspects of performance that reflected the level of PI experienced in PI-EARLY and the degree to which interference was successfully resolved in PI-LATE. However, it is possible that the functional networks identified relate in a more generic way to overall response speed. We correlated the brain scores (projection of brain LV onto each participant's brain activity) for each condition with absolute RTs, for conditions PI-EARLY and PI-LATE, of both groups. For LV 1, Spearman correlations ranged between –0.22 and +0.31 and were all nonsignificant ($P > 0.3$). For LV 2, Spearman correlations ranged between –0.45 and +0.13 and were also all nonsignificant ($P > 0.1$). Thus, we can rule out the alternate interpretation that the functional networks identified in the 2 LVs primarily drive RTs independent of PI-relevant behavior.

Early versus Late Activity

We next sought to understand the shifts from early to late conditions. Both design LVs contrast late conditions with early conditions. This raises the possibility that the brain LVs represent patterns of activity that reflect general practice. This alternate account leads to the prediction that the presence of brain LV activity should increase monotonically in the following rank order: BASE-EARLY < PI-EARLY < BASE-LATE < PI-LATE (or the reverse ranking). However, when one projects the brain LVs onto individual participants' brain activity to obtain brain scores, mean brain scores conform to this rank order for alcoholics but not for controls. This rules out the account that brain LVs 1 and 2 change simply with overall practice, without regard to conditions (PI vs. BASE).

The correlation between the brain LV and RT flips direction between PI-EARLY and PI-LATE for controls in LV 1 and for both controls and alcoholics in LV 2. However, recall that the RT measure has different implications for PI-EARLY than for PI-LATE. For PI-EARLY, the RT measure compares the RT during PI-EARLY with the RT during BASE-EARLY. Thus, this RT reflects the degree to which the participant expresses PI. For PI-LATE, the RT measure compares the RT during PI-LATE with the RT during BASE-LATE. Thus, this RT reflects the degree to which PI has been successfully resolved. A positive correlation with the RT measure for PI-EARLY indicates the network being invoked increasingly with increased expression of PI. A negative correlation with the RT measure for PI-LATE indicates the network being invoked increasingly with increased resolution

of PI. This seems fully consistent with what one would expect of a network that is both invoked in order to address PI and ultimately succeeds at resolving this PI.

Separate-Group Analysis

We next attempted to tease apart group commonalities versus group differences. When one applies the PLS to both groups simultaneously, one group could be dominating the analysis overall, or else each group might be principally responsible for a different LV. To further clarify the results we performed a follow-up analysis applying the identical multiblock PLS as before but for controls and alcoholics separately. This would enable us to identify LVs that best describe each group on its own.

By computing the correlation between the first 2 LVs and the first 2 LVs from the group analysis we can ask whether the control-specific LVs are similar or different than the group LVs. The correlation was computed as the dot product between 2 brain LV salience vectors. The control-only first LV (Fig. 5*a*,*b*) had a correlation of 0.98 with the group LV 1 and their second LV (Fig. 5) had a correlation of 0.71 with the group LV 2. Thus, the group LVs correspond closely with the control-only LVs. The alcoholic-only first LV (Fig. 5*e*,*f*) was dissimilar to LV 1 of the group analysis (correlation of 0.07) but had a high correlation (0.70) with LV 2 of the group analysis. Both correlations for the alcoholics' second LV (not plotted) were under 0.25. This suggests that the group analysis reflects the 2 networks that are at play in controls. Although alcoholics have evidence of both networks when they are included in the control-dominated group analysis (albeit with different functional connectivity and behavioral relevance), they are best described primarily by the network identified in LV 2.

