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Synchrony of corticostriatal-midbrain activation enables normal inhibitory control and conflict processing in recovering alcoholic men

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Abstract

Background—Alcohol dependence is associated with inhibitory control deficits, possibly related to abnormalities in frontoparietal cortical and midbrain function and connectivity.

Methods—We examined functional connectivity and microstructural fiber integrity between frontoparietal and midbrain structures using a Stroop Match-to-Sample task with functional MRI and diffusion tensor imaging in 18 alcoholics and 17 controls. Manipulation of color cues and response repetition sequences modulated cognitive demands during Stroop conflict.

Results—Despite similar lateral frontoparietal activity and functional connectivity in alcoholics and controls when processing conflict, controls deactivated the posterior cingulate cortex (PCC), whereas alcoholics did not. Posterior cingulum fiber integrity predicted the degree of PCC deactivation in controls but not alcoholics. Also, PCC activity was modulated by executive control demands: activated during response switching and deactivated during response repetition. Alcoholics showed the opposite pattern: activation during repetition and deactivation during switching. Here, in alcoholics, greater deviations from the normal PCC activity correlated with higher amounts of lifetime alcohol consumption. A functional dissociation of brain network connectivity between the groups further showed that controls exhibited greater corticocortical connectivity between middle cingulate, posterior cingulate, and medial prefrontal cortices than alcoholics. By contrast, alcoholics exhibited greater midbrain-orbitofrontal cortical network connectivity than controls. Degree of microstructural fiber integrity predicted robustness of functional connectivity.

Conclusion—Thus, even subtle compromise of microstructural connectivity in alcoholism can influence modulation of functional connectivity and underlie alcohol-related cognitive impairment.

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Keywords

Functional connectivity; functional MRI; diffusion tensor imaging; white matter fiber tractography; Stroop task; Alcohol Use Disorder

Introduction

Neuroadaptive changes occur in the brain's response to chronic alcohol consumption. The circuits involved in these neuroadaptive changes are anchored in midbrain areas with dopaminergic and glutamatergic projections to cortical and striatal sites: ventral striatum for cue-induced alcohol-seeking (1), striato-pallado-thalamic loops for automaticity of behavior (2), and prefrontal cortices for attentional selection and executive control of pre-potent responses (3–4). In alcohol abusers, neuroadaptation of reward circuits interferes with normal functional connectivity between midbrain, striato-thalamic, and prefrontal nodes involved in mediating attention (5) and decision making (6). Despite these clues, it is not yet fully understood how chronic alcoholism affects dynamic functional connectivity of brain systems while engaged in tasks.

Even minimal disruption of neural connectivity can have a significant impact on the interaction of brain circuits that regulate reward, attention, and executive control (7–8). Functional connectivity is typically defined in terms of synchrony between brain regions demonstrating spontaneous fluctuations in hemodynamic activity measured in the “resting state” that is, in the absence of externally-driven task demands, and are considered intrinsic activity of the brain (9). Alcoholism may affect intrinsic networks (10), including the default mode network (DMN) linking posterior cingulate and medial prefrontal cortices, that are normally decoupled while engaged in a task, presumably for efficient processing, but highly connected during rest (11). Consequently, primary nodes of the DMN such as the posterior cingulate cortex (PCC) (12–13) may play a role for the brain's balance between activation and deactivation to task demands (14) for resource maximization. The modulation of functional network connectivity by different task demands (15) may be affected in alcoholism. Because efficient communication between brain regions depends on white matter fiber tract integrity (16–17), compromised structural integrity may further alter functional connectivity between brain regions (12,18).

Excessive alcohol consumption can adversely affect white matter fibers, thereby disrupting transmission of information between brain sites (17–19). Even minor disruption of brain structural connectivity without frank lesions may pose the need for compensatory task-specific functional connectivity adjustments. Functional recovery in abstinent alcoholics may reflect recovery of structural connectivity or, alternatively, a strengthened functional connectivity to unaffected nodes forming a compensatory network (20). Thus, executive control, such as the successful inhibition of a pre-potent response, probably requires both intact structural and robust functional connectivity between multiple task-specific regions (19).

