ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

How Acute and Chronic Alcohol Consumption Affects Brain Networks: Insights into Multimodal Neuroimaging

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Background: Multimodal imaging combining 2 or more techniques is becoming increasingly important because no single imaging approach has the capacity to elucidate all clinically relevant characteristics of a network.

Methods: This review highlights recent advances in multimodal neuroimaging (i.e., combined use and interpretation of data collected through magnetic resonance imaging [MRI], functional MRI, diffusion tensor imaging, positron emission tomography, magnetoencephalography, MR perfusion, and MR spectroscopy methods) that leads to a more comprehensive understanding of how acute and chronic alcohol consumption affect neural networks underlying cognition, emotion, reward processing, and drinking behavior.

Results: Several innovative investigators have started utilizing multiple imaging approaches within the same individual to better understand how alcohol influences brain systems, both during intoxication and after years of chronic heavy use.

Conclusions: Their findings can help identify mechanism-based therapeutic and pharmacological treatment options, and they may increase the efficacy and cost effectiveness of such treatments by predicting those at greatest risk for relapse.

Key Words: Multimodal Neuroimaging, Acute and Chronic Alcohol.

THE RECENT DECADE has seen a rapidly emerging body of scientific advances in multimodal neuroimaging that has led to a better understanding of how acute and chronic alcohol consumption affects neural networks underlying cognitive, emotional, and reward processing mechanisms that promote drinking behavior. Recent developments enabling the combination of 2 or more neuroimaging methods (e.g., structural magnetic resonance imaging [MRI], diffusion tensor imaging [DTI], and functional MRI [fMRI], arterial spin labeling or perfusion MRI, MR spectroscopy [MRS], positron emission tomography [PET], magnetoencephalography [MEG], and event-related potentials [ERP]) have become increasingly important, as no single imaging approach has the capacity to elucidate all clinically relevant characteristics of a neural network and its adaptation to the acute and chronic effects of alcohol consumption.

Structural neuroimaging has revealed cortical shrinkage (Pfefferbaum et al., 1998) and white matter degradation in alcohol abuse and dependence (Harris et al., 2008; Pfefferbaum et al., 2009), with the greatest abnormalities appearing in frontal and superior compared with posterior and inferior sites. Functional neuroimaging has revealed alcohol-related differences in brain activity during task processing. fMRI can help identify regional brain activity associated with specific cognitive and emotional functions, and how differences in regional activation relate to performance deficits after acute alcohol (Marinkovic et al., 2011) and chronic alcohol abuse (Norman et al., 2011; Schulte et al., 2010). For example, recent fMRI studies found that *acute* alcohol impairs visual perception by reducing the normal activation response to visual stimuli (Esposito et al., 2010), and also affects cognitive control mechanisms typically invoked to process high-conflict and error trials by attenuating neural activity in the anterior cingulate cortex (ACC) activity (Marinkovic et al., 2011). PET has further shown that moderate doses of alcohol reduce brain glucose metabolism, likely reflecting decreases in brain activity (Volkow et al., 2006). The use of receptor-specific radioligands has also permitted studying the association between acute oral alcohol exposure and dopamine (DA) release (Boileau et al., 2003). Used in combination with fMRI, the potential exists to determine what in the fMRI response is directly related to DA, itself.

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Chronic alcohol abuse affects the brain in enduring ways, and these effects themselves may in turn contribute to the loss of control over drinking behavior. For example, deficits in executive functioning in chronic alcoholics involved in monitoring and resolving conflict have been associated with abnormal prefrontal activity (Oscar-Berman and Marinković, 2007). A blunted rostral anterior cingulate response has been linked to deficits in emotional functioning, specifically when decoding negative emotional facial expressions (Salloum et al., 2007). fMRI can be further enhanced when combined with ERP and MEG. These techniques are particularly accurate with regard to the time course of cognitive processing and, together with fMRI, provide information on the exact temporal sequence of processes within spatially defined neural networks (Dale et al., 2000).

Other recent neuroimaging combinations include DTI tractography and functional connectivity MRI (fcMRI), which facilitate exploration of the relationship between white matter fiber integrity and functional network connectivity between brain regions and how they are altered by chronic alcohol abuse (Chanraud et al., 2011; Schulte et al., 2010). DTI tractography has also been combined with MRS to better evaluate concrete white matter regions with microstructural injury in alcoholism (Zahr et al., 2010).

The use of neuroimaging has further proven relevant for defining a neurobiological relapse risk profile in alcohol dependence. For example, a recent study of alcoholics entering into treatment for alcohol dependence showed that future relapsers had smaller brain volumes than future abstainers in regions of the mesocorticolimbic reward system that is involved in impulse control, emotional regulation, and craving (Cardenas et al., 2011).

