Published in final edited form as:

Cortex. 2017 October ; 95: 15–28. doi:10.1016/j.cortex.2017.07.016.

Deviant Functional Activation and Connectivity of the Right Insula Are Associated With Lack of Awareness of Episodic Memory Impairment in Nonamnesic Alcoholism

Anne-Pascale Le Berre^a, Eva M. Müller-Oehring^{a,b}, Tilman Schulte^b, Matthew R. Serventi^{a,b}, Adolf Pfefferbaum^{a,b}, and Edith V. Sullivan^a

^aDepartment of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

^bNeuroscience Program, SRI International, Menlo Park, CA 94025, USA

Abstract

A disorder of metamemory, expressed as unawareness of mnemonic ability, is typically associated with the profound amnesia of Korsakoff's Syndrome (KS). A similar but less severe type of limited awareness can also occur in non-KS alcoholism and is observed as an impairment in generating Feeling-of-Knowing (FOK) predictions about future recognition performance. We previously found that FOK accuracy was selectively related to volumes of the insula in alcoholics involved in the present study. Unknown, however, are the neural substrates of unawareness of memory impairment in alcoholism. A task-activated fMRI paradigm served to identify neural nodes and networks implicated in inaccurate self-estimation of mnemonic ability in sober alcoholics while they made prospective FOK judgments in an episodic memory paradigm. Lower activation in the right insula correlated with greater overestimations of future memory abilities in alcoholics. Weaker connectivity of the right insula with the left dorsal anterior cingulate cortex, a node of the salience network, and stronger connectivity of the right insula with the right ventromedial prefrontal cortex, a node of the default mode network (DMN), co-occurred in alcoholics relative to the controls. Specifically, alcoholics, who failed to desynchronize insula-vmPFC activity, had greater overestimation of their memory predictions and poorer recognition performance. This study provides novel support that deviant functional activation and connectivity involving the right insula, a hub of the salience network, appears to participate in disrupting metamemory functioning in alcoholics. Compromised FOK performance might result from disturbance of the switching mechanism between brain networks serving self-referential processes (i.e., DMN network) and networks serving externally-driven activities like memory monitoring (i.e., fronto-parietal network). Thus, compromise in insular network coupling could be a neural mechanism underlying anosognosia for subtle mnemonic impairment in nonamnesic alcoholism.

Corresponding author: Edith V. Sullivan, Ph.D., Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford, CA 94305-5723, 650-859-2880 (phone), 650-859-2743 (FAX), edie@stanford.edu.

Conflict of Interest: None of the authors - Anne-Pascale Le Berre, Eva M. Müller-Oehring, Tilman Schulte, Matthew R. Serventi, Adolf Pfefferbaum, Edith V. Sullivan - has any conflicts of interest with the reported data or their interpretation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

alcoholism; anosognosia; brain; metamemory; functional MRI

1. Introduction

On formal testing, individuals with Alcohol Use Disorder (AUD) are commonly observed to have mild to moderate cognitive impairment involving episodic memory—the mnemonic system responsible for encoding, storing, and retrieving personally experienced events (Fama, Pfefferbaum, & Sullivan, 2004; Oscar-Berman et al., 2014; Pitel et al., 2007). Although typically associated with the profound amnesia of Korsakoff's Syndrome, limited awareness can be observed in alcoholics without neurological complication for their episodic memory deficits, a metamemory disorder (Le Berre et al., 2016; Le Berre et al., 2010). The limited awareness of mnemonic impairment may promote unawareness of functional compromise and undermine treatment efforts by engendering the false belief that nothing is wrong to be fixed.

Personal knowledge about one's own ability to remember and recall information, the process of metamemory, has implications for the accuracy of memory monitoring and control and for the efficient use of memory skills in everyday life (Flavell, 1971; Nelson & Narens, 1990). Abstinent alcoholics have been reported to make accurate judgments in retrospective confidence ratings of actual recognition performance (i.e., Retrospective Confidence Judgment, RCJ) but to be inaccurate in assessing future recognition performance for episodic information (i.e., Feeling-Of-Knowing judgments, FOK) (Le Berre et al., 2016; Le Berre et al., 2010). Our previous studies have shown that alcoholics exhibited a tendency to overestimate their prediction of future episodic memory performance, believing themselves capable of accurately recognizing information when they subsequently failed to do so. We have assumed that this cognitive dissociation of intact RCJ with impaired FOK in uncomplicated alcoholism is consistent with a secondary mnemonic anosognosia (Le Berre et al., 2016). In other words, when alcoholics fail to consolidate newly updated information about their memory abilities into their semantic and autobiographical personal long-term knowledge database, they then compare their current memory functioning to outdated self-beliefs (Le Berre & Sullivan, 2016; Morris & Mograbi, 2013).

The neural substrates of component mnemonic processes relevant to metamemory have been investigated in few other studies. Using an episodic FOK paradigm, a recent paper reported that structural integrity of the right insula supported memory awareness in a mixed group, which included patients with mild Alzheimer's disease and cognitively healthy older adults (Cosentino et al., 2015). Similarly, we found that FOK accuracy was selectively related to volumes of the insula in the uncomplicated alcoholics involved in the present study (Le Berre et al., 2016). Because the insula has been identified as a critical neural substrate of multiple components of self-awareness (Craig, 2009; Schmitz & Johnson, 2007), we posited that prospective episodic FOK implicates online memory monitoring mechanisms and additional self-referential processes to generate accurate future estimations. Structural damage in the medial prefrontal cortex also plays a critical role in disturbing episodic FOK

accuracy as demonstrated in patients with frontal brain damage (Modirrousta & Fellows, 2008; Schnyer et al., 2004). Further evidence provided by a functional neuroimaging study (Schnyer, Nicholls, & Verfaellie, 2005) revealed that accuracy in episodic FOK predictions in healthy subjects may be supported by a multi-functional, left fronto-temporal brain network: the inferior prefrontal cortex for the creation of cues activating information in memory, the hippocampus and temporal cortex for storage and retrieval memory contents, and the ventromedial prefrontal cortex for ensuring the ‘monitoring’ of these retrieval processes in memory. Further, brain activity in several frontal and also parietal cortices appeared to be modulated by FOK engagement in healthy control participants, with greater regional BOLD signal evident for high level of FOK and lower cortical activity evident for lower FOK (Chua, Schacter, & Sperling, 2009; Elman, Klostermann, Marian, Verstaen, & Shimamura, 2012; Maril, Simons, Mitchell, Schwartz, & Schacter, 2003; Schnyer et al., 2005).