To investigate the effects of chronic alcoholism on microstructural and functional brain networks that underlie inhibitory control function, we addressed automaticity of responses arising from repetition learning, a mechanism that likely plays a key role in situations when inhibition of over-learned behavior is required, such as abstaining from alcohol. We used task-related functional magnetic resonance imaging (fMRI) obtaining measures of functional activation and connectivity among midbrain, limbic, and prefrontal regions and between dorsolateral prefrontal and parietal cortices. This conflict resolution task varied visual attentional demands by using visual cues that either matched or did not match the color of

the upcoming Stroop stimulus (21). Executive control demands were manipulated by requiring subjects either to switch responses or to repeat the same response several times in a row. In addition, MR diffusion tensor imaging (DTI)-based fiber tracking quantified the microstructural integrity of cingulate fiber bundles, which connects frontal and posterior brain regions relevant to attentional control processes assessed with the Stroop task using fMRI and functional connectivity (fcMRI). We tested two principal hypotheses: 1) the levels of functional activity (fMRI) and connectivity (fcMRI), indexed as correlated time courses in task-related activation between cortical and subcortical network nodes, would be related to the degree of integrity of inter-nodal network microstructural connectivity of cingulate bundles (DTI tractography); 2) chronic alcoholism would exhibit compromised structural (DTI tractography) and functional connectivity (fcMRI) between distributed attention and executive control network nodes enabling efficient inhibitory control.

Methods and Materials

Participants

Groups comprised 18 alcoholic men and 17 control men. Alcoholics were recruited from local rehabilitation programs; controls were volunteers from the local community. All subjects were screened with the Structural Clinical Interview for DSM-IV (SCID) (22) and a clinical examination to rule out other Axis I diagnoses or non-alcohol substance abuse. All alcoholics met DSM-IV criteria for alcohol dependence; none had current dependence; 5 alcoholics met criteria for sustained full remission, and 13 alcoholics met criteria for early full remission. Subject groups were matched in age, handedness, and other demographic variables (Table 1; Supplement).

All participants gave written informed consent to participate in this study, which was approved by the Institutional Review Boards at SRI International and Stanford University School of Medicine.

Stimuli and experimental design

Study participants underwent cognitive testing and additional behavioral testing during fMRI image acquisition. Structural and functional MR imaging data were acquired using a clinical whole-body GE 3T scanner. Using a back-projection system during the fMRI session, participants viewed stimuli on a mirror attached to the head coil.

Stroop Match-to-Sample Task—Stimuli were created and presented with PsyScope software and were synchronized with MRI acquisition using a PsyScope button box as interface (23). Subjects matched the color of a cue stimulus displayed for 450 ms in the center of the screen to the color of a Stroop target stimulus that appeared for 1100 ms after an inter-stimulus interval of 300 milliseconds. Cue and target colors were red, green, or blue. Total trial duration was 3.3 sec. The color cue either matched or did not match the color of the Stroop target, which was either congruent (word blue written in blue font color) or incongruent (word blue written in red font color). The Stroop effect is defined as the difference in reaction time (RT) to incongruent and congruent stimuli. For incongruent-nonmatch conditions, the cue's color always matched the word's content (e.g., red cue, word RED written in green font color) (Figure 1) (21, 24–26).

Subjects pressed a YES-key for cue-target color matches and a NO-key for nonmatches using their right hand, yielding accuracy and RT measures. To test the effect of repetitive behavior on cognitive control and conflict resolution, we presented trials in two block types: mixed and same response blocks (Figure 1). In mixed-response blocks, both match and non-match trials were presented and required switching between YES and NO responses,

whereas same-response blocks contained either match (YES-responses) or nonmatch trials (NO-responses) and did not require response switches. To quantify Stroop effects within a block design, incongruent and congruent trials were never mixed within a block. Mixed-response and same-response blocks comprised the same number of trials. Total number of trials was 96 per run. Two runs were presented with 16 blocks each (1 block = 9TRs or 6 trials; TR=2.2sec). Test instructions were reviewed with the subject in a practice session before entering the scanner and again through the scanner's intercom system before each run. Subjects had a short break between run 1 and run 2, but remained in the scanner.