This mini-review[1] reports recent developments in combining with neuroimaging techniques to achieve a better understanding of alcohol effects on the brain: The first section reviews how dopaminergic PET imaging, combined with fMRI, can examine the response of the brain reward system (BRS) to alcohol and alcohol's sensory properties. The second section reviews the use of combined fMRI and MEG to study the effects of acute alcohol intoxication on executive functions, such as the capacity to inhibit impulsive behavior and to select optimal response strategies. The third section will demonstrate how DTI and fMRI methods can be combined to characterize the effects of chronic alcohol on the integrity of microstructural white matter fibers connecting cortical sites in relation to functional network connectivity measures and executive control. The fourth section introduces how combining DTI, magnetic resonance spectroscopic imaging (MRSI) and perfusion MRI enhance our knowledge of the effects of alcohol and nicotine dependence on different aspects of the BRS. The final section summarizes the different neuroimaging methods that have been recently combined to identify the interactive effects between brain structural degradation and brain function in alcoholism, and offers suggestions for future research on alcohol use disorders and the human brain.

PROSPECTS FOR ALCOHOL RESEARCH OF REWARD PATHWAYS USING COMBINED FMRI AND PET

The neural activity associated with alcohol-paired cues has attracted considerable attention among alcohol researchers in recent years (Bühler and Mann, 2011). The precise role of drug-paired cues in the etiology and maintenance of addiction is not yet clear. However, it does seem clear that dopaminergic transmission in the midbrain and ventral striatum occurs in response to the appearance of a drug cue and reward learning (Berridge, 2007; Schultz et al., 1997). While this provides an attractive target to pursue in the search for neural markers of alcoholism risk and recovery potential, how these phenomena are interpreted remains a matter of debate and how they are measured in humans remains a challenge.

Dopamine in the brain's mesocorticolimbic circuit was long ago implicated as a neural system involved in the abuse potential of mind-altering drugs. Originally thought to be rewarding in and of itself (for a critical review of the early self-stimulation literature, see Wise, 1978), views of dopaminergic transmission have since evolved. Current theories center largely around the concepts of "incentive salience," or DA's ability to track when reward should arrive based on prior experience, as described in models of reward prediction error (for review, see Glimcher, 2011). In the theoretical form of incentive salience, reward cues are thought to induce a strong "wanting" that is reflected in DA neurotransmission. In the context of substance abuse, this suggests that DA is involved in a dysregulated motivational (wanting) system. Alternatively, the DA response to reward cues can be conceptualized as encoding expectations about the delivery of a reinforcer after an interval, the so-called reward prediction. Here, however, DA signaling after cue presentation reflects less the aspect of wanting, and instead the expected (learned) presence or absence of reward (Schultz et al., 1993), or even the predicted amount of reward to be delivered (Galvan et al., 2005).[2]

Considerable latitude is permitted in animal experimentation; in contrast, in vivo research with humans is more complex and limited in what can be measured. First, although the rise of functional neuroimaging has enabled significant translation of these concepts from animals to humans, there remain many important challenges. Parsing the relative contributions of drug-related conditioned stimuli (CS) from intoxication itself is a challenge, in part since much stimulus-

[1]The majority of the studies described in this mini-review were presented in symposium at RSA in 2011.

[2]It should be noted that the dopaminergic dynamics discussed in this section are not specific to alcohol, but occur with many drugs of abuse, and with nondrug rewards.

reward learning has already occurred in humans, and the pharmacologic actions of drugs such as alcohol are long-acting (for a discussion, see Kareken et al., 2011). Second, although a tremendous advancement, functional neuroimaging in its most widely available form (fMRI) can only infer neuronal activity from its hemodynamic correlates. However, we surmise here that a combination of carefully designed experiments combined with multiple imaging modalities can help elucidate the neural mechanisms underlying motivation to drink alcohol, and ultimately facilitate better treatment outcomes.

Midbrain dopaminergic projections innervate both the striatum (including nucleus accumbens, ventral putamen, ventral caudate) and prefrontal cortex (Haber et al., 2006). Several studies of fMRI's blood oxygenation level-dependent (BOLD) response show that images of alcoholic drinks (vs. control cues) activate such regions, including ACC, medial prefrontal cortex (mPFC), ventral striatum (Ihssen et al., 2011; Myrick et al., 2008), and insula (Ihssen et al., 2011; Tapert et al., 2004), which has also been implicated in drug wanting (Naqvi et al., 2007). Chemical sense cues are ever-present given alcohol's oral route of administration and are arguably the most proximal CS to intoxication during drinking. A smaller number of chemical CS fMRI studies have been performed in heavy drinkers, but they are in general agreement with the established literature using visual cues (Bragulat et al., 2008; Filbey et al., 2008; Kareken et al., 2004, 2010a,b). However, not all fMRI studies detect activation in the ventral striatum as a function of alcohol-associated cues (e.g., Heinz et al., 2004, among others). The reasons for this discrepancy remain uncertain, although the lack of a true cue-reward contingency in the scanner, combined with the putative role of DA in coding for reward prediction, might be one factor. That is, human studies do not typically have an alcohol cue that leads subjects to believe that they will become intoxicated in the scanner (see Kareken et al., 2012)—a potentially critical factor if DA plays a role in coding learned expectations. And, while fMRI does provide excellent spatial and modest temporal information, it is unable to link "activation" to a specific neurotransmitter, or even identify whether a given response is excitatory or inhibitory, as would occur from VTA GABA interneurons (Düzel et al., 2009). It is at this juncture, however, that in vivo PET can help to target DA specifically.