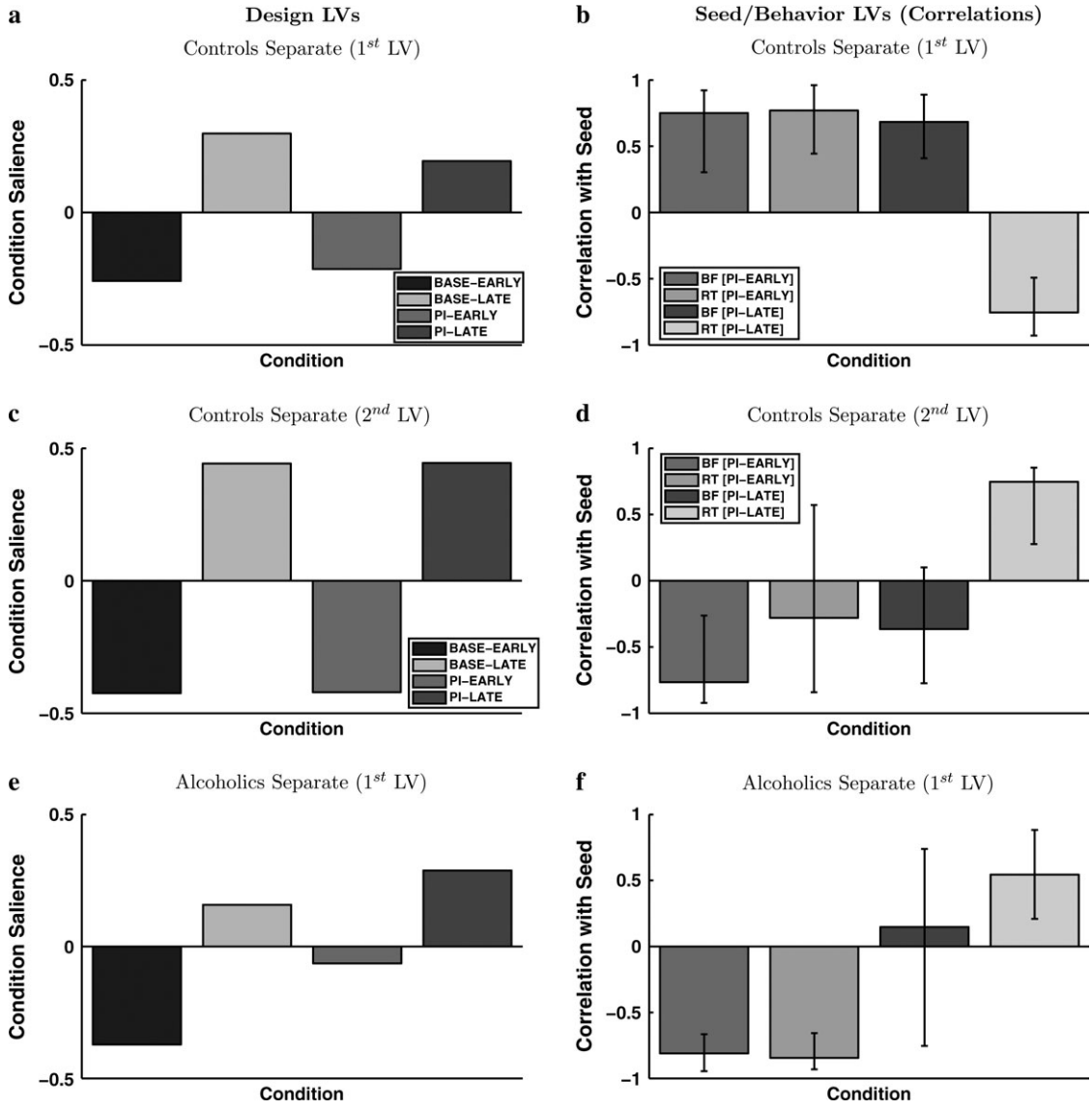

Figure 5. Separate-Group analyses. Design LVs and behavior/seed LVs are plotted for the separate-group analyses. Controls-only analysis, first LV (*a* and *b*) is similar to LV 1 from the combined analysis (cf. Fig. 3). Controls-only analysis, second LV (*c* and *d*) is similar to LV 2 from the combined analysis (cf. Fig. 4). Alcoholics-only analysis, first LV (*e* and *f*) is similar LV 2 from the combined analysis (cf. Fig. 4). Design LVs: Saliences reflect differences in the pattern activity of the brain LV as a function of condition. Behavior/seed LVs: Each bar plots the correlation with MS/DB (left bar of each pair) and RT (right bar of each pair) as a function of PI condition and participant group. Error bars denote 95% confidence intervals based on the permutation test.