Magnetic Resonance Imaging (MRI)

Data acquisition and analyses—Whole-brain functional MRI and DTI data were acquired with an 8-channel head coil at a 3T GE whole body scanner. Detailed description of fMRI (21) and diffusion tensor imaging (DTI) (19) data acquisition and analyses are provided in the Supplement.

For fMRI analysis, standard preprocessing and statistical analyses were performed using the SPM8 software package (Wellcome Department of Cognitive Neurology), and for functional connectivity analysis (fcMRI), the “conn” toolbox was used as implemented SPM8. Analyses were carried out with a joint-expected probability threshold of $p=0.01$ for height and $p=0.05$ for extent family-wise-error (FWE) corrected for the whole brain volume (27). Montreal Neurological Institute (MNI) coordinates are reported in the text, and fMRI and fcMRI result tables provided in the Supplement. DTI-based fiber tracking of cingulum tracts was performed with the software by Gerig et al. (28), based on the method of Mori and colleagues (29–31). Mean fractional anisotropy (FA), longitudinal diffusivity ($\lambda_l = \lambda_1$) and transverse diffusivity ($\lambda_t = [\lambda_2 + \lambda_3]/2$) for each of the three sections of the cingulate bundle (superior, posterior, inferior) were the units of analysis.

Statistical analyses

For behavioral data analysis, repeated measures analysis of variance (ANOVA) was used to test for group effects (alcoholics, controls) as between-subjects factor and to test for Stroop effects (incongruent/congruent), color match effects (nonmatch/match), and response block effects (mix/same) as within-subject factors. For DTI data analysis, group differences in FA and diffusivity measures (λ_l and λ_t) were tested with analysis of variance (ANOVA). To examine the relationships predicted between DTI measures (FA and diffusivity), task-related functional regional brain activation and the behavioral measures of Stroop performance, we used 2-tailed Pearson correlation in each group separately. We used 1-tailed Pearson correlation to test directional hypothesis on the effects of lifetime alcohol consumption on behavior and brain function. The alpha level was set to 0.05 for all statistical tests, including hypotheses-driven analyses of structure-function relationships. Bonferroni corrected p -levels were applied for multiple comparisons where applicable.

Results

Behavioral results

Stroop task performance—Overall reaction time (RT) during Stroop-task performance did not differ between alcoholics and controls ($F(1,33)=1.92, p=0.18$). An ANOVA on RT yielded a 4-way interaction involving group (ALC, CTL), Stroop (incongruent/congruent), color-match (nonmatch/match), and response block (repetition/switching) ($F(1,33)=5.09, p=0.031$) (Figure 2). Following up on the 4-way interaction, post-hoc analyses compared group differences for Stroop effects ($RT_{INC} - RT_{CON}$) from each condition (match/nonmatch; response-repetition/response-switching). Alcoholics showed smaller Stroop effects than controls for response-repetition-match ($F(1,33)=6.12, p=0.019$) but not

response-repetition-nonmatch ($F(1,33)=0.01$, $p=0.9$), response-switching-match ($F(1,33)=0.01$, $p=0.9$), or response-switching-nonmatch ($F(1,33)=0.48$, $p=0.5$) conditions. These smaller Stroop effects in alcoholics than controls resulted from less benefit from response-repetitions and valid color cueing in congruent trials.

In addition, the smaller Stroop-match effects during response-repetition (less benefit) in alcoholics correlated significantly with greater lifetime alcohol consumption (Figure 3). Smaller Stroop effects during response-repetition further correlated with younger age at onset of alcohol dependency ($r=.61$, $p=0.004$; $Rho=.61$, $p=0.003$). Length of sobriety was not related to performance.

Functional MRI results

With task-activated functional MRI data, we first asked which brain regions in alcoholics and controls were activated and which were deactivated during Stroop processing, i.e., when comparing incongruent and congruent trials. Given the 4-way interaction, we further asked whether Stroop activation would differ between groups as a function of response-repetition or color-cueing.