The PET ligand [11C]raclopride (RAC) is a DA D_2/D_3 antagonist that is useful for determining D_2/D_3 receptor availability (a.k.a., binding potential [BP]) in the striatum. However, it also is particularly well suited for detecting relative changes in striatal DA levels as a function of behavioral state (Yoder et al., 2011). For example, a study in cocaine addicts suggested that visual cocaine cues provoked DA release in the striatum, with a correlation between DA release and craving (Volkow et al., 2006). However, provoking DA release directly in cocaine addicts using methylphenidate did not elicit greater craving in a follow-up study (Volkow et al., 2008). In that study, an increase in craving was present only when visual cocaine cues were presented along with methylphenidate administration, which suggested an insufficient role for DA, but a necessary role for drug-paired cues in craving.

In alcohol studies, 2 RAC PET studies in social drinkers elicited striatal DA release to orally consumed alcohol (Boileau et al., 2003; Urban et al., 2010), where the alcohol was mixed with juice, and produced high blood alcohol concentrations (BAC) of 83 mg% and ~1.1 mg/ml body water, respectively. However, as per the discussion above, a large number of preclinical studies have focused on the significance of drug cues, as distinct from the drug's pharmacologic actions. In this case, oral ethanol (EtOH) administration does not separate the relative contributions of alcohol's taste/orosensory properties (i.e., the CS) from the effects of intoxication. Indeed, a microdialysis study in rats showed that DA was released in ventral striatum after initial oral contact (licking) with alcohol. As BAC in the brain rose, however, striatal DA release declined (Doyon et al., 2005). These data indicated that alcohol's sensory properties (a CS that predicts intoxication) were related to DA release, although DA and BAC were uncorrelated in time, again suggesting that striatal DA transmission is not a response to intoxication, per se. This idea is consistent with electrophysiological studies in animals that have shown an initial response of midbrain DA neurons to a reinforcer, but a shift of the DA response toward a predictive stimulus (CS) possessing a learned association with the reward. After the CS, DA neurons then signal unexpected outcomes by either increasing (unexpected reward following a CS indicating no reinforcement) or decreasing (unexpected reward absence) their firing rates (Schultz et al., 1997). In fact, data using the RAC PET technique with alcohol cues support the importance of the learned contingency and reward outcome (Yoder et al., 2009). In particular, alcohol's visual and olfactory cues, which subjects were told would herald imminent intoxication from intravenous alcohol, resulted in decreased striatal DA transmission when alcohol was withheld; nonalcohol cues (which subjects understood would predict saline infusion) increased DA transmission during unexpected alcohol infusion. Elsewhere, IV-EtOH alone (dissociating drug action from its gustatory and olfactory qualities) has not reliably increased DA in humans (Yoder et al., 2005; but for other reasons why a response to alcohol itself could and does occur see also Yoder et al., 2007; Ramchandani et al., 2011).

While PET can target specific receptors, it suffers from both limited temporal and spatial resolution. And, the signal-to-noise characteristics of RAC do not permit accurate detection of midbrain, limbic, and cortical DA D_2/D_3 receptors outside the striatum (for a discussion, see Yoder et al., 2011). However, RAC has the advantageous property of being easily "displaced" by endogenous DA, which allows the study of changes in DA transmission as a function of cognitive and behavioral state. It should be noted that there are practical limitations associated with this type of

experiment (cost and lack of temporal resolution). There can also be complications in designing an "ideal" experiment with an appropriate baseline that allows conclusive interpretations about whether DA is rising in one condition or falling in another (Yoder et al., 2011). RAC's insensitivity to extrastriatal DA is also an important consideration given the midbrain DA neurons that target mPFC, ACC, and orbitofrontal cortex (OFC) (for review, see Haber and Knutson, 2010). Given the lack of neurotransmitter specificity of fMRI, and PET's limitations in spatial and temporal resolution, a more complete picture of basal ganglia/limbic reward signaling might be ascertained if the 2 imaging techniques were used in tandem.

To the authors' knowledge, there has only been 1 published study using fMRI and PET conjointly to study alcohol cue reactivity in heavy drinkers (although for a similar application with monetary reinforcers, see Buckholtz et al., 2010). This interesting study by Heinz and colleagues (2004) demonstrated that ventral striatal DA D_2 receptor availability measured at rest was lower in detoxified alcoholics (compared to controls), and in alcoholics was inversely related with self-reported craving (i.e., higher craving = lower DA D_2 BP). Furthermore, striatal D_2 BP in alcoholics was also negatively correlated with (visual) alcohol cue-induced activation in rostral ACC and mPFC. Importantly, however, one cannot discern whether the relationships between striatal BP and craving (or cue-induced activation) are driven by fewer D_2 receptors or greater endogenous DA.

