Modulation of limbic-cerebellar functional connectivity enables alcoholics to recognize who is who

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Abstract

Chronic alcoholism is known to disrupt functions served by distributed brain systems, including limbic and frontocerebellar circuits involved in resting-state and task-activated networks subserving component processes of memory often affected in alcoholics. Using an fMRI paradigm, we investigated whether memory performance by alcoholics on a face-name association test previously observed to be problematic for alcoholics could be explained by desynchronous activity between nodes of these specific networks.

While in the scanner, 18 alcoholics and 15 controls performed a face-name associative learning task with different levels of processing at encoding. This task was designed to activate the hippocampus, cerebellum, and frontal cortex. Alcoholics and controls were also scanned at rest.

Twelve alcoholics and 12 controls were selected to be matched on face-name recognition performance. Task-related fMRI analysis indicated that alcoholics had preserved limbic activation but lower cerebellar activation (Crus II) than controls in the face-name learning task. Crus II was, therefore, chosen as a seed for fcMRI analysis. At rest, the left hippocampus and left Crus II had positively synchronized activity in controls, while hippocampal and cerebellar activities were negatively synchronized in alcoholics. Task engagement resulted in hippocampal-cerebellar desynchronization in both groups.

We speculate that atypical cerebello-hippocampal activity synchronization during rest in alcoholics was reset to the normal pattern of asynchrony by task engagement. Aberrations from the normal pattern of resting-state default mode synchrony could be interpreted as enabling preserved face-name associative memory in alcoholism.

Author Keywords Functional magnetic resonance imaging ; functional connectivity ; alcohol ; associative learning ; hippocampus ; cerebellum.

Introduction

Understanding the neurocircuitry that underlies normal and adaptive behaviors is a foundation for elucidating the pathology and pathophysiology of neuropsychiatric diseases. Recent functional imaging and electrophysiological studies note marked dysfunction of network synchronization and desynchronization in a number of neuropsychiatric conditions (Haber and Rauch 2001). Abnormal synchronization of the spontaneous fluctuations of resting-state brain networks, notably the Default Mode Network (DMN) (Fox and Raichle 2007; Raichle et al. 2001), has been reported in schizophrenia (Rotarska-Jagiela et al. 2010), bipolar disorder (Ongur et al. 2010), Alzheimer's disease (Zhou et al. 2010), autism (Assaf et al. 2010), and youth with a family history of alcoholism (Herting et al. 2011). A recent study conducted in alcoholics (Chanraud et al. 2011) revealed lower regional brain synchronization in the DMN at rest but greater synchronization in the same circuit during a spatial working memory task, suggesting that compensatory mechanisms were involved in the resynchronization of this circuit when necessary for performing on the task (Chanraud et al. 2012). Compared with controls, greater midbrain-orbitofrontal but poorer corticocortical functional connectivity has been found in alcoholics while performing a Stroop Match-to-Sample task (Schulte et al. in Press). These findings have also been interpreted as neuro-functional compensation.

Modulation of the level of brain synchronization from rest to task (Hampson et al. 2004; Jiang et al. 2004; Morgan and Price 2004) indicates that task engagement can modify hemodynamic coupling between regions. Functional brain networks reorganize while performing a task, resulting in changes in neuronal synchrony (Engel et al. 2001; Varela et al. 2001). Thus, abnormalities in brain synchronization at rest or dysfunction in the desynchronization of these regions from rest to task may underlie, or at least serve as markers for, behavioral symptoms observed in neuropsychiatric disorders. The goal of the present study was to monitor modulation of functional connectivity from rest to task between regions involved in two different brain networks described as structurally and functionally altered in alcoholism: the limbic system (Marinkovic et al. 2009; Pitel et al. 2009) and frontocerebellar circuitry (Chanraud et al. 2010; Sullivan et al. 2003).

The limbic system comprises the thalamus, mammillary bodies, amygdala, cingulate gyrus, nucleus accumbens, fornix, and hippocampal formation (Papez 1937). This anatomical network is part of the “reward system” that includes dopamine-releasing neurons, considered crucial in reinforcing behavior and in consolidating memory habit formation, therefore possibly contributing to the

development and maintenance of alcohol dependence (Everitt and Robbins 2005; Koob and Volkow 2010; Makris et al. 2008; Soderpalm et al. 2009). Limbic system nodes mediate aspects of emotional learning and facilitate memory operation, with the hippocampus playing a key role in episodic (Desgranges et al. 1998; Dickerson and Eichenbaum 2010; Milner 1959) and associative memory (Staresina and Davachi 2009). Alcoholism-related structural abnormalities have been reported in the hippocampus (Beresford et al. 2006; De Bellis et al. 2000; Sullivan et al. 1995) and may contribute to impairments in episodic memory (Pitel et al. 2007) and face-name association learning (Becker et al. 1983; Schaeffer and Parsons 1987).