To date, functional neural substrates of unawareness of memory impairment in alcoholism have not been systematically investigated. Thus, the aim of this task-activated fMRI study was to identify neural nodes and networks implicated in inaccurate self-estimation of mnemonic ability in sober alcoholic patients. Accordingly, we sought patterns of brain activation and functional connectivity between regions of interest evoked while making prospective metamemory judgments (i.e., FOK judgments) during an episodic memory paradigm. Further, we explored whether these brain activation and functional connectivity patterns during predictions of future recognition performance could contribute to subsequent memory performance, especially because efficient metamemory skills are implicated in efficient use of memory skills in daily life activities. Previously, we demonstrated that the insula was a key selective structural brain substrate of FOK accuracy in sober alcoholics participating in the present study (Le Berre et al., 2016). Herein, we used functional imaging to test the hypothesis that attenuated activation of the insula and compromised insula functional connectivity would contribute to overestimation of memory performance by uncomplicated alcoholics.

2. Materials and methods

2. 1. Participants

The two study groups comprised 24 alcoholics recruited from community treatment centers and 26 healthy controls recruited through flyers, announcements, or word of mouth (Table 1). All 50 participants were included in a previous structural neuroimaging investigation designed to examine prospective and retrospective metamemory monitoring processes and their structural brain correlates in nonamnesic alcoholism (Le Berre et al., 2016). All participants were volunteers and provided written informed consent obtained according to institutional review board guidelines of SRI International and Stanford University School of Medicine to participate in studies assessing the effect of alcohol on brain structure and function.

Diagnosis of alcohol dependence 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-TR (SCID (First, Spitzer, Gibbon, & Williams, 1998)).

Exclusion factors for all participants were lifetime DSM-IV-TR criteria for other Axis I diagnoses including schizophrenia, bipolar disorder, attention deficit hyperactivity disorder, and post-traumatic stress disorder (mood disorder other than bipolar was not an exclusion if the depression or anxiety onset postdated the alcoholism onset); history of central nervous system trauma, such as loss of consciousness for >30 min, seizures not related to alcohol withdrawal, or neurological disorders; or serious medical conditions, such as severe endocrine, hepatic, or renal disease, and HIV infection. All alcoholics and most controls underwent laboratory testing for HIV infection; none was positive. Control participants, also interviewed, did not meet criteria for any Axis I diagnosis, including alcohol or other drug abuse or dependence.

Approximate lifetime alcohol consumption was quantified using a modification (Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988) of a semi-structured, timeline interview (Skinner & Sheu, 1982). Drinks of each type of alcoholic beverage (wine, beer, and spirits) were standardized to units containing approximately 13.6 g of alcohol and summed over the lifetime. All subjects completed breathalyzer testing at the beginning of morning and afternoon testing sessions. Subjects were excluded from that day's study if the breathalyzer reading exceeded 0.0. Most of the alcoholic participants reported current (N=13) or past (N=6) dependence for tobacco.

The groups were comparable in age (Table 1). Although not statistically different, more women were in the control than the alcoholic group, but the proportion of men to women in the alcoholic group reflected the national prevalence of the sex distribution of alcohol use disorders in the United States (Grant et al., 2003). Compared with controls, the alcoholics had fewer years of education, yet both groups had an average education beyond high school level. Nevertheless, education was entered as a covariate in behavioral analyses, and the behavioral results did not differ with or without the education as a covariate. Beck Depression Inventory (BDI-2) scores were collected only in the alcoholics.

2. 2. The Feeling-Of-Knowing (FOK) paradigm

Our aim was to identify functional brain correlates of prospective FOK estimations in abstinent alcoholics. The behavioral data used in the present study were reported previously in our structural imaging study of metamemory disorders in chronic alcoholics (Le Berre et al., 2016). The FOK paradigm used a block design with the learning phase occurring before the fMRI session, the delayed recollection phase and the prospective FOK judgment occurring during the fMRI session, and the recognition task occurring after the fMRI session.

2. 2. 1. Learning phase of the episodic memory task before the fMRI session—

In the learning phase, the participants read aloud and tried to memorize 48 semantically and phonologically unrelated word pairs. In each word pair, the first word (i.e., cue) was matched in frequency and number of syllables with the second word (i.e., target). Later participants would be asked to judge their ability to remember the second word of each pair. Participants had 5 seconds to study a word pair before moving on to the next pair. The same learning conditions were implemented for all participants (controls and alcoholic patients), and no specific performance criterion was imposed during the learning phase. The

presentation of word pairs was randomized across participants. We created three lists of words equivalent in frequency; words were extracted from the SUBTLEXus database where frequencies are based on subtitles from American films and television series (Brysbaert & New, 2009). The assignment of the 3 lists of words was randomized across participants, anticipating future assessment in longitudinal study.

2. 2. 2. Delayed recollection phase of the episodic memory task and prospective FOK judgment during the fMRI session—

Approximately 40 min after the learning phase while in the scanner, participants performed two tasks in a block design: a control task and the recollection phase of the episodic memory task associated with the FOK measure. The control task required participants to answer whether 1, 2, or 3 Xs appeared on the screen when they saw a string of Xs and dashes (Figure 1). Participants had 3 sec to answer before moving to the next pair. For the FOK task, participants viewed the first word of each previously-learned word pair and judged their feeling about their memory for recollecting the second word with one of three options: 1) K (Know) judgment: I know that I can recall the second word; 2) Feeling-Of Knowing (FOK) judgment: I cannot recall the second word but I feel I will be able to recognize it later; 3) DK (Don't Know) judgment: I cannot recall the second word and I feel unable to recognize it later (Figure 1). Participants had 6 sec to answer before moving to the next pair. In addition, 24 FOK trials for word pairs not previously seen were used to estimate chance performance. Before the delayed recollection phase and the recognition phase of the episodic memory task, no information was provided to the participants regarding these FOK trials for word pairs not previously seen during the learning phase of the episodic memory task. Therefore, the participants were not aware of these trials or their temporal consistency at the beginning of each block during the fMRI experiment.

During the fMRI session, 4 runs with a balanced order were acquired for a total duration of 13:56 min (i.e., 3:29 min each); each run was synchronized with the beginning of the fMRI volume acquisitions. Each run comprised two blocks of the control condition (22 trials with a duration of 3 sec, 36 TRs) and two blocks of the metamemory condition (12 trials with a duration of 6 sec, 36 TRs), presented in balanced order in each run. For the whole fMRI session, 88 trials for the control condition and 48 trials for the metamemory condition were presented to the participants with a total of 144 brain volumes acquired for the control condition, and 144 volumes were acquired for the metamemory condition (Figure 2). Five dummy TRs were added at the beginning of each run. Blocks were separated by 2 FOK trials on new word pairs (6 FOK trials on new word pairs per run) used as control to estimate chance performance and not included in the fMRI and connectivity analyses. Different stimulus intervals were used between trials (400 ms, 600 ms, 800 ms, 1000 ms) to minimize anticipation effects before a stimulus appeared on the screen.