Stroop (INC>CON)—Over all subjects, incongruent Stroop targets (e.g., the word RED printed in blue) activated left middle [$x=-48$; $y=14$; $z=40$] and inferior frontal [$x=-51$; $y=20$; $z=22$] cortical regions and left inferior parietal lobe [$x=-51$; $y=-55$; $z=34$] more than congruent Stroop targets (e.g., the word RED printed in red). Groups did not significantly differ in left fronto-parietal activation pattern, but alcoholics activated midbrain regions [$x=9$; $y=-4$; $z=-5$] during Stroop conflict processing more than controls. The opposite contrast (CON>INC) revealed that alcoholics did not show the Stroop-related deactivation in the cuneus [$x=0$; $y=-79$; $z=34$] and posterior cingulate cortex (PCC) [$x=-12$; $y=-52$; $z=10$] seen in controls (Figure 4A; Table S1 in the Supplement).

Interaction between groups and Stroop response-repetition—Two regions showed a significant group-by-Stroop-response-block interaction: Relative to controls, alcoholics showed greater activation of bilateral PCC [$x=0$; $y=-40$; $z=19$] and midbrain areas (substantia nigra/subthalamic nuclei) [$x=12$; $y=-13$; $z=-5$] during response-repetition than switching (Figure 4B; Table S1 in the Supplement).

Interaction between groups and Stroop for color cueing—The block design allowed analyses of color-cueing effects separately for response-repetition blocks. PCC [$x=-9$; $y=-49$; $z=13$] and hippocampal [$x=-27$; $y=-16$; $z=-14$] activity differed between groups as a function of color-cue validity. When a valid cue correctly predicted the Stroop word's color (Stroop-match), alcoholics deactivated PCC and cuneus [$x=0$; $y=-79$; $z=34$] less than controls (between-groups contrast). The within-group contrast showed that controls deactivated the PCC [$x=0$; $y=-40$; $z=19$] more during incongruent-match trials (INC>CON); the other face of this contrast indicates that controls activated the PCC during congruent-match (CON>INC) response-repetition blocks. For Stroop (INC>CON) processing with invalid, nonmatching color cues (Stroop-nonmatch), alcoholics activated the left hippocampus [$x=-27$; $y=-16$; $z=-14$] less than controls (Table S1 in the Supplement).

Lifetime alcohol consumption and Stroop activation—Based on the assumption that lifetime alcohol consumption would predict group differences in brain activation, we used correlational analyses to test the relation between alcohol consumption and activity in PCC and midbrain during Stroop response-repetition and switching (Figure 2B). In support of our hypothesis, the amount of lifetime alcohol consumption predicted the deviant activation and deactivation patterns observed in alcoholics: During Stroop response-

repetition, higher amounts of alcohol consumption predicted greater PCC ($r=.50$, $p=0.003$; $Rho=.58$, $p<0.0001$, $n=33$) and midbrain activation ($r=.47$, $p=0.006$; $Rho=.44$, $p=0.01$, $n=33$). During Stroop response-switching, higher amounts of alcohol consumption predicted lower PCC ($r=-.49$, $p=0.004$; $Rho=-.51$, $p=0.002$, $n=33$) and midbrain activation ($r=-.43$, $p=0.013$; $Rho=-.41$, $p=0.017$, $n=33$) (Figure 5). Correlations were significant with Bonferroni-correction for multiple comparisons, which required $p<0.025$ for directional hypotheses.

Functional connectivity

ROI-to-voxel functional connectivity—For each group, we derived functional connectivity maps, indexing ROI-to-voxel synchronous activity, via time series correlations of activity over 324 time points for the regions showing significant group-by-task activation contrasts: PCC/cuneus and midbrain. Using the cortical PCC as seed region, both groups showed extensive functional connectivity to motor, supplementary motor areas, and bilateral temporal cortices. Controls showed extensive PCC connectivity to medial prefrontal cortices that was not as widespread in alcoholics. However, group comparison revealed that alcoholics had less synchronized activity than controls, mainly between posterior (PCC) and middle cingulate cortices (MCC) [$x=12$; $y=-4$; $z=37$] (Figure 4C; Table S2 in the Supplement).

Using the *midbrain* as the seed region, both groups showed synchronous time series with bilateral inferior frontal and orbitofrontal regions. Alcoholics showed more midbrain connectivity to the middle cingulate cortex [$x=9$; $y=-1$; $z=37$] and striatal regions [$x=-30$; $y=-1$; $z=7$] than controls (Figure 4C; Table S2 in the Supplement).