Nodes of frontocerebellar circuitry include the prefrontal cortex and cerebellum, which are particularly sensitive to the harmful effects of alcoholism (postmortem: Harper and Kril 1990; in vivo: Zahr et al. 2010). A constellation of cognitive and motor deficits typically described in alcoholics has been related to abnormalities of this circuitry (Chanraud et al. 2010; Sullivan et al. 2003). Neuroimaging studies implicate cerebellar involvement in augmenting performance and compensating for functional deficits in adolescent (Tapert et al. 2004) and adult alcohol abusers and dependents (Chanraud et al. 2011 and 2012; Sullivan and Pfefferbaum 2005; Zahr et al. 2010). Recent findings also indicate a cerebellar involvement in memory processing (Marvel and Desmond 2010; Schmahmann 2010) and potentially in associative learning (Drepper et al. 1999). The role of the frontal cortex in memory processing is well known (Blumenfeld and Ranganath 2007; Fletcher and Henson 2001; Rugg et al. 2002) and can be promoted by manipulating the level of processing at encoding. Deeper processing (e.g., the meaning of a word) at encoding results in enhanced memory performance (Craik and Lockhart 1972) and greater activation of the prefrontal cortex relative to shallow processing (e.g., the sound of a word) (for reviews, Buckner et al. 2000; Nyberg 2002).

Recently, we showed that face-name association learning is impaired in alcoholism, and that even though the level of processing at encoding had little effect on recognition performance, correlations with regional brain volumes differed depending on the encoding condition (Pitel et al. in press). To elucidate the functional networks and compensatory activities involved in executing this task, we conducted the functional magnetic resonance imaging (fMRI) experiment of face-name association learning described herein in alcoholics and controls. Our goals were to examine in new groups of alcoholics and controls, matched on age, IQ, and face-name learning performance, whether 1) associative learning conducted with a depth of processing paradigm would differentially activate limbic and frontocerebellar nodes in the two groups despite similar behavioral performance levels; and 2) functional connectivity magnetic resonance imaging (fcMRI) would distinguish the groups at rest but would show re-synchronization with engagement in the task, suggesting presence of compensatory mechanisms. We expected alcoholics and controls to show different patterns of activations evoked by the task in hippocampal and cerebellar regions, with the hippocampus being involved in the binding and long-term memory processes and the cerebellum having modulatory (Fitzpatrick et al. 2008) and compensatory (Zahr et al. 2010) roles. Given that the hippocampus and cerebellum are both potentially involved in the resting-state network (Andrews-Hanna et al. 2010; Habas et al. 2009) and recognizing their role in the two different task-related targeted networks herein, we expected to observe coupled cerebello-hippocampal activity at rest and decoupled activity during the task in controls. Based on previous studies showing abnormal resting-state functional connectivity in alcoholics (Chanraud et al. 2011; Kim et al. 2009) and compensatory mechanisms engaged in brain regions synchronization while tasking, we expected to find in alcoholics altered cerebello-hippocampal synchronization at rest with synchronization resetting when engaged in the task.

Material and Methods

Subjects

Of the 15 control and 18 alcoholic men recruited and examined, we selected 12 alcoholics and 12 controls matched in age and performance. Alcoholics were recruited from community treatment centers, outpatient clinics, and hospitals. Controls were recruited from the local community. All participants provided written informed consent and received a modest stipend for study participation. Diagnosis was determined by consensus of at least two calibrated interviewers (clinical research psychologists or research nurse) who used the Structured Clinical Interview for DSM-IV (SCID (First et al. 1995). Schizophrenia or bipolar disorders were exclusionary criteria. Estimated lifetime alcohol consumption was quantified using a modification (Pfefferbaum et al. 1988) of a semi-structured, time-line interview (Skinner 1982; Skinner and Sheu 1982). Drinks of each type of alcoholic beverage were standardized to units containing approximately 13.6g of alcohol and summed over the lifetime. Lifetime alcohol consumption was 20 fold higher in the alcoholic than control group (Table 1). Controls and alcoholics were matched on age, education and NART IQ (Nelson 1982). All were right-handed (Crovitz and Zener 1962). None of the participants had participated in our previous behavioral experiment (Pitel et al. in Press).

Behavioral paradigm during the fMRI acquisition

We modified and simplified the paradigm used in our previous behavioral study to accommodate the constraints of fMRI implementation (See Figure 1). The associative learning task involved learning of 14 unfamiliar faces arbitrarily paired with fictional last names (Pitel et al. in Press). Stimuli were presented by E-Prime® software (Psychology Software Tools Inc., Pittsburgh, PA). Subjects

used a keypad connected to the laptop running E-prime (http://www.pstnet.com) to perform the tasks according to the instructions. Before going into the scanner, all the participants practiced the face-name learning task until the experimenter (ALP) was confident they had understood the instructions and had reached a satisfactory level of performance.

The stimuli were organized in a block design paradigm, comprising 4 pseudo-randomized runs (Shallow/Shallow/Deep/Deep or Deep/Deep/Shallow/Shallow). Each run consisted of 3 blocks, with the first block being the encoding task, the second one being the perceptual task, and the third one the associative recognition task. The order of the blocks was not randomized to ensure the same delay between encoding and recognition for every subject. The encoding task entailed face-name association encoding during which subjects had to memorize which name was associated with which face. While memorizing the face-name association, subjects had to indicate whether the face represented an honest person [deep encoding (Bower and Karlin 1974)] or whether it was that of a man (shallow encoding). The perceptual task was a reaction time task that used the identical procedure but replaced the last names by the word "NAME" thereby minimizing association. During this task, subjects had to press a key as quickly as possible each time a face was presented. To avoid a habituation effect, the faces used in this task were different from those used in the memory tasks. The associative recognition task involved presentation of three face-name associations with only one correct pairing. The encoding, perceptual, and associative recognition tasks were performed in the scanner. An additional single-item (face and name) recognition task was performed outside of the scanner, immediately following the fMRI scan. This task consisted of randomized single-item recognition, during which subjects saw either three faces or three names (one target and two distractors) and decided which of the three had been presented during the encoding task. The distractors were chosen to be similar to the target: same sex, age and ethnicity for faces, and two identical first letters for last names. Figure 1 depicts the fMRI paradigm. Accuracy and reaction time (RT) for all answers were recorded.