At Indiana University, we (Oberlin, Yoder, Džemidžic, and Kareken) are currently studying the extent to which alcohol's taste (absent measureable pharmacologic levels) is associated with both BOLD activation and concomitant changes in striatal DA receptor availability, as inferred from RAC PET (Oberlin et al., 2011). In the emerging findings from 18 heavier beer drinkers (and as presented at the RSA symposium summarized by these studies), we have found that the taste of beer does, indeed, elicit a significant BOLD response in the brain's ventral striatum (peak voxels $p < 0.001$) as compared to the taste of Gatorade®, with similar activation in the right OFC and right rostral ACC. Using RAC PET in the identical subjects, there was a significantly lower BP in the right ventral striatum during the taste of beer (as compared to the taste of Gatorade®), suggesting greater endogenous DA transmission during beer tasting. In relating the two modalities, there was a positive correlation between DA transmission in the right ventral striatal area and the rostral ACC BOLD activation to beer. This result was highly similar to the region of correlation observed in baseline DA BP/BOLD activation to alcohol cues in the Heinz and colleagues' (2004) study. Collectively, these preliminary data suggest an important role for striatal DA and rostral ACC signaling in alcohol cue processing in heavy drinkers.

Thus, we posit that future multimodal combinations of imaging technologies in alcohol research may deepen our understanding of the ways in which addicted or at-risk brains process information about alcohol and its associated cues, and eventually how such signaling is related to the neural pathology of alcoholism.

ACUTE EFFECTS OF ALCOHOL ON EXECUTIVE FUNCTIONS USING FMRI AND MEG

Stimulus evaluation (the "input" processing stream), and response preparation and execution ("output") occur in parallel and are guided by regulative functions such as selective attention, inhibition of maladaptive responses, and error monitoring ("executive"), in a seamlessly integrated manner. Even though alcohol interacts with most levels of the neuraxis, the effects of acute intoxication are particularly deleterious in situations manipulating novelty and conflicting or ambiguous task demands (Marinkovic et al., 2001; Ridderinkhof et al., 2002). By disrupting strategic decision making, alcohol may interfere with goal-directed behavior, resulting in poor self-control. Indeed, a deficit in regulatory functions and the inability to maintain inhibitory control over drinking are considered fundamental to the development of alcohol abuse both as a dispositional risk factor and as a consequence of excessive drinking (Field et al., 2010).

To explore alcohol-induced impairment of cognitive control with precision in both space and time, we have used the multimodal approach relying on complementary brain imaging modalities. More specifically, the superior spatial resolution of fMRI permits identification of the areas that are essential in different tasks and can determine where the alcohol-induced changes are occurring. However, fMRI's temporal resolution is limited by the indirect coupling of neural activity with the hemodynamic response (Buxton, 2002). In contrast, MEG and electroencephalography (EEG) can elucidate the temporal sequence ("when") of the involved neural components as they are directly and instantaneously generated by synaptic and active currents in pyramidal neurons (Hämäläinen et al., 1993). Thus, excellent temporal sensitivity of the MEG/EEG is crucial in resolving alcohol-induced effects on different stages of cognitive control, whereas the high spatial resolution of the fMRI can identify the affected neural systems (Dale et al., 2000).

Extensive evidence points to the ACC as a central node in a predominantly frontal cortical network subserving cognitive control (Botvinick, 2007). Widespread anatomical connections of the ACC with lateral prefrontal cortex, motor cortex, spinal cord, and limbic structures make the ACC suitable for its multifaceted role in self-regulation (Devinsky et al., 1995). Neuroimaging studies of acute alcohol effects on cognitive control are scant (Gundersen et al., 2008; Paulus et al., 2006). Our own fMRI results, Fig. 1 (Marinkovic et al., 2011), show that acute moderate intoxication (0.6 g/kg EtOH for men, 0.55 g/kg for women) selectively attenuates the ACC activity during both high-conflict trials and erroneous responses across different inhibitory tasks, indicating the vulnerability of the top-down control to intoxication

