Neuroplasticity in Human Alcoholism: Studies of Extended Abstinence with Potential Treatment Implications

George Fein\textsuperscript{1,2} and Valerie A. Cardenas\textsuperscript{1}

\textsuperscript{1}Neurobehavioral Research, Inc., 1585 Kapiolani Blvd. Suite 1030, Honolulu, HI 95814, USA

\textsuperscript{2}Department of Psychology, University of Hawai‘i
2530 Dole Street, Sakamaki C 400
Honolulu, HI 96822, USA

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Corresponding author:

George Fein
Neurobehavioral Research Inc.
Ala Moana Pacific Center
1585 Kapiolani Blvd. Suite 1030
Honolulu, HI 96814

george@nbresearch.com

phone: (808) 250-3725

fax: (808) 442 0980
Abstract

Alcoholism is characterized by a lack of control over impulsive and compulsive excessive alcohol consumption despite significant negative consequences. These impulsive and compulsive behaviors may be related to the functional abnormalities within brain networks characterized by increased synchrony in the appetitive drive network and decreased synchrony in the inhibitory executive control network. Studies in abstinent alcoholics suggest that the alcohol-related imbalances in brain networks are reversed, helping to achieve and maintain abstinence by inhibiting behavior and reducing appetitive drive. The identification of EEG analogues of fMRI network synchrony and the establishment that these changes in network synchrony are progressive in longitudinal studies would motivate the pursuit of treatment interventions to augment brain network synchrony in the support of ongoing abstinence.
The diagnosis of alcoholism requires the continuing engagement in dangerous or risky drinking in the face of recurring negative consequences of the drinking behavior in the social, physical, work, or family domains. This propensity toward continued hazardous drinking despite continuing consequences suggests that the short-term appetitive outcomes of drinking (e.g., intoxication, disinhibition) have greater control over behavior than do the potential short-term and long-term negative consequences of drinking (e.g., drunk driving arrests, liver disease, loss of family or job, etc.). From a neurobiological perspective this pattern implies weak “top-down” executive control over impulsive and compulsive urges to consume alcohol, and a strong “bottom-up” appetitive drive to impulsively and compulsively consume alcohol.

The appetitive drive and reward network is comprised of mesocorticolimbic regions that mediate aspects of drug addiction such as responses to rewarding stimuli (e.g., ventral tegmental area and nucleus accumbens), memory of rewarding stimuli (e.g., amygdala and hippocampus), and regulation of emotion and executive function (e.g., prefrontal and anterior cingulate cortices) (Everitt and Robbins, 2005). The striatum (including nucleus accumbens, ventral putamen, and ventral caudate) and orbitofrontal cortex are key regions mediating appetitive drive and behavior towards reward (Elliott et al., 2010; Everitt and Robbins, 2005; Taha and Fields, 2006). A compromised top-down executive control network may underlie the poor regulation of behavior and emotion that has been considered primary in relapse (Berking et al., 2011; Cooper et al., 1995; Fox et al., 2008). The subgenual anterior cingulate cortex (sgACC) plays a central role within this predominantly frontal cortical network underlying executive control (Botvinick et al., 2001). The ACC has widespread connections with the lateral prefrontal cortex and limbic structures (including the hippocampus, amygdala, and anterior thalamus) that are involved in
emotional responsiveness and the regulation of behavior in the context of rewarding and punishing outcomes (Drevets et al., 1997; Kelly et al., 2009; Phan et al., 2005).

The alcoholic brain has been extensively probed using functional magnetic resonance imaging (fMRI). fMRI measures brain activity by detecting the blood-oxygen-level dependent (BOLD) contrast related to neural activity, and most fMRI experiments examine task-related differences in the locus and magnitude of the BOLD response, i.e. the task activation of the brain. Many observed differences in activation in the executive control and appetitive drive networks have been associated with alcohol use, abuse, and dependence, suggesting that these networks and the multiple brain regions they encompass can contribute to the poor decision making and risky behaviors seen in alcoholism (for a review, see Camchong et al., 2013a). Increased activity in the amygdala and insula associated with inflexible poor decision making (Xiao et al., 2012) is found in binge drinkers, lower activity in the dorsolateral prefrontal cortex is observed in short-term abstinent alcoholics during inhibition tasks (Li et al., 2009) and in those with a family history of alcoholism during risky vs. safe decisions (Cservenka and Nagel, 2012) or during response inhibition (Norman et al., 2011). Lesser activation of prefrontal executive control regions than seen in controls has been observed in alcoholics during spatial and verbal working memory tasks (Cservenka and Nagel, 2012; Desmond et al., 2003; Pfefferbaum et al., 2001). Active drinkers show enhanced BOLD activation in the ventral striatum when presented with visual alcohol cues, also supporting the notion of a stronger appetitive and reward drive in current alcohol dependence (Ihssen et al., 2011; Myrick et al., 2004; Myrick et al., 2008). Active drinkers with a diagnosis of alcohol dependence show higher activity in the dorsolateral prefrontal cortex (DLPFC) during a delayed reward decision task (Amlung et al., 2012) compared to active drinkers without alcohol dependence, which may reflect alcoholics’ increased
demand of the executive control network when required to make decisions to delay behavior ruled by appetitive drive.