Brain microstructure-function relationships

Cingulate fiber bundles—Separate group-by-regional cingulate bundle sector ANOVAs were calculated for FA, λ_l , and λ_t with group (alcoholics, controls) as between-subjects factor and the cingulate fiber bundle sectors (superior, posterior, inferior) and hemisphere as within-subject factors. Significant 3-way interactions occurred for FA ($F(1,31)=5.63$, $p=0.01$); although λ_t showed a trend ($F(1,33)=2.63$, $p=0.06$), λ_l did not ($F(1,33)=0.03$, $p=0.89$). Overall, cingulate bundle integrity was not affected in alcoholics except for statistically significant, albeit subtle, compromise in left-hemispheric posterior cingulate fibers.

Fiber integrity and brain activation—Using correlation analyses, we tested for group differences in the relationship between left-hemispheric posterior cingulum fiber integrity (FA) and PCC activation during Stroop response-repetition. In controls, but not alcoholics ($r=-.04$, *ns*), posterior cingulum fiber integrity, indexed by higher FA, predicted more pronounced PCC deactivations ($r=-.60$, $p=0.006$) (Figure 6). This posterior cingulate function–microstructure correlation differed significantly between alcoholics and controls ($z=1.75$, $p<0.05$) (r to z_r transformation [$z_r=0.5 \log_e(1+r)(1-r)$] (32)).

Fiber integrity and functional connectivity—To explore whether functional connectivity differences in alcoholics and controls were related to microstructural degradation in alcoholics, we correlated left posterior cingulum FA with the time-series correlation values (z -transformed) for posterior and middle cingulate cortex (PCC-MCC) connectivity (Table S1 in the Supplement) and midbrain-putamen and midbrain-MCC functional connectivity (Table S1 in the Supplement). In alcoholics, greater left posterior cingulum fiber degradation (lower FA) predicted stronger midbrain-MCC functional connectivity for Stroop processing during more difficult response-switching conditions ($r=-.56$, $p=0.016$). By contrast, in controls, greater fiber integrity (higher FA) predicted

stronger functional midbrain-putamen connectivity for Stroop processing during easier response-repetition conditions ($r=.70$, $p=0.002$). Correlations were significant when Bonferroni-corrected for multiple comparisons, which required $p<0.017$ for undirectional hypotheses.

Fiber integrity and brain activation as predictors of performance—Behavioral results indicated reduced benefits from valid color cues in congruent-match trials resulting in smaller Stroop effects ($RT_{INC}>RT_{CON}$) in alcoholics than controls, specifically in response-repetition blocks (Figure 2). To test whether this effect was predicted by brain function and its microstructure, we used multiple linear regression analyses and entered PCC activation during Stroop-match response-repetition (Table 2C), left posterior cingulum fiber integrity (FA), and lifetime alcohol consumption (kg) as predictors of Stroop-match performance. For alcoholics, all variables together accounted for 65% of the total variance of behavioral Stroop-match effects ($F(3,17)=8.8$, $p=0.002$), with posterior cingulum FA ($t=3.1$, $p=0.008$) and lifetime alcohol consumption ($t=3.5$, $p=0.003$) contributing independently over and above the contribution of PCC activity ($t=-1.5$, ns). The regression model was not significant for controls ($F(3,14)=0.05$, ns).

Discussion

Using multimodal neuroimaging this study revealed substantial diagnosis-specific differences in the neural substrates invoked to process Stroop conflict, i.e., when matching the font color of an incongruent color-word stimulus to the color of a cue. Although alcoholics and controls performed equally well overall on the Stroop Match-to-Sample task and showed similar regional brain activation patterns in response to incongruent relative to congruent color-word information, five critical differences between the groups emerged: 1) the only test condition more challenging for alcoholics than controls was the easiest; 2) level of posterior cingulate cortex (PCC) deactivation was less and midbrain activation was more in alcoholics than controls; 3) PCC and midbrain activity was modulated by executive control demands and differed between the two groups with the degree of this modulation being predicted by the amount of lifetime alcohol consumption; 4) alcoholics showed greater midbrain connectivity to striatal and middle cingulate cortex (MCC) regions but less PCC-MCC connectivity than controls; and 5) this enhanced midbrain-MCC connectivity, particularly for more difficult response-switching conditions, was related to white matter structural compromise of posterior cingulum fiber bundles. Further, better posterior cingulate white matter fiber integrity in controls predicted the degree of PCC deactivation during Stroop processing.