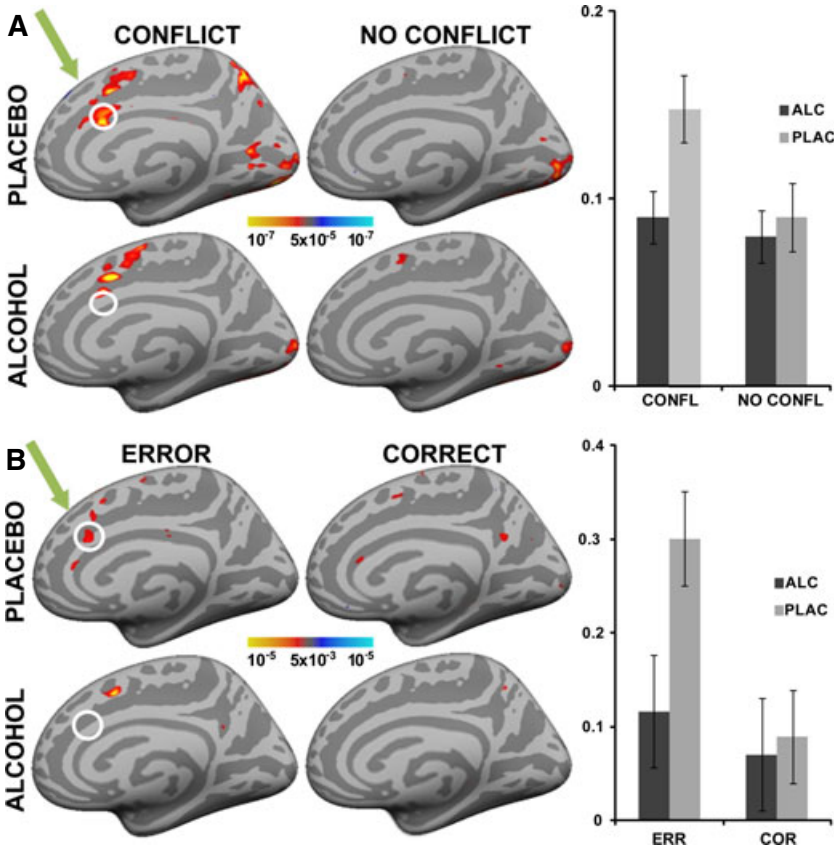

Fig. 1. Acute moderate intoxication attenuates anterior cingulate cortex activity during both high-conflict trials and errors during the Stroop task, suggesting vulnerability of the top-down processing. Shown are (**A**) the effects of Stroop conflict and (**B**) the error-related activity with voxel-wise group-average statistical maps on the left and percent signal change (±SEM) on the right. The figure is modified and used with permission of Wiley-Blackwell (Marinkovic et al., 2011).

(Ridderinkhof et al., 2002). Even though caution is warranted in interpreting fMRI-BOLD magnitude changes because of alcohol's vasoactive properties (Rickenbacher et al., 2011), this effect persists when alcohol-induced changes in cerebral perfusion are taken into account.

EEG studies indicate that event-related oscillations in theta frequency range (~4 to 7 Hz) increase as a function of cognitive control, with the ACC as a major generator (Wang et al., 2005). Reduced theta power has been observed in long-term alcoholics and individuals at risk for alcoholism (Andrew and Fein, 2010; Rangaswamy et al., 2007). In addition, the high heritability and genetic links of theta oscillations with alcohol dependence make them a suitable endophenotype of vulnerability to alcoholism (Porjesz et al., 2005). In light of this evidence, it is surprising to note that research on the acute effects of alcohol on theta oscillations has been exceedingly limited. Our own investigations have relied on the anatomically constrained MEG method that combines distributed source modeling of the MEG signal with high-resolution structural MRI, yielding "brain movies" that map statistical parametric activity estimates across time (Dale et al., 2000). The principal generator of event-related theta power to the Stroop conflict is estimated to be ACC, with contributions from fronto-parietal areas (Kovacevic et al., 2011). The conflict-related theta increase is selectively blunted by alcohol in ACC during both early, conflict detection, and later response selection stages. These results complement the evidence of the theta sensitivity to alcohol and confirm our fMRI findings that the top-down regulatory functions are selectively affected by alcohol intoxication (Marinkovic et al., 2011).

Combined neuroimaging methodology allows us to examine the spatio-temporal characteristics of alcohol-induced oscillatory changes during conflict. In addition, transient communication of the ACC with other principal executive structures relies on network oscillations, making this approach well suited for testing hypotheses about their interactions in real time and at the level of an interactive system. Our preliminary findings indicate that the alcohol-induced impairment of cognitive control may result from a disruption in synchronized theta co-oscillations between the ACC and lateral prefrontal cortex, the principal structures in the executive network. Although not discussed here, other multimodal imaging approaches show promise for mapping the changes in brain activity patterns and temporal characteristics owing to effects of acute intoxication or long-term abuse. Simultaneous acquisition of EEG and fMRI signal (Karch et al., 2008), in conjunction with

transcranial magnetic stimulation (De Ridder et al., 2011; Kahkonen, 2005), can offer insights into cortical excitability as a function of alcohol.

This research provides multidimensional insight into the neural underpinnings of alcohol's deleterious effects on regulative functions and may elucidate the neural basis of the inability to refrain from drinking, with ramifications for driving situations, work-related hazards, and other societally relevant concerns such as aggression.