MR Scanning Procedures and Analyses

Brain Data Acquisition

Images were collected on a 3T (General Electric Medical Systems, Signa, Waukesha, WI, USA) whole-body MRI scanner with an 8-channel head coil. Whole-brain fMRI data were acquired with a gradient echo-planar pulse sequence (axial, mode = 2D, Scan timing: TE = 30 ms, TR = 2200 ms, flip angle = 90°, matrix = 64 × 64, slice thickness = 5 mm, 36 slices). The first run consisted of a resting-state condition (4:57 min; eyes closed). Then 4 pseudorandomized runs of the task (4:07 min, 4032 functional images each), synchronized with the beginning of fMRI volume acquisitions, were acquired. Each block consisted of 2 TRs for instructions and 26 TRs for task. Also acquired were a dual-echo fast spin-echo anatomical scan (axial acquisition; TE = 12/98 ms, TR = 5000 ms, FOV = 24 cm, 256 × 192 matrix, NEX = 1.0, slice thickness = 5 mm, 36 slices) and a field map, generated from a gradient recalled echo sequence pair (TE=3/5ms, TR = 460ms, slice thickness=2.5 mm, 62 slices).

fMRI preprocessing

The first two volumes of each run were discarded to allow for signal equilibration. Image spatial preprocessing and statistical analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology). Functional images were realigned for motion correction, and functional runs in which a subject moved more than 2mm in any direction were excluded from the analysis. Then, functional images were unwarped (correction for fields distortions) using the gradient echo field maps (constructed from the complex difference image between 2 echoes (3 and 5 ms) of the gradient-recalled echoes series). Unwarped functional images were coregistered to structural images for each subject. The anatomical volume was then segmented into gray matter, white matter, and cerebrospinal fluid. The gray matter image was used for determining the parameters of normalization onto the standard Montreal Neurological Institute (MNI) gray matter template. The spatial parameters were then applied to the realigned and unwarped functional volumes that were resampled to voxels of 3 × 3 × 3 mm and smoothed with an 8mm full-width at half-maximum Gaussian smoothing kernel.

Task-Related fMRI Analyses: Comparison of BOLD Signals

We first generated contrasts for each subject. Because the perceptual and encoding tasks used exactly the same procedure, the perceptual load of the two tasks was identical. Therefore, the perceptual task was an appropriate condition to contrast to the encoding condition for examining activations specific to memory processes. The perceptual condition was also used as a control condition for the recognition task. The following contrasts were computed: Shallow Encoding-Perception; Deep Encoding-Perception; Shallow Recognition-Perception; Deep Recognition-Perception. In a second level random effects analysis, we employed a factorial design with the group (controls versus alcoholics), memory task (encoding versus recognition), and depth of processing at encoding (shallow versus deep) as main factors. Because groups were matched in performance, a height threshold of $p<.001$ uncorrected was applied (see Table 2 for more details).

Functional Connectivity Analyses at Rest and during Task

A connectivity analysis for rest and task trials considered separately was conducted on preprocessed fMRI data with the "conn" toolbox (Benjamin et al. 2010), implemented in SPM8. Correlational analyses between the BOLD signal from a seed selected a priori and every other brain voxel provided seed-to-voxel connectivity estimations. The seed was taken from the Tzourio-Mazoyer template

(Tzourio-Mazoyer et al. 2002) and corresponded to the region that showed between-groups difference in activation during the task. This analysis was conducted on 135 TRs for the rest and on 52 TRs (26 TRs of encoding + 26 TRs of recognition tasks) for the task. Before averaging individual voxel data, the waveform of each brain voxel was filtered using a bandpass filter (.0083/sec < f < .15/sec for the rest and .0083/sec < f <infinite for the task). Several sources of spurious variance along with their temporal derivatives were then removed from the data through linear regression, namely, the signal from ventricular regions and that from the white matter. Global signal was not included as a regressor, given evidence that this may introduce spurious negative correlations into the data (Murphy et al. 2009). The negative correlations that could have been observed would, therefore, have been misinterpreted as having a biological basis. Because further steps included between-groups comparisons, temporal connectivity maps were generated for each subject. These images were then included in a second-level between-groups, random-effects analysis. The magnitude and extent of temporal connectivity between the groups were thresholded using a p< .05 FDR (false discovery rate) corrected with a minimal cluster of 10 voxels.

Results

Behavioral Results

RT in the Perceptual and Encoding Tasks

The ANOVA revealed a significant effect of processing level effect [F(2,66)=40.72; p<.001] but neither a group effect [F(1,66)=1.88; p =.18] nor a group-by-task interaction [F(2,66)=.02; p=.98]. Follow-up t-tests indicated shorter RT for shallow than deeply encoded associations and even shorter RT in the perceptual task in both groups (p<.01 in each case; Figure 2A).