First, performance differences were observed only for the easiest Stroop condition. When a valid color cue predicted the Stroop word's color correctly during response repetition blocks, alcoholics showed smaller Stroop effects, suggesting that the benefit from repetitive congruent-match trials typically seen in healthy adults was attenuated in alcoholics (cf., 21). When a stimulus sequence follows an underlying regularity, adaptation from implicit learning can occur (33), and one would expect less cognitive effort processing regular stimulus-response sequences (34–36). That alcoholics derived less benefit from repetitive valid cueing could indicate compromised implicit learning for repetitive, more automatic stimulus-response mappings (37).

Second, despite the fact that both groups activated lateral frontoparietal regions well known to be associated with voluntary, top-down attention (38–40) and conflict resolution (21, 41–42), the groups differed in regional deactivation and interaction of brain systems that regulate reward, attention, and executive control. Alcoholics, in contrast to controls, did not deactivate the PCC in the easiest task condition, i.e., repetitive Stroop-match trials. It can be

speculated that the task-dependent balance of activation and deactivation allows maximization of resources (14). The PCC has been associated with an intrinsic task-independent network, is considered a hub in the default mode network (DMN) because of its functional interconnectedness to other DMN regions, and appears to be preferentially deactivated during cognitive tasks (14,43) and active during rest, i.e., when individuals are not focused on external environments (13,44–45). In our study, activity of the PCC was modulated by task demands, suggesting that regions that are part of the DMN also play an active role during task processing. The normal DMN deactivation pattern was disturbed in chronic alcoholism, possibly via alcohol-related neuroadaptation of mesostriatal-cortical pathways. For example, a recent study combining positron emission tomography (PET) and fMRI showed that striatal dopamine transporter (DAT) availability can modulate task-related DMN deactivation (46). Also, similar to a recent fMRI study in cirrhotic patients (47), absence of PCC deactivation during a Stroop task may predict or be a marker of a greater need in alcoholics to use reserve network resources to achieve comparable performance levels to that of controls.

Third, in addition to the enhanced PCC activation, alcoholics also activated a midbrain cluster that involved substantia nigra and subthalamic nucleus and extended to the red nucleus and ventral tegmental area during response-repetition in contrast to response-switching, whereas controls deactivated these regions. That the amount of lifetime alcohol consumption predicted the degree to which this modulation of brain activity was deviant from the normal modulation suggests that the observed group differences do, at least to some extent, result from heavy drinking and not solely from differences predating the onset of alcoholism. Recently, an fMRI study demonstrated that blood-oxygen-level-dependent (BOLD) responses in the ventral tegmental area reflect midbrain dopaminergic signals (48). In healthy adults, dopamine transporters in striatum (measured with PET) modulated BOLD neuronal activity in the precuneus and cingulate gyrus (46). Furthermore, cocaine abusers have shown enhanced midbrain activation to drug cues and disrupted midbrain-thalamo-cortical functional connectivity suggesting drug-related neuroadaptions of dopaminergic midbrain systems (49). Considering the multiple roles of midbrain regions in reward (2, 50), sensorimotor integration (51) and motor-based learning (52–53), we speculate that greater midbrain activation during Stroop response-repetition than switching in alcoholics may reflect poor down-regulation of midbrain responsiveness to repetition learning, or relative to controls, up-regulation of midbrain responsiveness to low cognitive demand ((21) for less cognitive conflict with repetition in healthy subjects). This group difference in activation pattern cannot be explained by task difficulty per se because, although same-response blocks were easier than mixed-response blocks, as indicated by faster reaction times for response-repetitions than switches, this advantage was similar in both groups.