CHRONIC EFFECTS OF ALCOHOL ON MICROSTRUCTURE IN RELATION TO BRAIN FUNCTIONING USING COMBINED FMRI AND DTI

Animal research and human neuroimaging studies have identified neuroadaptive changes in the brain in response to chronic alcohol consumption. The neural circuits documented are anchored in midbrain areas and their dopaminergic and glutamatergic projections to other brain structures associated with key features of addiction, such as the ventral striatum for cue-induced drug seeking (Millan et al., 2010), striatal-palladic-thalamic loops for automaticity of behavior (Koob and Volkow, 2010), and prefrontal cortices for attentional selection, and executive control of prepotent responses (Bowirrat and Oscar-Berman, 2005). To better understand the neural networks in chronic alcoholism, scientists have started to use fcMRI to measure synchrony of spontaneous or task-related fluctuations in hemodynamic activity between brain regions. This technique has identified a so-called default mode network (DMN) by documenting synchronized spontaneous fluctuations of BOLD responses between posterior cingulate cortex (PCC), cuneus, and mPFC during rest (Raichle et al., 2001). Regions of the DMN are normally highly connected during rest and functionally decoupled during task performance, presumably for efficient processing (Andrews-Hanna et al., 2010). Chanraud and colleagues (2011) recently found compromised intrinsic functional connectivity in alcoholics and recovery of functional network efficiency with prolonged abstinence.

In healthy subjects, combined DTI and fMRI data provided the first evidence that resting-state functional connectivity in the DMN reflects structural connectivity (Greicius et al., 2009). The brain's white matter fibers depict structural networks connecting subcortical and cortical brain sites. Because efficient communication between brain regions depends on white matter fiber tract integrity (Damoiseaux and Greicius, 2009; Pfefferbaum et al., 2010), compromised structural integrity from excessive alcohol use may alter functional connectivity between brain regions (Chanraud et al., 2009; Schulte et al., 2010).

To test this, we combined DTI and fMRI to characterize disruption of neural connectivity in alcoholism and its impact on the interaction of brain circuits that regulate reward, attention, and executive control (Schulte et al., 2012). Task-activated fMRI employed a Stroop Match-to-Sample task (Schulte et al., 2009) to target inhibitory control function together with automaticity of responses arising from trial repetition. This mechanism likely plays a key role in situations requiring inhibition of over-learned behavior, such as abstaining from alcohol. Overall performance was similar in abstinent alcoholics and controls; however, alcoholics showed attenuated benefits from repetition of validly cued congruent Stroop trials. This can be interpreted as compromised implicit learning for repetitive, more automatic stimulus–response mappings. The behavioral results were reflected in brain activity showing similar lateral frontoparietal activity during Stroop task processing in both groups, but a failure in alcoholics, in contrast to controls, to deactivate the PCC. Deactivation of the PCC, a key node in the DMN, during task processing is a normal pattern and was related to higher fractional anisotropy (FA), that is, integrity, of posterior cingulum fibers in controls. Furthermore, PCC and midbrain activities were modulated by task demands in controls showing deactivated PCC and midbrain during more automatic, repetitive task conditions and activated PCC and midbrain during more effortful, switching conditions. Alcoholics, however, showed the exact opposite pattern, and the degree to which this modulation was deviant to that of controls was predicted by the amount of lifetime alcohol consumption. Thus, the observed brain activity differences can be explained, at least in part, by past heavy drinking and may include conditions mitigating lifetime alcohol consumption, some of which possibly predating the onset of alcoholism.

Midbrain regions are involved in multiple brain functions involving reward (Koob and Volkow, 2010; Wise, 2009), sensorimotor integration (Dypvik and Bland, 2004), and motor-based learning (Bédard and Sanes, 2009). That alcoholics activated midbrain regions to a greater extent during repetitive than switching task conditions is consistent with their failure to benefit behaviorally from congruent Stroop trial repetitions. This may reflect poor down-regulation of midbrain responsiveness to repetition learning or, relative to control subjects, up-regulation of midbrain responsiveness to low cognitive demand. Alcoholics, compared to controls, also showed less PCC connectivity to the middle cingulate cortex (MCC), a region associated with response selection and decision making (Rushworth et al., 2007), and more midbrain connectivity to MCC and striatal regions. The enhanced midbrain–MCC connectivity in alcoholics, particularly for more difficult task conditions, was related to subtle but significant white matter structural compromise of posterior cingulum fiber bundles (Fig. 2). These findings provide evidence that even subtle disruption of white matter fiber integrity in alcoholism can affect functional circuitry of executive control and repetition learning (Schulte et al., 2012).