2. 2. 3. Recognition task after the fMRI session—

Approximately 60 min after the delayed recollection phase, participants performed the recognition task. The first word of each previously learned or new word pairs was presented in the center of the screen, and the second word of each word pair was presented among 4 items (Figure 1). Subjects chose which of the 4 words was originally paired with the center word. We created a neutral

distractor, a phonological distractor, and a semantic distractor for each correct matching second word. The phonological and semantic distractors were then shuffled and associated with a different second correct matching word to increase the level of difficulty for the recognition task. No time limit was imposed for the recognition. The interval between the delayed recollection and recognition phases included structural MRI and unrelated fMRI series. Stimuli were presented by E-Prime® software (Psychology Software Tools Inc., Pittsburgh, PA).

Behaviorally, as we reported earlier (Le Berre et al., 2016), we calculated the proportion (%) of K, FOK, and DK judgments made. Alcoholics and controls did not differ in the percentage of K judgments [$F(1,47)=0.01$, $p=0.91$], FOK judgments [$F(1,47)=0.15$, $p=0.70$], or DK judgments [$F(1,47)=0.22$, $p=0.64$] made; thus, the groups responded similarly in making judgments on their feeling about their memory for the second word of a pair. In addition, alcoholics involved in the present study achieved lower scores than controls on total recognition (number of words correctly recognized on 48 words) (Table 2). Moreover, no significant group differences emerged for the percentage of correct DK predictions (i.e., DK Hits %), while alcoholics generated significantly lower percentage of correct FOK predictions (i.e., FOK Hits %) than controls, suggesting that alcoholics overestimated their future recognition performance (Table 2 and Le Berre et al., 2016).

For brain-behavior correlation, we used the total recognition score as the measure of episodic memory and the FOK Hits % as the measure of metamemory performance.

2. 3. MR scanning procedures and analyses

2. 3. 1. Brain data acquisition—Whole-brain structural and functional MRI data were acquired using a 3T General Electric (GE) Signa scanner (9 controls and 4 alcoholics) and using a 3T GE Discovery MR750 (17 controls and 20 alcoholics) with an 8-channel head coil. Subject motion was minimized by following best practices for head fixation and image series were inspected for residual motion. Whole-brain fMRI data were acquired with a T_2^* -weighted gradient echo-planar pulse sequence (2D axial, echo time [TE] = 30 ms, repetition time [TR] = 2200 ms, flip angle = 90°, matrix = 64 × 64, slice thickness = 5 mm, 36 slices). A dual-echo fast spin-echo (FSE) sequence (2D axial acquisition; TE = 17/102 ms, TR = 8585ms, FOV = 24 cm, matrix = 256 × 192 matrix, NEX = 1.0, slice thickness = 2.5 mm, 62 slices) was used for spatially registering the fMRI data. A field map for correction of spatial distortions in the echo-planar images was generated from gradient-recalled echo (GRE) sequence with the following parameters for the 3T GE Signa scanner (TE = 3/5 ms, TR = 460 ms, slice thickness = 5 mm, 36 slices) and for the 3T GE Discovery MR750 (TE = 7/9 ms, TR = 1000 ms, slice thickness = 5 mm, 32 slices.)

2. 3. 2. fMRI post-acquisition processing—The first five volumes of each run were discarded to allow for signal equilibration. Standard spatial preprocessing and statistical analysis of functional images were performed using Statistical Parametric Mapping (SPM8) software package (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm/software/spm8/). The fMRI analysis focused on the whole brain. The functional images were realigned for motion corrections and unwarped (correction for

magnetic field distortions) using the gradient-echo field maps. Motion artifacts were assessed in each individual by visual inspection of realignment parameter estimations to confirm that the maximum head motion in each axis was less than 2 mm, without abrupt head motion. These criteria excluded three alcoholics from the task-related fMRI and functional connectivity analyses.

The FSE structural images were co-registered to the mean unwarped and motion-corrected functional image for each subject. The anatomical volume was then segmented into gray matter, white matter, and cerebrospinal fluid images. 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 finally resampled to voxels of $2 \times 2 \times 2$ mm and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum.

2. 3. 3. Task-related fMRI analyses: Localized Functional Activation—First, ‘metamemory task over control task’ contrast images were computed for each subject in a first-level analysis. To remove slow signal drifts, a high-pass filter at 128 seconds was implemented in the individual models. The contrast images were then used in second-level within-group analyses (i.e., functional activation in each group) and between-group contrast analyses (i.e., group differences in functional activation). Analyses of fMRI data for the whole brain were corrected for multiple comparisons at $p_{corrected} < 0.05$ for combined spatial extent and peak intensity using a peak threshold of each voxel of $p = 0.001$ and minimum cluster size of $k = 85$ voxels, as calculated by Monte Carlo simulation using 3dClustSim (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) [see also (Eklund, Nichols, & Knutsson, 2016)]. Using MarsBaR (Brett et al., 2002) (<http://marsbar.sourceforge.net/>), we extracted the mean signal intensity values in the significant clusters (i.e., Regions Of Interest, ROIs) activated during the ‘metamemory task over control task’ contrast for each participant. We then correlated the extracted regional MR signal change with memory and metamemory performance measures. Spearman rank-order correlations were conducted within the whole group (including control and alcoholic participants) to test relations between education and mean signal intensity values in the regions of interest associated with behavioral performance. Because no significant correlation was observed, education was not entered as a covariate in the brain imaging analyses.

2. 3. 4. Functional Connectivity during Task—Functional connectivity analyses were conducted for the ‘metamemory task over control task’ contrast on preprocessed individual images with the conn toolbox, implemented in SPM8 (www.nitrc.org/projects/conn/). The ‘metamemory task’ condition and the ‘control task’ condition were defined in the connectivity analysis by entering onsets and durations (in seconds) of each experimental condition. Before averaging individual voxel data, the waveform of each brain voxel was filtered ($0.0083/s < f < \text{infinite}$) to minimize effects of low-frequency drift and high-frequency noise. Linear regression then removed several sources of spurious variance along with their temporal derivatives from the data, namely, signal from CSF and white matter. The effects of task conditions were also entered as confounding regressors in the subject-

level general linear model. Motion parameters were carefully considered in the analyses using the component-based noise correction method (CompCor) of noise reduction along with the efficient rejection of motion and artifactual time points (i.e., 5 for global-signal z-value threshold and 1 for subject-motion translation/rotation thresholds [mm, rad]) (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Between-group random-effects analysis used temporal connectivity maps generated for each subject and a seed region selected from the alcoholic group. Correlational analyses conducted between the BOLD signal from the seed and every other brain voxel provided seed-to-voxel connectivity estimations. These images were then included in a second level, between-groups, random-effects analysis. In the alcoholic group, poorer metamemory accuracy was associated with lower activation in the right insula; therefore, the right insula [$x = 32$; $y = 24$; $z = -4$] was chosen as a seed for the functional connectivity analyses. This seed was created using MarsBaR (Brett, Anton, Valabregue, & Poline) (<http://marsbar.sourceforge.net/>) from the significant cluster derived by the within-group analysis in the alcoholic group and entered as the seed region in the between-group functional connectivity analyses for the “metamemory > control” condition contrast. To test for group differences in functional connectivity, between-group contrast analyses were performed with standard cluster-forming statistical thresholds of $P_{FDR-corrected} < 0.05$ (Poline, Worsley, Evans, & Friston, 1997), which required a minimum cluster size of $k=943$ voxels, as calculated Monte Carlo simulation using 3dClustSim (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) [see also (Eklund et al., 2016)].