Accuracy and RT in the Associative and Single-Item Recognition Tasks

The ANOVA for accuracy showed significant effects of stimulus [F(2,132)=92.48; p<.001], with associative recognition scores lower than in the single-item recognition (p<.001 in each case), and name recognition scores lower than face recognition but only at a trend level (p=.059). There was no significant effect of group [F(1,132)=.68; p=.41], depth of processing at encoding [F(1,132)=.81; p=.37], or interaction (all p values >.05, Figure 2B).

The ANOVA for RT revealed a significant effect of stimulus [F(2,132)=36.00; p<.001] with RT in associative recognition longer than in single item recognition. There was no significant effect of group [F(1,132)=.03; p=.87] or depth of processing at encoding [F(1,132)<.01; p=.99] and no interaction (Figure 2C).

In summary, these results indicate that the groups did not differ significantly in any performance measure on any test condition.

fMRI and fcMRI Results

Task-Related fMRI Activations

The factorial analysis (group x memory task x depth of processing) revealed a significant effect of group for the left cerebellar Crus II, which was more activated in controls than alcoholics. A significant effect of memory task indicated greater activation in both groups in the recognition than encoding task in bilateral calcarine, lingual and fusiform gyri, superior cerebellar cortex, bilateral angular and precentral gyri, parietal and frontal cortices, right middle cingulate, caudate and left hippocampus. There was also a significant effect of depth of processing, with the right superior temporal pole being more activated in shallow versus deep, and the left superior medial frontal gyrus more activated in deep versus shallow. A significant group-by-depth of processing interaction was present in bilateral inferior orbitofrontal gyrus, cingulate gyrus, and left inferior parietal cortex, with a greater activation in these regions for deep than shallow in controls but not alcoholics (Figure 3; Table 2).

Functional Connectivity

The left cerebellar Crus II was less activated during the association task in the alcoholics than controls and, therefore, was chosen as a seed for the functional connectivity analysis. When exploring the internal architecture of this region in the two groups by examining correlations of the spontaneous fluctuations at rest between this seed and all other brain voxels, we found that at rest only connectivity between the left hippocampus and left Crus II was lower in the alcoholics than controls (t=7.10; p=.007 FDR corrected; peak coordinate: x =−15, y=−13, z=−20; k=54; Figure 4). During the task, the groups did not differ significantly in functional connectivity.

The strength of the functional connectivity between the left cerebellar Crus II and the left hippocampus was extracted using MarsBaR (Brett et al. June 2–6, 2002) for each subject both at rest and during the task. The average correlation was significantly greater than 0 for the controls (t=6.428, p=.001) and significantly less than 0 for the alcoholics (t=−2.805, p=.017). We then conducted a group-by-condition (rest versus task) ANOVA on this connectivity measure to examine the modulation from rest to task within- and between-groups. ANOVA yielded a significant group effect [F(1,48)=18.97; p<.0001], a trend for the condition effect [F(1,48)=3.42; p=.07], and a significant interaction [F(1,48)=31.59; p<.0001]. Post-hoc Mann-Whitney tests confirmed the previous whole-brain fcMRI analysis with a significant

between-groups difference at rest (p<.0001) but not during the task (p=.20). Post-hoc Wilcoxon tests revealed a significant decrease in controls (p=.004) and a significant increase in alcoholics (p=.02; Figure 4) of connectivity between the left Crus II and left hippocampus from rest to task.

Next, we examined the relationships between connectivity at rest and during the task with respect to learning accuracy. Performance on the associative recognition after shallow encoding correlated positively with connectivity measures during the task in the controls (Rho =.65, p=.021) and negatively in the alcoholics (Rho=−.65, p=.023; Table 3). In the alcoholics, greater connectivity at rest correlated with better performance on the face (Rho=.81, p=.001) and name (Rho=.65, p=.022) recognition after deep encoding.

In the alcoholics, the strength of the connectivity between the left cerebellar Crus II and the left hippocampus at rest or during the task was not correlated with any drinking history variable, including duration of alcoholism, lifetime alcohol consumption, or length of sobriety (all p values >.20).

Discussion

Even though the hippocampus and cerebellum are involved in two anatomically distinct neural networks, these brain regions exhibited synchronized activity supportive of functional connectivity at rest in controls (Figure 5). The level of cerebello-hippocampal functional connectivity was modulated by engagement in an associative memory task, resulting in loss of synchronized activity from rest to task in controls. Unlike controls, alcoholics exhibited abnormal (i.e., negatively correlated) synchronization of cerebellar and hippocampal activity at rest, yet, like controls, exhibited desynchronized activity of these regions during task engagement. We speculate that engagement in the associative learning task reset and normalized these functional connectivity patterns by unlinking them, thereby enabling the alcoholics to perform on par with controls.