The combination of fMRI-connectivity and DTI-tractography enables the investigation of structure–function relations by assessing network differences in functional

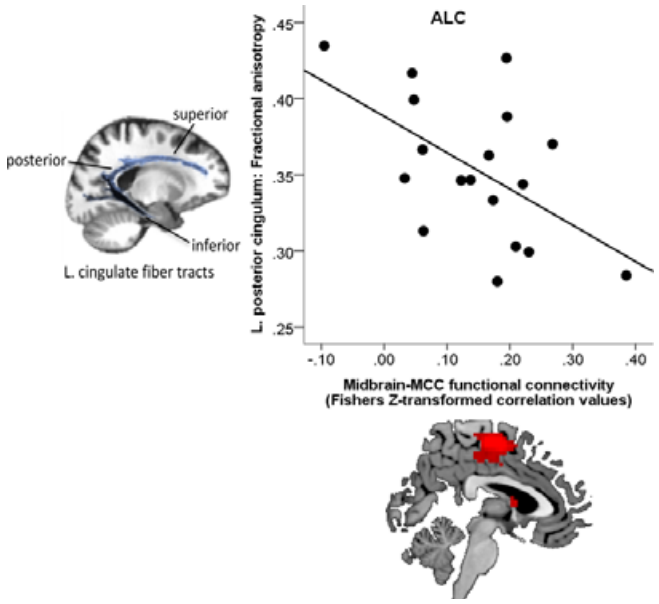

Fig. 2. Structural and functional connectivity in alcoholism: poorer integrity in left (L) posterior cingulate fiber bundles correlated with stronger midbrain–middle cingulate cortex (MCC) functional connectivity (Fishers Z-transformed correlation of blood oxygenation level-dependent signal time series in the midbrain and the MCC) (Schulte et al., 2012).

and microstructural connectivity in neuropsychiatric relative to healthy conditions. Understanding of the neurobiological substrate of behavioral dysfunction and clinical symptoms may potentially impact future clinical diagnosis and treatment.

NICOTINE DEPENDENCE AND ITS POTENTIAL IMPACT IN CLINICAL TREATMENT

Here we present recent research using multiple MR modalities in the same individual aimed at identifying biomarkers of cigarette smoking in alcohol dependence and at understanding neural correlates of all-too-common relapse after treatment for alcohol use disorders. We showed previously (Durazzo et al., 2008) that the concentration of N-acetylaspartate (NAA; a neuronal marker) in frontal white matter and temporal gray matter as well as that of choline-containing metabolites in frontal gray matter were independent predictors of relapse to alcohol consumption (in addition to processing speed and comorbid unipolar mood disorder). A model containing these imaging biomarkers accurately classified 83% of abstainers and 90% of relapsers in the study and accounted for 72% of the variance in drinking status at follow-up. More recently, we turned our attention to the BRS as an important neural target for reward-related drinking behavior: The BRS is complex functional neurocircuitry critically involved in experiencing pleasure and aversion, and in monitoring and regulating emotions and behavior according to the environment and goals. Any reinforcing stimulus increases DA transmission in the nucleus accumbens, which is regulated by frontal brain structures (top-down control). Proper function of the BRS is critical in self-administration and for voluntary cessation of drug use, both hallmarks of addiction. Years of research have suggested that premorbid BRS abnormalities may facilitate the development and evolution (perhaps maintenance) of all forms of addiction, whereas abnormalities acquired from chronic substance use relate to maintenance/persistence of addiction, including relapse.

Recent research (e.g., Durazzo et al., in press; Makris et al., 2008) has characterized specific neurobiological BRS abnormalities in alcohol use disorders, at times as a function of cigarette smoking status, and has described their relations to alcohol consumption both before and after treatment. Based on MR DTI findings of reduced FA in regions of the superior corona radiata (a fiber tract connecting the frontal cortex to subcortical BRS components) of alcohol-dependent individuals, we extracted spectral information from the corresponding co-aligned multislice proton MRSI data and showed that smoking alcoholics (sALC) had lower NAA concentrations in a frontal white matter region that corresponds to the superior corona radiata than nonsmoking alcoholics (nsALC); NAA levels in surrounding frontal white matter were normal (Wang et al., 2009). This information on microstructural white matter integrity was obtained from DTI scans and could not have been extracted from MRSI + MRI alone because of the homogeneity of the white matter on structural MR images. Additional studies of the effects of smoking on structural MRI using FreeSurfer methodology (Dale et al., 1999) revealed thinner cortices in sALC versus nsALC at 1 week of abstinence predominantly localized to frontal gray matter including BRS, but not affecting the entire neocortex (Durazzo et al., in press). The same group difference was significant for NAA concentrations derived from MRSI data of the same research participants, again specific to the BRS components, not the entire frontal gray matter, white matter, or neocortex (Durazzo et al., 2010). Further analyses related these biological abnormalities to greater neurocognitive deficits in sALC than nsALC (Durazzo et al., 2008, 2010). Interestingly, the significant smoking-related differences in ALC were not mediated by alcohol drinking history or medical/psychiatric comorbidities; this suggests that deficits in BRS of sALC are premorbid or that other unknown environmental factors influenced our BRS measures.