Fourth, up-regulation of midbrain activity occurred in alcoholics. Also present were larger midbrain–striatal and midbrain–middle cingulate cortex functional connectivity and lower corticocortical posterior–middle cingulate cortex connectivity in alcoholics than controls. The middle cingulate cortex is associated with processes of response selection (54) and decision-making (55–57). Its enhanced synchrony with activity in the striatum and midbrain but dampened synchrony with activity in the posterior cingulate cortex (PCC) in alcoholics may reflect difficulty in adapting functional network activity to upcoming executive task demands. In particular, the PCC is considered a ‘hub’ for multiple networks involving both rest and task-related networks that function together to support complex behavior (58). Within the Stroop task-related network, the posterior and middle cingulate cortices appear to mediate functional connections between voluntary (top-down) attention, executive control network regions, and midbrain nodes of the reward network associated with automatic (bottom-up) attention and behavioral conditioning to optimize utilization of resources for response selection (59–61). It can be speculated that functional recovery occurs through

network adaptation or reorganization (62). In the present study, abstinent alcoholics did not significantly differ from controls in overall task performance and Stroop-related BOLD response but did so in the functional connectivity of network nodes mediating executive control demands. We interpret this functional difference as reflecting neuro-functional compensation, similar to recruitment of additional brain regions, beyond those normally needed to accomplish the task (20, 63–64).

In alcoholics, we further observed task-related activation synchrony between limbic (hippocampus, amygdala) and midbrain regions. An association between reward-related fMRI activation of dopaminergic midbrain with hippocampus-dependent long-term memory formation has been recently found in healthy subjects (65). Stroop stimulus processing may involve association learning where past events are integrated into mnemonic representations to enhance integrative encoding for upcoming events and to reduce effort, especially during repeated trials. For example, in a recent fMRI study using an association-learning task, coupled changes in the learning-phase activity between hippocampus and midbrain (ventral tegmental area/substantia nigra) predicted successful behavioral generalization for future events (66). In alcoholics and controls, the midbrain cluster was also functionally connected to orbitofrontal regions possibly conveying the learning-behavior translation for repetitive stimulus-response mappings (52).

The fifth finding was a subtle microstructural deficit in posterior cingulum fiber tracts of alcoholics. The cingulate bundle of the limbic system has long and short fibers that course along cingulate cortex and parahippocampal gyrus (67–68). Its anterior extent is connected to amygdala, nucleus accumbens, thalamus, and dorsolateral prefrontal cortex, and the posterior extent to temporal association, medial temporal, parietal, and orbitofrontal cortices. In alcoholics, poorer posterior cingulate fiber integrity predicted greater midbrain-MCC connectivity for more difficult Stroop response-switching conditions, whereas in controls greater fiber integrity predicted greater midbrain-striatal connectivity for the more automatic Stroop response-repetition conditions. In other words, when executive control demands were high, alcoholics engaged a midbrain-MCC network. This alternative network engagement closely depended on the degree of microstructural fiber compromise likely forming a compensatory network supporting normal performance.

One of the first combined structure-function connectivity studies reported that resting-state functional connectivity reflects structural white matter fiber connectivity (69). Our results add to this finding by demonstrating that in both groups task-related functional connectivity in a cingulate-midbrain network was associated with the condition of cingulate white matter fibers. As hypothesized, greater microstructural integrity predicted greater functional connectivity, suggesting that even subtle compromise of structural connectivity in alcoholism has potential to modulate functional connectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(Top) Stroop Match-to-Sample paradigm, illustrating four conditions: (1) congruent-match, (2) incongruent-match, (3) congruent-nonmatch, and (4) incongruent-nonmatch. A color cue (XXXX) presented for 450 ms was followed by an incongruent or congruent Stroop target stimulus that appeared for 1100 ms after an inter-stimulus interval (ISI) of 300 ms. The inter-trial interval (ITI) was 1450 ms. Subjects matched the color (red, green or blue) of the cue to the ink color of the Stroop stimulus. (Bottom) fMRI block design illustrated for 8 blocks: Stroop stimuli in each block were either congruent (word BLUE written in blue font) or incongruent (word BLUE written in red font). Four blocks contained mixed YES- and NO responses: 2 incongruent with match and non-match trials (incongruent, INC), 2 congruent with match and nonmatch trials (congruent, CON). In addition, four same-response blocks were presented: congruent-match, congruent-nonmatch, incongruent-match, incongruent-nonmatch. Trials presented in same- and mixed-response blocks were the same, only the order of trials differed, i.e., in same response blocks, either six match trials or six non-match trials were presented in a row, whereas in mixed-response blocks, three match and three nonmatch trials were presented in random order. Each block consisted of 6 trials, and lasted for of 19.8 s. In response-repetition blocks, cue-target color either matched or did not match, in response-switching blocks, match and nonmatch trials were mixed. In total 32 blocks were presented in pseudo-random order ensuring that each condition was equally often represented (24).