Cerebello-Hippocampal Connectivity at Rest

We examined regional architecture in health and alcoholism by focusing the functional connectivity analysis on the left cerebellar Crus II, which was diagnosis-sensitive during the task condition. At rest, activities of the left Crus II seed and the left hippocampus were synchronous and negatively correlated in alcoholics, whereas in controls, activities in these regions were synchronous and positively correlated (Figure 5 presents an hypothetical schema of these synchronous and desynchronous patterns.). This pattern of functional connectivity comports with prior studies indicating that the medial temporal lobe and the cerebellum are regions functionally connected in the DMN network (Habas et al. 2009 for the lobule IX of the cerebellum). The correlation between activities in these two regions was negative in the alcoholics at rest; a similar relationship had been previously observed and interpreted as a sign of “erroneous function in the network” (Kim et al. 2009) and adds evidence for DMN alteration in alcoholics (Chanraud et al. 2011).

Modulation of Cerebello-Hippocampal Connectivity from Rest to Task

In both groups, the level of functional connectivity between Crus II and hippocampus changed from rest to task, indicating modulation of brain synchronization by task engagement (Daniels et al. 2010; Jiang et al. 2004). Controls exhibited decreased functional connectivity from positively coupled activity at rest to decoupled activity during the task. This modulation of the level of connectivity between the two regions may reflect the switch from their involvement in the same network at rest to two different networks during the task. The hippocampus is well-known to be included in the brain network underlying episodic memory (Dickerson and Eichenbaum 2010), and Crus II of the cerebellum has been shown to be part of the executive control network (Habas et al. 2009). Alcoholics exhibited change in cerebello-hippocampal connectivity from being abnormal at rest (negatively correlated) to control-level decoupled activity during the task. That is, the pattern of rest-to-task functional connectivity modulation differed between the two groups and was accompanied by normal-level performance by the alcoholic group. Therefore, the modulation occurring from rest to task may reflect the presence of compensatory mechanisms enabling alcoholics to perform at control levels. This finding supports the role of the cerebellum in augmenting performance in controls (Desmond et al. 1997) and in compensating for functional deficits in alcoholics (Desmond et al. 2003; Chanraud et al. 2012).

Depth of Processing Effect on Neural Activity

Our results also showed a depth of processing effect in both groups in the prefrontal cortex (for review, Buckner et al. 2000; Nyberg 2002) with greater activity for deep than shallow encoding. However, the depth of processing effect also modulated local brain activity differentially in each group. Specifically, the inferior orbitofrontal, cingulate and left parietal cortices were more activated for deep than shallow encoding in controls, whereas in alcoholics these brain regions were equally activated in the two encoding conditions. These group differences in regional brain activation indicate that alcoholics may be unable to modulate with task demand the level of brain activity in certain regions. This finding is in agreement with the observation that alcoholics invoke high-order cognitive functions than controls to perform low demand tasks at control levels (De Rosa et al. 2004; Pfefferbaum et al. 2001).

Relationship Between Connectivity and Learning Performance

Even though alcoholics did not differ from controls in task performance or in functional connectivity during the task, the strength of the connectivity between Crus II and hippocampus, in relation to the associative learning performance, was different in the two groups. Consistent with previous investigations reporting the predictive value of functional connectivity during a task (Hampson et al. 2006; Nagano-Saito et al. 2008; Summerfield et al. 2006), controls with greater cerebello-hippocampal synchronization during the task performed better on associative recognition. By contrast, alcoholics with more negatively correlated activity during rest performed better on the associative recognition. The lower activation of Crus II in response to the task together with the negative correlation between resting cerebello-hippocampal functional connectivity and learning highlight the importance of considering non-task demand brain activity in understanding group differences in task-demand brain activity, especially in the context of similar task performance. This constellation of relations gives credence to the possibility that compensatory mechanisms can be involved to enable alcoholics to perform on par with controls despite different patterns of brain activations and perhaps because of these differences (cf., Chanraud et al., 2012).

Conclusion

Alcoholics performed at control levels yet had lower than control task-related BOLD activation in some brain regions, including Crus II. In previous fMRI experiments (De Rosa et al. 2004; Desmond et al. 2003; Pfefferbaum et al. 2001; Chanraud et al. 2012), we observed that, when alcoholics performed at control levels, they either exhibited greater activation or activated more brain areas than controls, which we interpreted as resource recruitment compensation. In the present experiment, we did not observe this pattern but have sought explanation by examining the task demands within the context of the entire experiment and also by examining the non-task demand, resting state activity immediately preceding the task and functional connectivity across states. That the functional connectivity of the alcoholics differed profoundly from that of controls during rest suggests that the alcoholics approached the task demands differently and may even have been “rehearsing” procedures rather than “resting.”

The combination of rest-related and task-related fMRI and functional connectivity analyses revealed that alcoholism is characterized by atypical cerebello-hippocampal synchronization of the resting brain but with apparent preserved decoupling of these two sites during the associative memory task. This difference in profiles of functional connectivity at rest and when engaged in the task presents a neural systems understanding determined from a physiological probe of the observed preserved associative learning performance by alcoholics.

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Footnotes:

Conflict of interest None of the authors Anne-Lise Pitel, Sandra Chanraud, Eva M. Müller-Oehring, Adolf Pfefferbaum, Edith V. Sullivan have any conflicts of interest with the reported data or their interpretation. All work was supported from grants from the NIH-NIAAA.

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Figure 1

FMRI paradigm

The protocol included 4 runs (2 Shallow and 2 Deep). Each run consisted of an encoding, perceptual, and recognition task. During the encoding task, the name was presented first; then name together with the face was presented next, with the name/face side of presentation balanced across trials. In addition to the associative face-name recognition task performed in the scanner, a single item (face or name) was conducted outside the scanner (not represented in the Figure).