These studies demonstrate that excessive alcohol use and even the genetic vulnerability to alcoholism (observed prior to initiating alcohol use) is associated with activation patterns different than controls in brain regions that are part of the executive control and appetitive drive networks. More recent work suggests that faulty co-activation or synchrony of brain networks, or an imbalance between opposing brain networks, is important in alcoholism. Network synchrony is often referred to in the literature as “functional connectivity,” and fMRI, EEG, and MEG can be used to investigate different properties of brain networks, such as spatial specificity or timing of event processing.

In this chapter, we review fMRI evidence that, compared to non-substance abusing controls (NSAC), brain executive control networks are weakened or ‘tuned down’ and appetitive drive networks are strengthened or ‘tuned up’ in active alcoholism. We also present cross-sectional fMRI data showing that abstinence maintenance is associated with compensatory changes in the synchrony in these networks, such that the executive control network has greater synchrony and the appetitive drive network has lower synchrony, both in comparison to NSAC. We propose that EEG analogues of these alcohol-related network synchrony differences exist and should be characterized, as EEG could reveal different properties of these brain networks, such as timing of event processing, and may be more amenable to active interventions such as neurofeedback. These clinical neuroscience results may thus suggest treatment interventions under the premise that successful long-term abstinence from alcoholism should inform alcoholism treatment. We review a wide literature that supports the potential efficacy of an EEG
neurofeedback intervention to mimic or augment the network changes seen in long-term abstinence and present a prototype showing that such neurofeedback is technically feasible.

**Synchrony in Brain Networks**

Early fMRI studies focused primarily on changes in the magnitude of the BOLD response, and activation and de-activation of brain regions during a task. More recently, attention has been focused on using fMRI to probe the similarity or synchrony of the BOLD response across spatially disparate regions, especially at rest, building upon the EEG literature that long ago established the existence of spontaneously oscillating brain networks. Synchrony of oscillatory activity is thought to support neural communication and plasticity (see (Fell and Axmacher, 2011) for review). Electrophysiological studies suggest that gamma band (>30 Hz) synchronization is responsible for the integration of brain regions involved in specific attributes of stimulus processing. Synchrony of gamma oscillations enhances neural communication between regions, and lack of phase synchronization may actually prevent neural communication between cell assemblies. It has also been proposed that synchronization facilitates neural plasticity by enabling spike-field coherence that promotes the induction of long-term potentiation. This idea is supported by studies that show higher phase synchronization during encoding of information that is remembered than during encoding of information that is not remembered. Therefore, high correlation or synchrony is typically interpreted as a more integrated and responsive network, and a low correlation or synchrony interpreted as a dysfunctional network or one with impaired communication.

It is widely recognized that cortical oscillations evident in the EEG are related to the BOLD signal, although the precise mechanism is an area of active research (Thompson et al., 2014a; Thompson et al., 2014b; Whitman et al., 2013). This relationship suggests that there
might exist changes in synchrony of the BOLD response analogous to changes in synchronous EEG oscillations that reflect network integrity. In fMRI, synchrony or “functional connectivity” between two brain regions is typically measured by the correlation between each region’s fMRI timeseries over a period of several minutes, although other multivariate methods, such as structural equation modeling, psycho-physiological interactions, independent components analysis (ICA), etc., can also produce indices of synchrony.