Additional research strives to determine factors that identify patients at greatest risk for relapse, with the ultimate aim to focus treatment resources and thereby increasing treatment efficiency long-term. We found that at 1 week of abstinence from alcohol, those individuals who relapse 6 to 12 months later showed smaller tissue densities/volumes and smaller surface areas in components of the BRS (OFC, ACC, dorsolateral prefrontal cortex [DLPFC], and insula) (Cardenas et al., 2011; Durazzo et al., 2011), but similar cortical thickness than abstainers (Durazzo et al., 2011). Cortical volume was also lower in relapsers than controls, and intermediate in abstainers. In a similar population, we found

lower NAA (suggesting neuronal injury or mitochondrial compromise) in ACC, DLPFC, insula, cerebellar vermis, and superior corona radiata as well as lower levels of creatine-containing metabolites (Cr; reflecting lower cellular bioenergetics) in most of these regions of relapsers compared with abstainers. Most importantly, and in support of the clinical/behavioral relevance of abnormalities of the BRS, surface area and volume as well as BRS metabolite concentrations were strongly associated with posttreatment drinking (i.e., severity of relapse), but not with the individual's history of alcohol consumption. These studies point to the clinical relevance of neuroimaging abnormalities in the BRS that appear to be associated with the chronic relapse/remit cycle in alcohol dependence. If these abnormalities will be irreversible upon longitudinal study, they may be of genetic origin and suggest premorbid vulnerability/resilience of the BRS in alcohol dependence.

Abnormalities in DLPFC and ACC have been related to deficits in executive skills; abnormalities in the same regions and OFC, insula, superior corona radiata and ventral striatum have been related to greater impulsivity as well as impaired stimulus-reinforcement association learning (particularly OFC). Changes in many of these regions plus the amygdala and hippocampus are implicated in mood and anxiety disorders that are often comorbid with alcohol dependence and have been shown to be critically involved in the relapse/remit cycle. As such, relapse to alcohol use should be viewed and assessed as a bio-psycho-social phenomenon. Future work will benefit from more advanced multimodal neuroimaging approaches that allow measurement of various aspects of substance-related brain injury in the same "imaging space" to define BRS biological phenotypes of relapse, relate them to cognitive, psychiatric, personality/character factors, lack of control, and genetic makeup. Further research may ask the questions to what degree BRS dysfunction affects success of cognitive/behavioral treatment interventions, if specific BRS dysfunction is amenable to tailored treatment and how it might be related to pharmacological treatment outcome. Answers to these kinds of questions will influence substance use treatment approaches, designs, and ultimately outcome.

DISCUSSION

This review highlights recent innovative approaches to examining the acute and chronic effects of alcohol exposure on the brain, employing multiple imaging approaches within the same individual to broaden the interpretation beyond what a single neuroimaging modality could provide. These exciting studies elucidate the neurochemical, neural activity, and underlying morphometric changes stemming from acute or chronic EtOH exposure, with a focus on uncovering and further characterizing affected neural networks. The incorporation of subject characteristics, task performance, and drinking history and other behavioral outcome data further inform the nature and extent of these effects. On the other hand, future multimodal imaging studies will benefit from larger sample sizes with sufficient power to evaluate sex differences, and longitudinal evaluations that will connect the scan observations with clinical and behavioral outcomes. Ideally, the conclusions will point more specifically to intervention pathways that may curb the progression of dependence, or the degradation of neural integrity produced by excessive alcohol use.

The multimodal endeavors described here have shown that, both acutely and chronically, the brain's reward and executive control systems are each altered in the course of alcohol use disorders. The BRS responds to tastes of preferred alcohol beverages and can be measured not only as a BOLD contrast, but also more specifically as changes in DA receptor availability. Combined fMRI and MEG showed that acute alcohol intoxication-induced impairment of cognitive control stem from a disrupted synchrony between the ACC and lateral prefrontal cortex. DTI in combination with fMRI revealed that chronic heavy drinkers may have poor down-regulation of midbrain-centered repetition learning, or poor up-regulation of low cognitive demand, and that even modestly disrupted white matter fiber integrity may affect functional circuitry of executive control and learning. MRI, DTI, and MRSI in combination have further clarified the effects of chronic alcohol and nicotine use on top-down components of the BRS and, importantly, that a collection of related brain integrity measures early in the course of treatment can predict outcome.

The strong suggestion of abnormalities in these reward and control networks point to interventions that are critical to test in greater depth and will hopefully be a focus of future research. First, tasks that may train the brain to have action tendencies toward nonalcohol stimuli appear very promising. These include approach avoidance paradigms (Wiers et al., 2011), implicit association tasks (Wardell et al., 2012), cue extinction (Vollstadt-Klein et al., 2011), and delay discounting training (Bickel et al., 2011). Executive control may be bolstered by employing cognitive rehabilitation approaches (Twamley et al., 2011) and possibly physical exercise. Pharmacologic interventions may favorably moderate the enhanced outcomes (Anton et al., 2012). These multimodal neuroimaging findings can assist in identifying mechanism-based therapeutic and pharmacological treatment options, monitor various neural effects of their application, predict treatment outcome, and can increase the efficacy and cost effectiveness of alcoholism treatments.

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