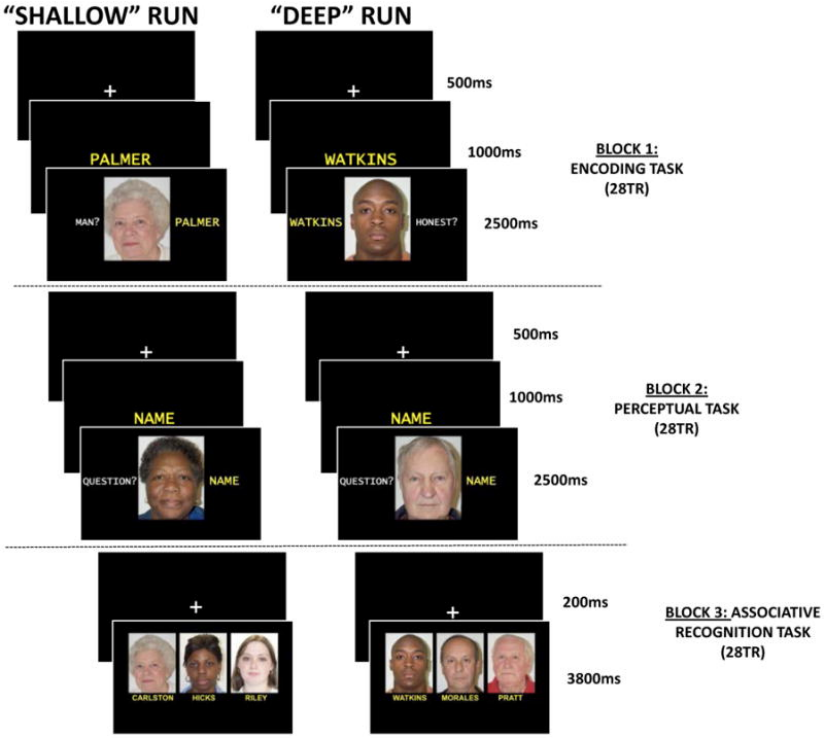

Figure 2

Behavioral result. A: Reaction time in the perceptual and encoding tasks; B: Accuracy in the face-name recognition tasks; C: Reaction time in the face-name recognition tasks

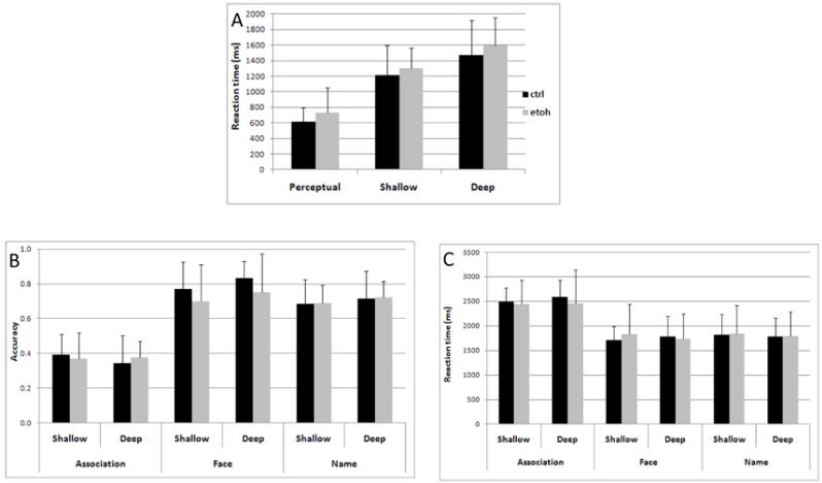

Figure 3

Whole brain statistical activation maps representing the results of the factorial design with the group (controls versus alcoholics), memory task (encoding versus recognition), and depth of processing at encoding (shallow versus deep) as main factors with all levels crossed and using the perceptual task as reference task (height threshold: p<0.001 uncorrected; cluster threshold: p<0.005 uncorrected). For the Group by Depth of processing interaction, an example of the percentage signal change in the left orbitofrontal gyrus is provided with higher activation in controls in Deep than Shallow conditions and higher activation in alcoholics in Shallow than Deep conditions.