Studies of the synchrony of the fMRI BOLD response during rest have gained in popularity, leading to the identification of several networks that are intrinsic to the brain’s function (see (Lee et al., 2013) for review). The most widely studied network is perhaps the default mode network (DMN), which is a group of brain regions that are active at rest but deactivated during cognitive tasks, and which exhibits a highly synchronous low frequency (<0.1 Hz) BOLD signal at rest. Many other networks that are highly synchronous at rest have been identified, including the somatosensory, visual, auditory, language, attention, and executive control networks. Networks identified during rest are robust, reliably detected in most people, and remain intact during task performance, although task synchrony may differ from synchrony observed during rest (Wilcox et al., 2011). The success of using synchrony or connectivity measures in resting state fMRI has led to increased interest in measuring the synchrony of regions of activation in more traditional task-related fMRI studies. This has led to the identification of synchronous networks related to appetitive drive, cue salience, or behavior (Lee et al., 2013).

Resting state fMRI synchrony studies of the executive control and appetitive drive networks

Studies in active users and very early abstinence
Although fMRI activation studies have included cohorts of active drinkers, there is almost no research on fMRI resting state synchrony in these samples. Recent work has examined resting state fMRI synchrony in multiple brain networks in individuals with current AUDs (Weiland et al., in press). The fMRI time series measures of synchrony (i.e., average within network correlations of BOLD signal magnitude across the network’s nodes) were computed for 14 networks in each of 422 individuals with active AUDs and 97 controls. For alcoholism, the left and right executive control network (LECN and RECN), and an anterior salience network (comprised of nodes including bilateral middle frontal gyrus, middle cingulate gyrus, and insula) were relevant to our earlier discussion of a top-down executive control network and a bottom-up appetitive drive network. Network strength on average for all networks (multivariate test) was lower for AUDs than controls. Univariate tests showed lower synchrony in AUDs vs. controls for the LECN, sensorimotor, basal ganglia, and primary visual networks. For the LECN alone, lower synchrony was associated with greater alcoholism severity and more years of drinking.

A study of fronto-striatal functional connectivity in cocaine use disorders supports the model that a strong bottom-up appetitive drive network is active in addiction (Wilcox et al., 2011). Fourteen subjects with chronic cocaine abuse or dependence (92% with comorbid alcohol abuse or dependence) in very early abstinence (but unlikely to be in significant acute withdrawal) and 16 healthy controls had resting state fMRI recorded. The chronic cocaine patients exhibited increased synchrony between the ventral striatum and orbitofrontal cortex, key regions of the reward and appetitive drive network.

**Studies in long term abstinence**

While the above section suggests that current dependence and abuse is associated with exaggerated bottom-up and compromised top-down neural network functioning, previous task studies suggest that there might be compensatory mechanisms in long-term abstinence from
nicotine and alcohol that exert control over reward seeking and attenuate the appetitive drive (Beck et al., 2009; Grüsser et al., 2004; Nestor et al., 2011; Wrase et al., 2007). To identify brain functional organization associated with long-term abstinence, we examined resting state fMRI synchrony in 23 LTAA (8 females, age = 48.5 ± 7.1 yrs, abstinent 7.91 ± 7.80 years), and 23 NSAC (8 females, age 48.0 ± 6.7 yrs) (Camchong et al., 2013c). We used bilateral nucleus accumbens (NAcc) seeds to probe the reward and appetitive drive network and a subgenual anterior cingulate cortex (sgACC) seed to probe the executive control network. All subjects also performed the intra/extradimensional set shift task (IED, Cambridge Cognition 2006) outside of the scanner. The IED assesses cognitive flexibility by examining an individual’s ability to change a learned behavior with changing response contingencies. Compared to NSAC, LTAA showed (a) decreased synchrony of limbic reward regions (e.g., caudate and thalamus) with both bilateral NAcc and sgACC seeds (Figure 1), and (b) increased synchrony of bilateral NAcc seeds and left DLPFC (suggesting greater inhibitory control) and between the sgACC seed and right DLPFC (consistent with greater emotion regulation) (Figure 2). The synchrony of bilateral NAcc seeds and left DLPFC was positively correlated with IED task performance outside of the scanner. Additionally, duration of abstinence in LTAA was negatively correlated with the synchrony between sgACC and right DLPFC. The lower synchrony of the limbic reward network in LTAA may reflect an ongoing compensatory effort to lower the induction of brain activity in regions known to be involved in reward processing. Increased synchrony between the NAcc and left DLPFC is consistent with literature showing that DLPFC input to the NAcc is involved in inhibition of behavior (Ballard et al., 2011; McClure et al., 2004), as is the correlation of this synchrony measure with IED performance. LTAA with a shorter length of abstinence had higher synchrony between sgACC and right DLPFC. It may be that individuals
with shorter abstinence are more vulnerable to relapse than individuals with longer abstinence, and thus may need more vigilant emotional regulation (reflected here by increased synchrony between sgACC and right DLPFC) to successfully manage emotional situations and avoid relapse. On the other hand, individuals with longer abstinence, who are in lower risk for relapse, may have a lower need for regulating emotion, hence lower synchrony between sgACC and DLPFC in LTAA being associated with longer (multi-year) abstinence durations. In total, the results here support the notion of compensatory mechanisms in LTAA evident during rest, in which enhanced synchrony within the executive control networks and attenuated synchrony within appetitive drive networks may facilitate the behavioral control required to maintain abstinence.