Discussion

Electrophysiological data and computational modeling (Hasselmo and Bower 1993; Hasselmo and Schnell 1994; Hasselmo and McGaughy 2004), rat pharmacology and immunotoxic lesion experiments (De Rosa and Hasselmo 2000; De Rosa and others 2001), human pharmacology (Atri and others 2004) and an univariate analysis of human fMRI data (De Rosa and others 2004) all point to the notion that the modulatory influence from the BF is critical for efficient resolution of PI. Our current findings confirm the importance of cholinergic neuromodulation to interference resolution, revealing that the MS/DB nuclei of the BF specifically form a functional network with attention and mnemonic areas activated during resolution of PI. Our current findings also implicate a second network, operational in control participants, that becomes especially important when BF function is compromised (namely, in alcoholics). Further, our findings suggest that participants with compromised MS/DB function invoke this alternate network whose functional connection to the MS/DB is not necessary for PI resolution.

The multiblock PLS approach, in the spirit of the approach suggested by Thiel (2003), enabled us to identify functional networks testing 2 properties: 1) whether the regions covaried with a cholinergic modulatory source (i.e., MS/DB) and 2) whether the presence of the networks covaried with performance (RT slowing due to the presence of PI and RT recovery upon resolution of PI). We were able to confirm both properties.

Latent Variable 1

Many of the brain regions identified in the functional networks here were previously found to exhibit elevated *average* activity with univariate analyses in controls (De Rosa and others 2004). Further, the positive-salience regions associated with the first LV included right hippocampus, a direct target of cholinergic modulation from the MS/DB (Mesulam and others 1983; Ghashghaei and Barbas 2001). This brain LV, especially frontal areas and precuneus, also resembled a pattern of activity found while participants overcome prepotent responses (Barber and Carter 2005). The heavy involvement of bilateral insula may reflect general response inhibition processes as identified by Wager and others (2005). Anterior cingulate cortex activity may relate to response selection (Turken and Swick 1999) or online monitoring of errors (Carter and others 1998; Holroyd and others 2004).

The hypothesis that hippocampal activity would covary with MS/DB function and PI resolution was confirmed (LV 1), supporting Hasselmo and Schnell's (1994) cholinergically mediated interference-handling model. It is also consistent with substantial prior evidence that the hippocampus underlies learning of associations (Rudy and Sutherland 1989, 1995; O'Reilly and McClelland 1994; O'Reilly and Rudy 2001; Gilbert and Kesner 2002; Frank and others 2003; Van Elzakker and others 2003) including human neuroimaging studies (Henke and others 1997; Sperling and others 2003; Giovanello and others 2004; Kirwan and Stark 2004; Meltzer and Constable 2005) as well as data from hippocampal amnesic patients (Holdstock and others 2002; Mayes and others 2004). Winocur and others (1996) found hippocampal lesions in humans to be particularly disruptive to implicit tests associative memory involving associative interference, which are properties of the present task.

An alternate interpretation of the functional coupling of the task-relevant regions is that cholinergic modulation from the MS/DB may induce theta oscillations in its target areas. MS/DB induces theta oscillations in rats in the hippocampal formation (Bland 1986) and theta oscillations have been found in humans during learning tasks in neocortex (Kahana and others 1999; Raghavachari and others 2001; de Araújo and others 2002; Caplan and others 2003) and in hippocampus (Ekstrom and others 2005). Thus, if the MS/DB covariance with the LV 1 network reflects the induction of theta oscillations, then theta-related function may underly the facilitation of PI-resolution behavior, including facilitating stimulus–response learning (Seager and others 2002; Griffin and others 2004), enhancing stimulus discriminability (Cleland and Linster 2002) or subserving efficient sensorimotor integration (Komisaruk 1977; Bland 1986; Caplan and others 2003), or more general functions of attention and mnemonic integration.

The left ventrolateral prefrontal cortex (vlPFC), identified in this LV, has been implicated in prior studies of PI (Jonides and Nee 2005). Jonides and others (1998) found this region specifically during presentation of recent negatives in a recognition memory task in a block-design positron emission tomography study. D'Esposito and others (1999) replicated this finding in an event-related fMRI study and suggested that this region relates to response inhibition, consistent with Wager and others (2005). Postle and others (2001, 2004) suggested that this region underlies handling of both item-specific and item-nonspecific PI. Badre and Wagner (2005) implicated this region in overcoming interference from recent nontargets in a recognition memory task. These studies used tasks involving more explicit memory than the implicit learning task examined here. It is possible that our brain LV 1 represents a network that nonetheless relies partially on explicit processing. Alternatively, the activity of the vlPFC may underlie more implicit aspects PI.