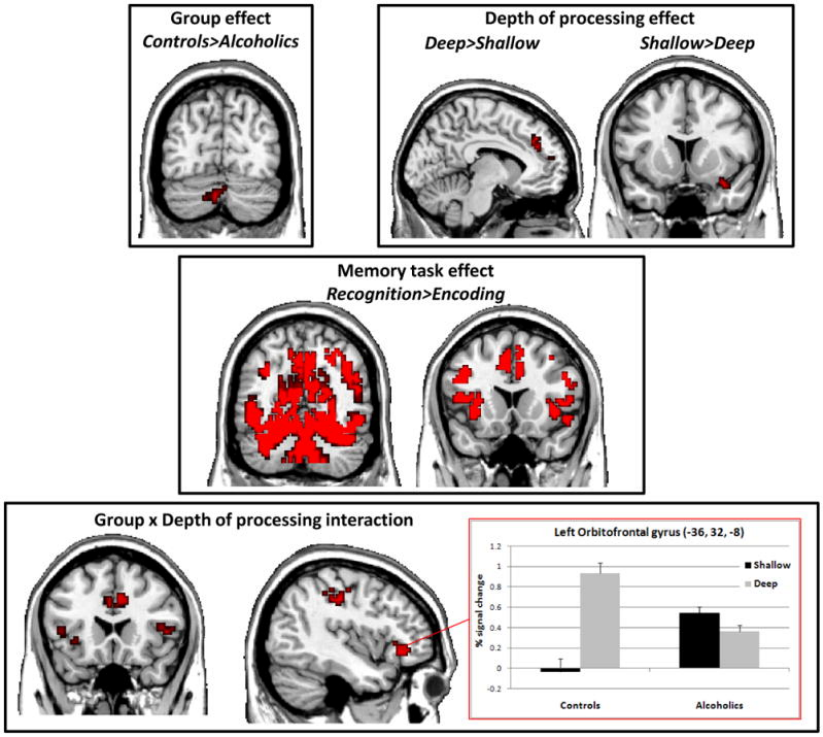

Figure 4

Functional connectivity analysis and results. 1: Choice of the seed region using the task-related fMRI results showing the left Crus II as differently activated in the two groups. 2: Resting-state functional connectivity results indicating less cerebello-hippocampal synchronization at rest in alcoholics than controls. There was no significant difference between the two groups on the connectivity during the task. 3: Between- and within-group differences in cerebello-hippocampal synchronization. Y-axis represents z-transformed correlation values between the left cerebellar Crus II and the left hippocampus. *: Between-group difference (significant difference between controls and alcoholics for p<0.05) †: Within-group difference (significant difference from rest to task for p<0.05)

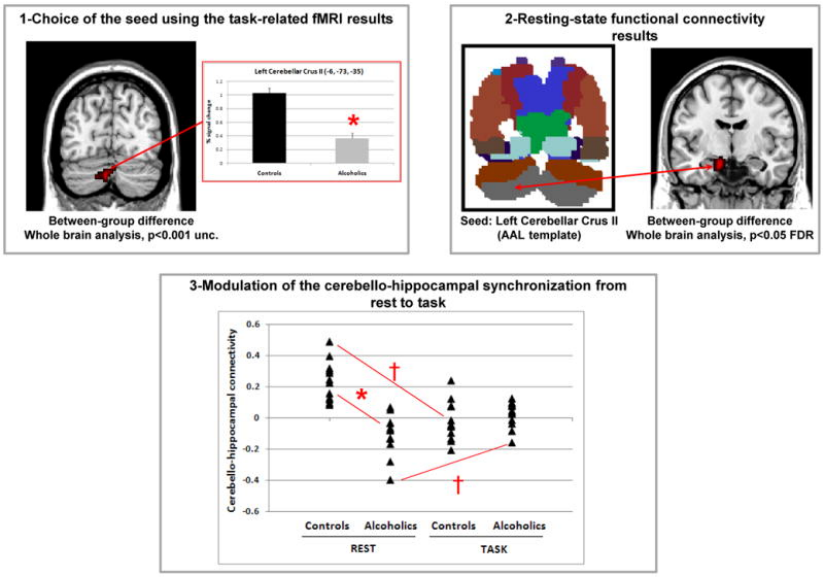

Figure 5

Schematic hypothetical representation of the modulation of the cerebello-hippocampal synchronization from positively in controls and negatively in alcoholics coupled activity at rest to decoupled activity when engaged in the associative learning task. In both groups, this modulation of the functional connectivity with task engagement consisted of a decoupling of the cerebello-hippocampal activity. Specifically, controls exhibited decreased functional connectivity from positively coupled activity at rest (same network) to decoupled activity during the task (two different networks). Alcoholics exhibited change in cerebello-hippocampal connectivity from being abnormal at rest (negatively correlated) to control-level decoupled activity during the task. Given the preserved learning abilities in the alcoholic group, the modulation occurring from rest to task in the alcoholic group may reflect compensatory mechanisms. Please note that the waveforms represent hypothetical, idealized BOLD responses to illustrate coupling and decoupling of cerebello-hippocampal time series.