Thus, Debriefing after fMRI scanning revealed that none of our subjects was aware about the blocked nature of the task.

Figure 2.

Mean reaction times (ms) and standard errors for each condition (congruent-match, incongruent-match, congruent-nonmatch, and incongruent-nonmatch) and response block (response repetition, response switching) for alcoholics (ALC) and controls (CTL).

Figure 3.

Pearson correlation between lifetime alcohol consumption (kg) and the behavioral Stroop-match effects ($RT_{\text{incongruent}} - RT_{\text{congruent}}$) for response repetition trials for alcoholics (ALC) and controls (CTL). In ALC, higher amounts of lifetime alcohol consumption were associated with smaller Stroop-match effects during response repetition (less benefit).

A. Stroop-related activity

B. Group-by-Stroop interaction as a function of response-repetition

C. PCC and midbrain seed-to-voxel functional connectivity

Figure 4.

Functional magnetic resonance imaging (fMRI): (A) Stroop-related brain activation (incongruent, INC > congruent, CON) (left) and deactivation (CON > INC) (right) merged over response blocks; alcoholic subjects (ALC), control subjects (CTL). (B) Group-by-Stroop interaction (left) showing higher activation in the posterior cingulate cortex (PCC) and a ventral midbrain cluster (vMB) for response repetition than switching in ALC relative to CTL, and bar graphs (right) illustrating the extracted mean signal change (INC – CON) from the PCC and vMB clusters for each response block (repetition, switching) and for each group. (C) Functional connectivity MRI: Seed-to-voxel synchronous activation for the PCC seed (upper panel) and the ventral midbrain (vMB) seed (lower panel) for each response block and group. BOLD, blood oxygen level dependent; MR, magnetic resonance; L. SMG, left supramarginal gyrus; IPL, inferior parietal lobe; L. DLPFC, left dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; MCC, middle cingulate cortex; SMA, supplementary motor area.

Figure 5. Pearson correlation between lifetime alcohol consumption (kg) and activity in PCC and midbrain for response-repetition and response-switching blocks for alcoholics (ALC) and controls (CTL). In ALC, higher amounts of lifetime alcohol consumption predicted the degree to which this brain activity was deviant from the normal modulation.

Figure 6.

(TOP LEFT) DTI-based visualization of cingulate fibers divided into three sectors: superior, posterior, and inferior bundles. (TOP MIDDLE) Illustration of posterior cingulate cortex (PCC) deactivation during Stroop processing and (TOP RIGHT) bar graphs illustrating the extracted mean signal change (INC – CON) from the PCC cluster for each response block (repetition, switching) and group (ALC, CTL). (BOTTOM) Pearson correlation between fiber integrity, indexed as high fractional anisotropy (FA), of the posterior cingulate fiber sector and Stroop-related deactivation of the posterior cingulate cortex during response repetition blocks (LEFT) and response switching blocks (RIGHT) for each group: controls (CTL), alcoholics (ALC).

Table 1

Group	Age	Education	NART IQ	Handedness	CROVITZ	Visual Acuity	Lifetime Alcohol Consumption (kg)	Length of Sobriety (days)
ALC	51 (6.6)	15 (3.1)	110 (7.6)	21 (5.5)	1.3 (0.6)	1.3 (0.6)	1549 (620.7)	257.7(219)
CTL	50 (14.9)	16 (2.5)	115 (6.9)	21 (8.9)	1.8 (0.9)	1.8 (0.9)	29 (45.1)	-
<i>P</i>	0.7	0.15	0.06	0.9	0.08	0.08	0.0001	

Means and standard deviations (SD) of demographic data of the two study groups: Chronic alcoholics (ALC) and controls (CTL). Between group t-tests: significance at $p < 0.05$, 2-tailed.