2. 3. 5. Correlations—We conducted a number of exploratory correlations (using Spearman rank-order correlation analysis less sensitive to outliers) to investigate the relations between level of change in functional activation within brain regions of interest, Fisher-transformed Z-value measures of functional connectivity using the right insula as a seed, and behavioral measures [i.e., total recognition score as measure of episodic memory performance and the percentage of correct FOK predictions (i.e., FOK Hits %) as measure of metamemory accuracy]. Given the few published studies in alcoholic patients and healthy subjects on relationships among functional activation, functional connectivity, and metamemory performance, we comprehensively explored the associations without correction for multiple comparisons. Additional correlations tested relations between fMRI metrics and alcoholic history variables (i.e., duration of abstinence, duration of alcohol dependence, and lifetime alcohol consumption).

3. Results

3. 1. Localized Functional Activations

3. 1. 1. Functional activation pattern in the control group during the delayed recollection phase of the episodic memory task and prospective FOK judgment—The control group showed significant bilateral activation in the superior medial frontal cortices (BA8/9) extending to the anterior cingulate cortex (BA32), dorsolateral prefrontal cortices (BA9/46), inferior orbitofrontal cortices (BA47), insula (BA13), inferior parietal cortices (BA39/40), occipital cortices (lingual and cuneus regions, BA17/18), in the

left precuneus (BA7), and in the right cerebellum (posterior lobe, Crus I/Crus II) (Table 3). Better total recognition and higher percentage of correct FOK predictions (i.e., FOK Hits%) were correlated with greater activation in the occipital cortices [$x = -6$; $y = -86$; $z = 0$] (with recognition: $\rho = 0.46$, $p = .0195$ and with FOK Hits%: $\rho = 0.40$, $p = .0454$; Figure 3A) and in the right cerebellum, Crus I/Crus II, [$x = 40$; $y = -66$; $z = -28$] (with recognition: $\rho = 0.49$, $p = .0119$ and with FOK Hits%: $\rho = 0.42$, $p = .0332$; Figure 3B) and [$x = 10$; $y = -76$; $z = -30$] (with recognition: $\rho = 0.69$, $p < .001$ and with FOK Hits%: $\rho = 0.71$, $p < .001$; Figure 3C).

3. 1. 2. Functional activation pattern in the alcoholic group during the delayed recollection phase of the episodic memory task and prospective FOK judgment

The alcoholic group showed bilateral activation in the occipital cortices (lingual and cuneus regions, BA17/18), left superior medial frontal cortex (BA8), inferior orbitofrontal cortex (BA47), dorsolateral prefrontal cortex (BA46), inferior parietal cortex (BA39/40), middle temporal cortex (BA21), and right insula and cerebellum (posterior lobe, Crus I/region VI) (Table 3). Lower activation in the right insula [$x = 32$; $y = 24$; $z = -4$] was associated with lower percentage of correct FOK predictions (i.e., FOK Hits%; $\rho = 0.45$, $p = .0395$), but not with the memory measure (Figure 4). In our previous study conducted in the same alcoholic group (Le Berre et al., 2016), FOK accuracy was selectively related to volumes of the insula. Therefore, we conducted a supplementary correlation analysis between volumes in the insula ROI created with FreeSurfer (for more details, see Le Berre et al., 2016) and the mean signal intensity values extracted from the right insula ROI observed in the present study. We did not observe any significant correlation, suggesting that lower activation in the right insula was not related to volume deficits in this brain region. No correlation was detected with the alcohol history variables.

3. 1. 3. Group differences in the functional activation pattern during the delayed recollection phase of the episodic memory task and prospective FOK judgment

Controls showed lower activation in the right and left superior frontal cortices (BA 9) and greater activation in the left superior parietal cortex (BA7) than alcoholics (Table 3). In the control group, lower activation in the right superior frontal cortex [$x = 22$; $y = 40$; $z = 40$] correlated with higher percentage of correct FOK predictions (i.e., FOK Hits%; $\rho = -0.44$, $p = .0262$) and with better memory performance (i.e., total recognition score; $\rho = -0.46$, $p = .0188$) (Figure 5). No correlation was found in the alcoholic group.

3. 2. Right Insula seed-based Functional Connectivity during Task

Weaker connectivity between the right insula and the left dorsal anterior cingulate cortex (BA32) [$x = 0$; $y = 14$; $z = 44$], whereas stronger connectivity between the right insula and the left lingual gyrus (BA18) [$x = -6$; $y = -84$; $z = -8$] and the right ventromedial prefrontal cortex (BA10/11) [$x = 10$; $y = 50$; $z = -10$] occurred in the alcoholics relative to the controls (Table 4). In the alcoholic group, greater connectivity between the right insula and the right ventromedial prefrontal cortex correlated with lower percentage of correct FOK predictions (i.e., FOK Hits%; $\rho = -0.47$, $p = .0316$) and with worse memory performance (i.e., total recognition score; $\rho = -0.59$, $p = .0051$) (Figure 6). These correlations were not found in the control group.

4. Discussion

The aim of this fMRI study was to seek a neural mechanism underlying unawareness of the mild to moderate memory impairment often detectable in recovering alcoholic individuals. Accordingly, we used the BOLD signal to identify local brain responsivity involved in inaccurate self-estimation of future mnemonic ability. As we previously reported (Le Berre et al., 2016), alcoholic patients participating in this fMRI study demonstrated episodic memory deficits and inaccuracy in FOK predictions for newly learned information and showed a tendency to overestimate their memory skills. In the present study, we furthered this finding by showing that deviant activation patterns and functional connectivity with the right insula, a region known to support facets of self-awareness (Craig, 2009; Schmitz & Johnson, 2007), emerged as a potential functional neural substrate of metamemory impairment in these recovering alcoholics.

The alcoholic pattern of lower activation in the right insula associated with overestimation of future memory abilities supports our hypothesis that a compromised insula may be a critical brain substrate of FOK inaccuracy in alcoholism. This result is consistent with our previous observation (Le Berre et al., 2016), where poorer FOK accuracy selectively related to smaller insular volumes in uncomplicated alcoholics. Investigating the neural correlates of FOK using general knowledge questions, Kikyo et al. (2002) showed that greater activation in the bilateral anterior insula (AI)/inferior frontal gyrus (IFG) and the anterior cingulate cortex (ACC) correlated with a stronger sense of feeling of knowing in healthy participants (Kikyo, Ohki, & Miyashita, 2002). Interestingly, the bilateral AI/IFG regions were not recruited during the successful recall processes, thereby supporting the assumption that these brain regions could be specifically involved in the metamemory processes, i.e., the feeling of knowing, but not in episodic memory retrieval process itself. This interpretation could also be applied to our study in the context of an episodic memory paradigm because no association was found between activation in the right insula and successful recognition performance in the alcoholics.