In order to determine whether network synchrony abnormalities also underlie stimulant dependence, we examined LTAA with comorbid stimulant dependence (LTAAS, n = 35, 20 females, age: 47.9 ± 7.3, averaging 5.67 ± 4.80 yrs. abstinence), comparing them to 23 LTAA without comorbid drug dependence (Camchong et al., 2013b) and 23 NSAC. Given the finding that reduced insula activity in stimulant addicts during decision-making (Paulus et al., 2005) or attention tasks (Clark et al., 2012) may predict subsequent relapse, the evidence that the insula has reciprocal connections with the executive control (sgACC) and appetitive drive seeds (NAcc) (Craig, 2009; Kelly et al., 2012), and the accumulating evidence of insula involvement in behavioral aspects of addiction such as stress coping, decision-making or cue-responsivity (Naqvi and Bechara, 2010), we examined synchrony of our seeds with insular activity in all three groups. The results showed commonalities in LTAA and LTAAS network synchrony (compared to NSAC, both groups showed enhanced executive control synchrony and enhanced synchrony between NAcc and mid-posterior insula) as well as differences (no attenuation of appetitive drive...
network synchrony in LTAAS, with appetitive drive synchrony higher in LTAAS than LTAA, and with enhanced synchrony between sg-ACC and anterior or mid-insula) vs. NSAC. These findings implicate insula involvement in the top-down and bottom-up network adaptive synchrony phenomena in alcohol abstinence, especially in individuals with comorbid drug dependence. These results suggest common as well as specific targets for treatment to support abstinence in chronic alcoholics with vs. without comorbid stimulant dependence. The results do not speak to possible similar effects in drug addicts without comorbid alcohol dependence, but suggest that studying such individuals with the paradigms presented here may prove very fruitful.

**Studies in short-term abstinence**

If the enhanced executive control network synchrony and suppressed appetitive drive network synchrony observed in LTAA truly represent adaptive network changes during extended abstinence, then we would anticipate similar but smaller magnitude effects on network synchrony in short term abstinence. We investigated whether resting-state fMRI synchrony patterns found in LTAA can be identified in short-term abstinent alcoholics (STAA, abstinent 72.59 ± 18.36 days) (Camchong et al., 2013d). Using the same methodology as in (Camchong et al., 2013c), we examined network synchrony in 27 STAA, and compared them to the 23 LTAA and 23 NSAC from our previous study. We found ordered synchrony effects from NSAC to STAA and then to LTAA within both the appetitive drive and executive control networks: with abstinence duration associated with lower synchrony of the appetitive drive network (NSAC>STAA>LTAAD) and higher synchrony of the executive control network (NSAC<STAA<LTAAD) (see Figures 1 & 2). We also found a significant positive correlation in STAA between strength of synchrony between NAcc and left DLPFC and IED performance and
(b) a significant positive correlation in STAA between strength of limbic reward network synchrony and current antisocial symptoms (i.e., antisocial behavior). These findings suggest that abstinent alcoholics have adaptive differences in synchrony patterns compared to controls, with the magnitude of the difference increasing with duration of abstinence.