Latent Variable 2

Control participants recruited both the MS/DB-dependent functional network (LV 1) and a second, network that was independent of the MS/DB for resolution of PI (although a functional connection to the MS/DB was present in early experience of PI). In the face of a compromised MS/DB, the alcoholics did not reliably recruit the MS/DB-dependent LV 1 network but did recruit the LV 2 network which may not rely on cholinergic modulation from the MS/DB. The areas in the second LV generally excluded cholinergic targets of the MS/DB. Instead it included executive regions commonly found in more cognitively demanding interference tasks, including lateral orbital gyrus and anterior cingulate (Henson and others 2002). This secondary network, in the absence of the MS/DB-dependent LV 1 network, may have enabled to alcoholics to achieve control levels of performance. This brain LV, especially frontal areas, also resembled a pattern of activity found while participants overcome prepotent responses (Barber and Carter 2005).

One might be tempted to interpret this second LV as a latent network that is inactive until such time as the first LV network is unavailable. However, if that were the case, it would be difficult to identify it in controls. In contrast, our findings suggest that control participants may have 2 alternate networks at their disposal, whereas alcoholic participants have only the second LV network.

The primary dependence of the patient population on LV 2, an alternate network to the MS/DB network, is comparable with the data of rats after receiving selective cholinergic immunotoxic lesions of the BF nuclei (De Rosa and others 2001). The immunotoxic-lesioned 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 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 challenged the resources available to the nonamnesic alcoholic patients, for example, a global pharmacological challenge or an executive resource challenge, the PI effect of the alcoholics would have been exacerbated relative to controls. Finally, our data do not suggest that the BF was completely impaired in alcoholics. Rather, consistent with the lack of volumetric differences in BF between alcoholics and controls, and also consistent with postmortem data, it is primarily the cholinergic function of the BF, not the entire integrity of the BF that is compromised in these patients. Thus, the BF might be subserving certain functions, but evidently not the PI-resolving function that is the focus of our study, which presumably relies on the integrity of the cholinergic function of the BF.

Conclusion

The results of the PLS analysis are quite consistent with the prior, univariate findings reported by De Rosa and others (2004). However, they move beyond those prior findings in several ways. First, simultaneous activation of brain regions does not necessarily imply a functional network. Beyond simultaneous activation, the 2 sets of brain areas identified here modulate their activity together, along with RT measures of performance. Thus, we suggest that the 2 brain LVs identified here comprise functional networks, not simply a set of regions that act independently. Second, prior univariate analyses pointed to 2 networks for resolving PI but what was not known was whether both networks were represented in both controls and alcoholics versus each network being exclusively relevant to a single participant population. The fact that we included group as a factor in the PLS analysis allows us to answer this question directly. Specifically, the first, MS/DB-dependent, functional network is present in controls but is not reliably reflected in alcoholics. In contrast, the second functional network is comparably represented in both participant groups. Thus, we can conclude that the second network does not reflect simply an alternate strategy that is used when the first network fails but a secondary, comparably valid network that is functioning in controls anyway; this second network is simply the *only* strategy available to alcoholics. Third, although it was expected that the hippocampus should be essential to performance on task, its involvement was not observed in prior analyses that considered only changes in mean activity levels. Here we found that the variability of hippocampal activation about its mean is meaningful and, in particular, that it appears to participate in a functional network involving the MS/DB, a specific generalization of a neuromodulatory functional pathway from the rat.

Taken together, our analyses identified 2 distinct, but not necessarily mutually exclusive, networks for the resolution of PI. The first network shows that the involvement of the MS/DB and a network dependent on cholinergic modulation, including hippocampus and vlPFC, for efficient resolution of PI is preserved across species. The second network consisted of more executive-function areas including lateral orbitofrontal cortex. For cases in which the first network is disrupted due to compromised MS/DB function, human participants can rely more exclusively on a second network independent of MS/DB-mediated cholinergic modulation and achieve adequate performance in situations with PI.

Notes

We thank Edith V. Sullivan, Adolf Pfefferbaum, John E. Desmond, Adam K. Anderson, and National Institute on Alcohol Abuse and Alcoholism for their support. This project was supported by a Canadian Institutes of Health Research grant to A.R.M. and Natural Sciences and Engineering Research Council of Canada and Canada Foundation for Innovation/Ontario Innovation Trust grants to E.D.R. *Conflict of Interest*: None declared.

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