Conversely, the control group displayed greater activations in the right cerebellum that were related to better episodic FOK accuracy and also to greater recognition performance. One aim of the present study was to investigate brain regions activated during an episodic FOK judgment and how these brain activations could contribute to subsequent recognition performance. The recognition part of our episodic memory task was assessed outside the scanner and not during the fMRI session. Thus we did not directly assess the brain regions activated during the recognition part of the episodic memory task, which could potentially explain why usual memory-related regions such as the hippocampus or other limbic structures were not activated. Rather, we sought activations of metamemory-related brain regions and explored those that could potentially participate in the subsequent recognition performance. In the controls, the pattern of activation suggests that the cerebellum could normally support cognitive processes common to both metacognitive and recognition mechanisms in episodic memory. The trace-access hypothesis has been proposed as a cognitive explanation of FOK judgment creation (Koriat, 1993). When a person attempts to recall target information but fails to do so, his or her FOK judgment would depend on the partial recovery of the non-recalled target. Given the role played by the cerebellum in

conscious retrieval processes in episodic memory and executive functioning (Buckner, 2013; Desmond & Fiez, 1998; Stoodley, 2012), control participants with higher activation in the right cerebellum might demonstrate better ability in partial recovery of non-recalled words from memory that could enhance the feeling-of-knowing about the target and facilitate the subsequent recognition performance. Moreover, in the control group, better metamemory accuracy and also greater episodic memory performance were related to lower activations in the right superior frontal cortex. Given that the superior frontal cortices are known to be part of the Default Mode Network (DMN), particularly implicated in internally focused tasks such as autobiographical memory retrieval and self-reference activities (Buckner, Andrews-Hanna, & Schacter, 2008), one potential explanation is that accurate episodic FOK and subsequent memory performance may be supported by a shift towards effortful executive processes used to monitor the ongoing memory activity and away from self-referential, DMN-like processes used to retrieve information from autobiographical (subjective) knowledge about past memory abilities. We speculate that the controls, unlike alcoholics, had already achieved this shift, which likely occurs through greater cerebellar involvement.

Functional connectivity studies have posited the insula to be a central node in the salience network, which is a large-scale system involving the anterior insula and dorsal anterior cingulate cortex (dACC) (Eckert et al., 2009; Menon, 2015; Menon & Uddin, 2010; Seeley et al., 2007; Uddin, 2015). Relevant to the present finding, the salience network was reported to play a pivotal role in initiating and enabling a dynamic switching between other large-scale networks (Menon & Uddin, 2010), especially between the DMN, supporting self-referential mental activity, and the central executive (i.e. fronto-parietal) network, subserving attention and executive monitoring (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). During effortful cognitive tasks, the salience network as well as the fronto-parietal network reportedly showed increased activation, while the DMN showed decreased activation (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Raichle et al., 2001). Consistent with the hypothesis of a disconnection or an impaired switching mechanism between self-referential mechanisms and online memory monitoring processes in alcoholics, we observed that weaker connectivity of the right insula with the left dACC (i.e., in the salience network) and stronger connectivity of the right insula with the right ventromedial prefrontal cortex (i.e., vmPFC, a node of the default mode network) co-occurred in alcoholics than the controls. Specifically, alcoholics, who failed to desynchronize insula-vmPFC activity, had greater overestimation of their memory predictions and poorer recognition performance. These functional connectivity patterns suggest that compromised uncoupling of insula-vmPFC activity could contribute to alcohol-related impairment in metamemory. Supporting our hypothesis of an impaired switching mechanism in alcoholics and using an arterial spin labeling (ASL) perfusion imaging method, Sullivan et al. (2013) have proposed that attenuated insular cerebral blood flow was a mechanism underlying compromised connectivity among salience network nodes in recovering alcoholic men. This selective insular perfusion deficit could have the potential to impair alcoholics' ability to switch from self-referential processes to cognitive control processes.

Given the implication of the insula in the integration and representation of ascending interoceptive and viscerosensory signals, this brain structure has been considered as a key node in the generation of subjective feelings that guide decision-making (Craig, 2009;

Damasio, 1994). Many recent studies have revealed that the insular cortex, especially anterior regions, plays a critical role in decision-making under conditions of uncertainty related to the inability to predict an outcome (Critchley, Mathias, & Dolan, 2001; Feinstein, Stein, & Paulus, 2006; Grinband, Hirsch, & Ferrera, 2006; Huettel, Song, & McCarthy, 2005; Jung et al., 2014; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Volz, Schubotz, & von Cramon, 2003). Development of FOK judgments relies on generating predictions about future memory performance that relies on probability estimates rather than precise knowledge about the outcome (i.e., the actual memory performance). Therefore, this subjective assessment of one's knowledge regarding prospective memory abilities involves a cognitive component of decision-making under uncertainty. The low relative activity in the anterior insula of some alcoholics may prevent the feeling of uncertainty inherent in a feeling-of-knowing experience when uncertainty should but does not prevail. Consequently, it could compromise the processing and resolution of uncertainty by setting up more effortful executive processes useful to retrieve information about the actual episodic memory experience and to support the cognitive comparator mechanisms to enhance the detection of a memory failure. By default, alcoholics may base their memory predictions only on the subjective and affective self-referential information stored in their personal database [cf., (Le Berre & Sullivan, 2016; Morris & Mograbi, 2013)] rather than on an objective assessment based on online memory monitoring processes. However, according to our previous study conducted in the same group of alcoholics, the subjective representation of the alcoholics' actual memory functioning, i.e., their personal database, may not have been completely updated over time and would only reflect their memory skills at some time earlier in life, perhaps before or at the beginning of their alcoholism onset (Le Berre et al., 2016). Therefore, when the function of the insula is compromised, alcoholic patients may experience a greater subjective feeling of certainty when asked to predict their future memory performance and tend to overestimate their prospective memory abilities.

Limitations of these findings must be acknowledged with respect to the sex distribution, which precluded reliable testing of potential sex differences in brain activation patterns. Although not statistically different, more women were in the control than the alcoholic group, but the proportion of men to women in the alcoholic group reflected the national prevalence of the sex distribution of alcohol use disorders in the United States (Grant et al., 2003). Furthermore, most of the alcoholic participants reported current or past dependence for tobacco. Chronic cigarette smoking represents a highly prevalent comorbidity in alcoholism and must be considered as a potential confounding variable given that chronic smoking can contribute to cognitive dysfunction in alcohol dependence (Durazzo et al., 2010; Durazzo & Meyerhoff, 2007). To minimize potential effects of acute cigarette smoking on cognition and brain functioning, participants were not allowed to smoke at least 1 hour before the beginning of the fMRI experiment.