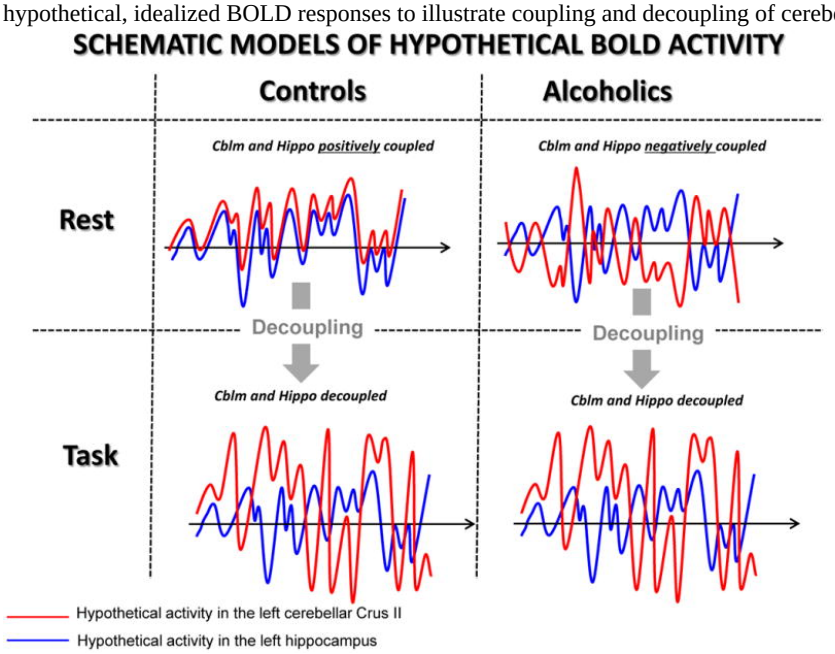

Table 1

demographic and clinical characteristics in the control and alcoholic group

	Control group	Alcoholic group	*p value*
	N=12	N=12	
Sample size (men)	12(12)	12(12)	
Age	43.00 ± 11.00	38.00 ± 7.90	0,17
Education (years)	14.42 ± 1.51	13.08 ± 1.93	0,13
NARTIQ	110.00 ± 10.03	107.73 ± 8.82	0,59
Lifetime alcohol intake (kg)	45.43 ± 53.90	883.81 ± 966.27	0,01
Sobriety (days)	NA	66.58 ± 3977	NA

Table 2

Results of the factorial analysis

Effect	Brain region	Cluster size k	Peak T value	MNh coordinates		
				X	y	z
GROUP EFFECT						
Controls>Alcoholics	**Left cerebellar Crus II**	**22**	**3,38**	**−6**	**−73**	**−35**
DEPTH OF PROCESSING EFFECT						
Shallow>Deep	**Right superior temporal pole**	**13**	**3,25**	**36**	**11**	**−23**
Deep>Shallow	**Left superior medial frontal gyrus**	**17**	**3,01**	**−9**	**41**	**31**
MEMORY TASK EFFECT						
Recognition>Encoding	**Left calcarine gyrus**	**4606**	**12.81** *	**0**	**−85**	**−5**
				−6	−76	−5
				−21	−76	−11
	Left inferior parietal gyrus	**61**	**8.53** *	**−27**	**−55**	**46**
				−39	−46	46
				−48	−28	43
	Right angular gyrus	**39**	**8.53** *	**33**	**−52**	**46**
				27	−64	46
				27	−55	52
	Left precentral gyrus	**438**	**7.15** *	**−45**	**8**	**31**
				−33	5	52
				−45	29	22
	Left angular gyrus	**17**	**6.67** *	**−33**	**−61**	**37**
	Right inferior frontal gyrus	**293**	**6.21** *	**48**	**17**	**28**
				48	8	28

				48	29	19
	Left superior medial frontal gyrus	**218**	**5.89** *	**−3**	**23**	**43**
				−3	2	61
	Right middle cingulate gyrus	**150**	**5.86** *	**6**	**23**	**40**
				6	−4	64
	Left precentral gyrus	**48**	**5.11** *	**−39**	**−16**	**52**
				−24	5	52
				−27	−10	58
	Right superior parietal gyrus	**18**	**4.82** *	**21**	**−55**	**58**
				27	−46	49
	Right precentral gyrus	**27**	**4.13** *	**30**	**−1**	**49**
				36	2	55
				27	11	49
	Right caudate	**10**	**3.96** *	**12**	**5**	**16**
	Right insula	**16**	**3,79**	**48**	**17**	**−8**
	Left hippocampus	**12**	**3,08**	**−21**	**−22**	**−8**
GROUP × DEPTH OF PROCESSING INTERACTION						
Controls: Deep>Shallow; Alcoholics: Shallow>Deep	**Left inferior orbitofrontal gyrus**	**61**	**3,74**	**−36**	**32**	**−8**
				−48	20	4
	Right inferior frontal gyrus	**65**	**3,7**	**51**	**17**	**7**
				57	8	10
				42	8	13
	Left inferior parietal gyrus	**20**	**3,56**	**−48**	**−28**	**43**
				−39	−25	40
	Right middle cingulate gyrus	**40**	**3,32**	**6**	**20**	**34**
	Right inferior orbitofrontal gyrus	**29**	**3,29**	**42**	**35**	**− 8**
				39	41	1
	Left middle cingulate gyrus	**14**	**3,12**	**−3**	**20**	**31**

Cluster threshold: P<0.005 uncorrected

* : peak also significant for p<0.05 FDR corrected

Table 3

Correlations (Spearman's Rho) between the connectivity between the left Crus II and the left hippoc and face-name learning performance (accuracy)

		CONTROL GROUP		ALCOHOLIC GROUP	
Stimulus	**Depth of processing**	**Connectivity at rest**	**Connectivity during task**	**Connectivity at rest**	**Connectivity during task**
Association	Shallow encoding	−0,09	***0,65***	0,26	***−0,65***
	Deep encoding	−0,45	−0,12	−0,16	0,04
Face	Shallow encoding	−0,38	0,09	0,45	−0,45
	Deep encoding	−0,14	−0,13	***0,81***	0,06
Name	Shallow encoding	0,08	0,03	0,20	−0,55
	Deep encoding	0,33	−0,08	***0,65***	−0,14

Significant correlations for p<0.05 in bold and italic