Although typically associated with the profound amnesia of Korsakoff's Syndrome, limited awareness for their episodic memory deficits can be observed in alcoholics without neurological complication. Our study is novel in finding that deviant functional activation and connectivity in the right insula, a hub of the salience network, might disrupt metamemory functioning in chronic alcoholism by disturbing the switching mechanism between brain networks serving self-referential processes (i.e., DMN network) and other

networks serving externally-driven activities like memory monitoring (i.e., fronto-parietal network). Thus a decoupling compromise could contribute to anosognosia for mnemonic impairment in chronic, nonamnesic alcoholism. In addition, in our previous investigation (Le Berre et al., 2016), we reported that alcoholics included in the present study generated accurate retrospective confidence (RCJ) judgment assessed during the recognition, despite inaccurate prospective FOK judgment. Patients accurately judged their success in recognizing episodic information suggesting that they were able to perceive a memory failure consciously when it occurred during the recognition task, showing therefore effective online error monitoring skills.

Taken together, our functional and structural MRI studies using FOK/RCJ paradigm provide initial evidence for the insula itself and its abnormal functional connectivity with the vmPFC as potential substrates of inaccurate perception of future mnemonic performance by alcoholics. The dissociation between objective abilities and subjective awareness of those abilities can be characterized as a mild form of anosognosia and have implications for readiness and acceptance of cognitive rehabilitation efforts (Le Berre & Sullivan, 2016).

Acknowledgments

The current analysis, writing, and manuscript preparation were supported by the U.S. National Institute on Alcohol Abuse and Alcoholism grants AA017168, AA017923, and AA010723.

References

- Brett, M., Anton, J.L., Valabregue, R., Poline, J.B. Region of interest analysis using an SPM toolbox [abstract]; Presented at the 8th International Conference on Functional Mapping of the Human Brain; June 2-6, 2002;
- Brysbaert M, New B. Moving beyond Kucera and Francis: a critical evaluation of current word frequency norms and the introduction of a new and improved word frequency measure for American English. *Behav Res Methods*. 2009; 41(4):977–990. DOI: 10.3758/brm.41.4.977 [PubMed: 19897807]
- Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron*. 2013; 80(3):807–815. DOI: 10.1016/j.neuron.2013.10.044 [PubMed: 24183029]
- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008; 1124:1–38. DOI: 10.1196/annals.1440.011 [PubMed: 18400922]
- Chua EF, Schacter DL, Sperling RA. Neural correlates of metamemory: a comparison of feeling-of-knowing and retrospective confidence judgments. *J Cogn Neurosci*. 2009; 21(9):1751–1765. DOI: 10.1162/jocn.2009.21123 [PubMed: 18823230]
- Cosentino S, Brickman AM, Griffith E, Habeck C, Cines S, Farrell M, et al. Stern Y. The right insula contributes to memory awareness in cognitively diverse older adults. *Neuropsychologia*. 2015; 75:163–169. DOI: 10.1016/j.neuropsychologia.2015.05.032 [PubMed: 26049091]
- Craig AD. How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009; 10(1):59–70. DOI: 10.1038/nrn2555 [PubMed: 19096369]
- Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*. 2001; 29(2):537–545. [PubMed: 11239442]
- Damasio, AR. *Descartes' Error: emotion, reason and the human brain*. New York: Putnam and Sons; 1994.
- Desmond JE, Fiez JA. Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn Sci*. 1998; 2(9):355–362. [PubMed: 21227232]

- Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. *Trends Cogn Sci*. 2008; 12(3):99–105. DOI: 10.1016/j.tics.2008.01.001 [PubMed: 18262825]
- Durazzo TC, Fryer SL, Rothlind JC, Vertinski M, Gazdzinski S, Mon A, Meyerhoff DJ. Measures of learning, memory and processing speed accurately predict smoking status in short-term abstinent treatment-seeking alcohol-dependent individuals. *Alcohol Alcohol*. 2010; 45(6):507–513. DOI: 10.1093/alcalc/agq057 [PubMed: 20923865]
- Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. *Front Biosci*. 2007; 12:4079–4100. [PubMed: 17485360]
- Eckert MA, Menon V, Walczak A, Ahlstrom J, Denslow S, Horwitz A, Dubno JR. At the heart of the ventral attention system: the right anterior insula. *Hum Brain Mapp*. 2009; 30(8):2530–2541. DOI: 10.1002/hbm.20688 [PubMed: 19072895]
- Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A*. 2016; 113(28):7900–7905. DOI: 10.1073/pnas.1602413113 [PubMed: 27357684]
- Elman JA, Klostermann EC, Marian DE, Verstaen A, Shimamura AP. Neural correlates of metacognitive monitoring during episodic and semantic retrieval. *Cogn Affect Behav Neurosci*. 2012; 12(3):599–609. DOI: 10.3758/s13415-012-0096-8 [PubMed: 22562436]
- Fama R, Pfefferbaum A, Sullivan EV. Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function, and age. *Alcohol Clin Exp Res*. 2004; 28(11):1657–1665. [PubMed: 15547452]
- Feinstein JS, Stein MB, Paulus MP. Anterior insula reactivity during certain decisions is associated with neuroticism. *Soc Cogn Affect Neurosci*. 2006; 1(2):136–142. DOI: 10.1093/scan/nsl016 [PubMed: 18985124]
- First, MB., Spitzer, RL., Gibbon, M., Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) Version 2.0. Biometrics Research Department, New York State Psychiatric Institute; New York, NY: 1998.
- Flavell JH. First Discussant's Comments: What is Memory Development the Development of? *Human Development*. 1971; 14:272–278. DOI: 10.1159/000271221
- Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend*. 2003; 71(1):7–16. [PubMed: 12821201]
- Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A*. 2003; 100(1):253–258. DOI: 10.1073/pnas.0135058100 [PubMed: 12506194]
- Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci*. 2004; 16(9):1484–1492. DOI: 10.1162/0898929042568532 [PubMed: 15601513]
- Grinband J, Hirsch J, Ferrera VP. A neural representation of categorization uncertainty in the human brain. *Neuron*. 2006; 49(5):757–763. DOI: 10.1016/j.neuron.2006.01.032 [PubMed: 16504950]
- Huetzel SA, Song AW, McCarthy G. Decisions under uncertainty: probabilistic context influences activation of prefrontal and parietal cortices. *J Neurosci*. 2005; 25(13):3304–3311. DOI: 10.1523/jneurosci.5070-04.2005 [PubMed: 15800185]
- Jung YC, Schulte T, Muller-Oehring EM, Hawkes W, Namkoong K, Pfefferbaum A, Sullivan EV. Synchrony of anterior cingulate cortex and insular-striatal activation predicts ambiguity aversion in individuals with low impulsivity. *Cereb Cortex*. 2014; 24(5):1397–1408. DOI: 10.1093/cercor/bht008 [PubMed: 23355606]
- Kikyo H, Ohki K, Miyashita Y. Neural correlates for feeling-of-knowing: an fMRI parametric analysis. *Neuron*. 2002; 36(1):177–186. [PubMed: 12367516]
- Koriat A. How do we know that we know? The accessibility model of the feeling of knowing. *Psychol Rev*. 1993; 100(4):609–639. [PubMed: 8255951]
- Le Berre AP, Muller-Oehring EM, Kwon D, Serventi MR, Pfefferbaum A, Sullivan EV. Differential compromise of prospective and retrospective metamemory monitoring and their dissociable

structural brain correlates. *Cortex*. 2016; 81:192–202. DOI: 10.1016/j.cortex.2016.05.002 [PubMed: 27244277]

Le Berre AP, Pinon K, Vabret F, Pitel AL, Allain P, Eustache F, Beaunieux H. Study of metamemory in patients with chronic alcoholism using a feeling-of-knowing episodic memory task. *Alcohol Clin Exp Res*. 2010; 34(11):1888–1898. DOI: 10.1111/j.1530-0277.2010.01277.x [PubMed: 20735374]

Le Berre AP, Sullivan EV. Anosognosia for Memory Impairment in Addiction: Insights from Neuroimaging and Neuropsychological Assessment of Metamemory. *Neuropsychol Rev*. 2016; doi: 10.1007/s11065-016-9323-3

Maril A, Simons JS, Mitchell JP, Schwartz BL, Schacter DL. Feeling-of-knowing in episodic memory: an event-related fMRI study. *Neuroimage*. 2003; 18(4):827–836. [PubMed: 12725759]

Menon, V. Salience Network. In: Toga, AW., editor. *Brain Mapping: An Encyclopedic Reference*. Vol. 2. Academic Press Elsevier; 2015. p. 597-611.

Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct*. 2010; 214(5-6):655–667. DOI: 10.1007/s00429-010-0262-0 [PubMed: 20512370]

Modirrousta M, Fellows LK. Medial prefrontal cortex plays a critical and selective role in ‘feeling of knowing’ meta-memory judgments. *Neuropsychologia*. 2008; 46(12):2958–2965. DOI: 10.1016/j.neuropsychologia.2008.06.011 [PubMed: 18606176]

Morris RG, Mograbi DC. Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex*. 2013; 49(6):1553–1565. DOI: 10.1016/j.cortex.2012.09.006 [PubMed: 23117055]

Nelson, TO., Narens, L. Metamemory: a theoretical framework and new finding. In: B, GH., editor. *The Psychology of Learning and Motivation*. New York: Academic Press; 1990. p. 125-141.

Oscar-Berman M, Valmas MM, Sawyer KS, Ruiz SM, Luhar RB, Gravitz ZR. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. *Handb Clin Neurol*. 2014; 125:183–210. DOI: 10.1016/b978-0-444-62619-6.00012-4 [PubMed: 25307576]

Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*. 2003; 19(4):1439–1448. [PubMed: 12948701]

Pfefferbaum A, Rosenbloom M, Crusan K, Jernigan TL. Brain CT changes in alcoholics: effects of age and alcohol consumption. *Alcohol Clin Exp Res*. 1988; 12(1):81–87. [PubMed: 3279864]

Pitel AL, Beaunieux H, Witkowski T, Vabret F, Guillery-Girard B, Quinette P, et al. Eustache F. Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcohol Clin Exp Res*. 2007; 31(7):1169–1178. DOI: 10.1111/j.1530-0277.2007.00418.x [PubMed: 17511749]

Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage*. 1997; 5(2):83–96. DOI: 10.1006/nimg.1996.0248 [PubMed: 9345540]

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98(2):676–682. DOI: 10.1073/pnas.98.2.676 [PubMed: 11209064]

Schmitz TW, Johnson SC. Relevance to self: A brief review and framework of neural systems underlying appraisal. *Neurosci Biobehav Rev*. 2007; 31(4):585–596. DOI: 10.1016/j.neubiorev.2006.12.003 [PubMed: 17418416]

Schnyer DM, Nicholls L, Verfaellie M. The role of VMPC in metamemorial judgments of content retrievability. *J Cogn Neurosci*. 2005; 17(5):832–846. DOI: 10.1162/0898929053747694 [PubMed: 15904549]

Schnyer DM, Verfaellie M, Alexander MP, LaFleche G, Nicholls L, Kaszniak AW. A role for right medial prefrontal cortex in accurate feeling-of-knowing judgements: evidence from patients with lesions to frontal cortex. *Neuropsychologia*. 2004; 42(7):957–966. DOI: 10.1016/j.neuropsychologia.2003.11.020 [PubMed: 14998710]

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007; 27(9):2349–2356. DOI: 10.1523/jneurosci.5587-06.2007 [PubMed: 17329432]

- Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *J Stud Alcohol*. 1982; 43(11):1157–1170. [PubMed: 7182675]
- Stoodley CJ. The cerebellum and cognition: evidence from functional imaging studies. *Cerebellum*. 2012; 11(2):352–365. DOI: 10.1007/s12311-011-0260-7 [PubMed: 21373864]
- Sullivan EV, Muller-Oehring E, Pitel AL, Chanraud S, Shankaranarayanan A, Alsop DC, et al. Pfefferbaum A. A selective insular perfusion deficit contributes to compromised salience network connectivity in recovering alcoholic men. *Biol Psychiatry*. 2013; 74(7):547–555. DOI: 10.1016/j.biopsych.2013.02.026 [PubMed: 23587427]
- Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015; 16(1):55–61. DOI: 10.1038/nrn3857 [PubMed: 25406711]
- Volz KG, Schubotz RI, von Cramon DY. Predicting events of varying probability: uncertainty investigated by fMRI. *Neuroimage*. 2003; 19(2 Pt 1):271–280. [PubMed: 12814578]
- Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect*. 2012; 2(3):125–141. DOI: 10.1089/brain.2012.0073 [PubMed: 22642651]

Figure 1.
Design of the behavioral paradigm implemented in an fMRI experiment.

Figure 2.
Example of an fMRI session (Total duration = 13:56 min; Total of 144 volumes for the control condition and 144 volumes for the metamemory condition). Blue = block of control condition; Red = block of metamemory condition.

Figure 3.

In the control group (blue dots), correlations between brain regional activation for 'metamemory task over control task' contrast from the within-group analysis in controls, memory performance, and metamemory accuracy measure. Better memory performance and greater FOK accuracy correlated with greater activation in the left lingual gyrus (A) and in the posterior cerebellum, i.e., Crus I/region VI (B and C) in the control group.

Within-group analysis in the alcoholic group: 'metamemory task over control task' contrast

Figure 4.

In the alcoholic group (A, red dots) and in the control group (B, blue dots), correlations between brain regional activation in the right insula for 'metamemory task over control task' contrast from the within-group analysis in alcoholics and metamemory accuracy measure. Greater FOK accuracy correlated with greater activation in the right insula in the alcoholic group, while no significant correlation was observed in the control group.

Between-group contrasts: 'metamemory task > control task' contrast

Figure 5.

In the control group (blue dots), correlations between brain regional activation for 'metamemory task over control task' contrast from the between-group analysis, memory performance, and metamemory accuracy measure. Better memory performance and greater FOK accuracy correlated with lower activation in the right superior frontal cortex in the control group.

Figure 6.

In the alcoholic group (red dots), correlations between task-activated functional connectivity, memory performance, and metamemory accuracy measure. Synchronous activity between the right insula and the right ventromedial prefrontal cortex (vmPFC) was stronger in the alcoholic group compared to the control group (A). Stronger insula-vmPFC synchrony correlated with lower metamemory accuracy (B) and lower memory performance (C).

Table 1
Demographic Characteristics of Participants: Mean (Standard Deviation)

	Controls	Alcoholics	χ^2, t	<i>p</i> value
Sex (Women/Men)	13/13	6/18	3.31 ^a	0.07
Age (years)	44.7 (12.4) Range: 24-63	48.7 (10.6) Range: 26-69	-1.22 ^b	0.23
Education (years)	16.8 (2.8)	13.3 (2.6)	4.55 ^b	<0.001 [*]
Caucasian/Non-Caucasian	21/5	15/9	2.07 ^a	0.15
Lifetime alcohol consumption (kg)	30.8 [‡] (29.2)	1061.9 (711.8)	-6.78 ^b	<0.001 [*]
Duration of abstinence (days)	-	95.8 (66.4) Range: 9-219	-	-
Duration of alcoholism (years)	-	23.1 (10.0)	-	-
Beck Depression Inventory score	-	12.5 (8.7) Range: 0-43	-	-
Smoking status Current and past dependence	0 current 0 past	13 current 6 past	-	-

[‡] collected on 22 controls

^a Pearson χ^2 .

^b Student's unpaired t-test.

^{*} Significant at $p < 0.05$

Table 2
Episodic memory and Feeling-Of-Knowing measures in the control and alcoholic groups:
Mean (Standard Deviation)

	Controls	Alcoholics	<i>p</i> value
Episodic Memory			
Total recognition score /48	35.5 (7.7)	27.3 (7.6)	0.0457 *
Feeling-Of-Knowing judgment (FOK)			
FOK Hits %	76.6 (16.3)	55.8 (17.8)	0.0064 *
DK Hits %	34.1 (15.5)	44.9 (16.9)	0.38

* Significant at $p < 0.05$, two-tailed test

Table 3
Results of the within-groups and between-group contrasts analyses

Brain regions	Peak <i>T</i> values	MINI coordinates		
		x	y	z
Within-groups Analyses				
Left lingual gyrus ^{**/¥¥}	12.30	4490	- 6	- 86 0
<i>Right lingual gyrus</i>	<i>9.18</i>		<i>12</i>	<i>- 88 6</i>
<i>Left lingual gyrus</i>	<i>8.64</i>		<i>- 16</i>	<i>- 90 4</i>
Left superior medial frontal cortex ^{**/¥¥}	10.60	1944	- 4	32 42
<i>Right anterior cingulate cortex</i>	<i>4.60</i>		<i>10</i>	<i>36 22</i>
Left insula/Left Inferior orbitofrontal cortex ^{**/¥¥}	9.80	3671	- 36	24 - 4
<i>Left dorsolateral prefrontal cortex</i>	<i>7.69</i>		<i>- 44</i>	<i>28 22</i>
<i>Left dorsolateral prefrontal cortex</i>	<i>6.43</i>		<i>- 42</i>	<i>14 28</i>
Right Insula ^{**/¥¥}	8.71	958	34	24 - 4
<i>Right Insula/Right inferior orbitofrontal cortex</i>	<i>8.03</i>		<i>44</i>	<i>22 - 8</i>
Left inferior parietal cortex ^{**/¥¥}	8.66	1279	- 44	- 56 42
<i>Left inferior parietal cortex</i>	<i>7.71</i>		<i>- 42</i>	<i>- 58 52</i>
Left precuneus ^{**/¥¥}	6.31	256	- 8	- 70 40
Right cerebellum, posterior lobe, Crus I ^{*/¥¥}	5.56	185	40	- 66 - 28
Right inferior parietal cortex ^{**/¥¥}	5.23	297	48	- 48 42
Right cerebellum, posterior lobe, Crus I/Crus II ^{*/¥¥}	5.21	152	10	- 76 - 30
Right dorsolateral prefrontal cortex ^{**/¥}	4.80	347	44	28 26
<i>Right dorsolateral prefrontal cortex</i>	<i>4.08</i>		<i>52</i>	<i>28 30</i>
Left superior medial frontal cortex ^{**/¥¥}	8.35	4826	- 4	34 40
Alcoholics				

Brain regions	Peak <i>T</i> values	k	MNI coordinates		
			<i>x</i>	<i>y</i>	<i>z</i>
<i>Left inferior orbitofrontal cortex</i>	7.19		-38	24	-6
<i>Left dorsolateral prefrontal cortex</i>	6.39		-42	26	22
Left lingual/calcarine cortex ^{**} / _{‡‡}	8.04	3813	-6	-86	0
<i>Right lingual gyrus/cuneus</i>	7.63		8	-88	2
<i>Right cuneus</i>	6.32		16	-90	22
Left inferior parietal cortex ^{**} / _{‡‡}	5.86	494	-46	-54	44
<i>Left inferior parietal cortex</i>	4.76		-42	-60	50
Right cerebellum, posterior lobe, Crus I/lobule VI ^{‡‡}	5.56	190	16	-82	-22
Left middle temporal cortex ^{‡‡}	5.21	126	-58	-24	-4
Right insula [‡]	5.11	218	32	24	-4
Between-group contrasts					
Controls > Alcoholics contrast	Left superior parietal cortex ^{**}	395	-20	-54	52
Alcoholics > Controls contrast	Right superior frontal cortex ^{**} / _{‡‡}	392	22	40	40
	Left superior frontal cortex ^{**}	252	-20	46	36

^{*} Activation clusters significant at $P_{FDR} < 0.05$ corrected
[‡] Activation peak significant at $P_{FDR} < 0.05$ corrected
^{**} Activation clusters significant at $P_{FWE} < 0.05$ corrected
^{‡‡} Activation peak significant at $P_{FWE} < 0.05$

Table 4
Group differences in functional connectivity using the right insula as seed

Brain regions	Peak <i>T</i> values	<i>k</i>	MNI coordinates		
			<i>x</i>	<i>y</i>	<i>z</i>
Seed from the within-group analysis in the alcoholic group					
Right insula [32 24 -4] as seed					
Controls > Alcoholics	Left dorsal anterior cingulate cortex *	4.00	1212	0	14 44
Alcoholics > Controls	Left lingual gyrus *	4.63	3073	- 6	- 84 - 8
	Right ventromedial prefrontal cortex *	4.31	1111	10	50 - 10

* Clusters significant at $P_{FWE} < 0.05$ corrected