**Summary of resting state fMRI synchrony studies**

These studies suggest that active alcoholics exhibit lower top-down executive control network synchrony and higher bottom-up reward and appetitive drive network synchrony, and that these phenomena are more than reversed with successful abstinence. During its early stages, alcohol consumption is a goal-directed behavior, initiated and executed by regions within the executive control network (such as dorsolateral prefrontal cortex and anterior cingulate cortex), with its rewarding effects processed by appetitive drive regions (such as nucleus accumbens). After alcohol is repeatedly consumed, consumption becomes more automatic (with more involvement of appetitive drive regions such as caudate and putamen) and less voluntary (with less involvement of executive control regions) (Everitt and Robbins, 2005). Alcohol consumption shifts to a more habitual mode, particularly to avoid withdrawal symptoms. The behavioral fate of repetitive actions, such as compulsive alcohol consumption, appear to be instantiated in mesostriatocortical networks in a process referred to as the ‘chunking’ of action repertoires (Graybiel, 1998; Volkow et al., 2013). An individual with alcohol dependence seeks alcohol compulsively, a behavior that has been associated with increased activity of appetitive drive regions when presented with an alcohol cue, and a lack of engagement of prefrontal regions, which is needed to inhibit or stop a prepotent, maladaptive behavior such as alcohol consumption. We speculate that our observed “overcompensation” in network synchrony, greater (i.e., not equal) executive control network synchrony observed in STAA and LTAA compared
with controls, may be necessary in order to inhibit the habitual response to alcohol. This is consistent with our 2013 paper showing that antisocial disposition does not change with long-term abstinence, while antisocial behavior is inhibited, with antisocial symptoms approaching zero in LTAA (Fein and Fein, 2013). Given this observation of no change in antisocial disposition (or antisocial thinking) in LTAA, it is not surprising that a very strong inhibitory control system is needed to inhibit antisocial behavior (including drinking).

**Task-related fMRI synchrony studies**
Several fMRI task studies have demonstrated altered executive control network activation and connectivity in alcoholism, suggesting that the resting state fMRI synchrony differences we have observed are present during task processing. Research to determine the association of resting state fMRI network synchrony with network performance during tasks that involve appetitive drive and executive control is warranted. A modified Stroop task (with nicotine vs. neutral cues) has been used to assess appetitive drive and executive control networks in nicotine addicts (Nestor et al., 2011), providing evidence that higher executive control network activation when viewing nicotine cues occurs in former vs. current smokers (i.e., higher executive control network activation with nicotine abstinence). Jazmin Camchong developed an alcohol-cue analog of this task (see Figure 3). In a pilot study in our laboratory, she studied five LTAA and 2 NSAC that demonstrated resting state fMRI synchrony differences, and found an alcohol-cue interference effect in LTAA (longer RTs to alcohol vs. neutral cues) and higher synchrony of executive control regions in LTAA vs. controls when viewing alcohol cues. These pilot results suggest that synchrony within the executive control network is higher in LTAA both at rest and during task performance.
Park et al. (Park et al., 2010) tested models of the decision-making deficits in alcoholics and the networks underlying these deficits. One way of conceptualizing the core problem in alcoholism and other addictions is that reinforcements consequent to behavior do not appropriately guide future behavior. Adaptive learning involves computation of reward prediction errors (PEs) in the midbrain, reflecting the difference between expected and actual outcomes. The PEs affect behavior via their influence on higher order executive functioning of the DLPFC, a region involved in goal-directed behavior. They examined striatal PEs and functional connectivity between the striatum and DLPFC. Twenty male alcoholics in early abstinence (average 16.9 days abstinent) and 16 male healthy controls were studied using fMRI during a reward-guided decision making task with dynamically changing response-outcome contingencies. Alcoholics needed significantly more trials than controls to meet learning criteria. In both groups, trial-wise PE correlated significantly with the BOLD midbrain signal, and there were no differences between groups in the striatal PE signal. The influence of the striatal PE signal on the DLPFC was markedly attenuated in the alcoholics. Moreover, striatal - DLPFC connectivity correlated significantly with learning during the task and was strongly negatively correlated with craving, especially in alcoholics.

In another study, twenty non-treatment seeking problem drinkers were studied with fMRI during a stop-signal task to assess response inhibition (Courtney et al., 2013). Weaker functional connectivity between frontal regions and the striatum was correlated with the severity of alcohol dependence. It was concluded that, as alcoholism progresses, the fronto-striatal pathway is weakened, leading to less inhibitory control.

Other studies of network functioning in alcoholics during active tasks have revealed abnormalities in networks other than the executive control and appetitive drive networks. Within
the default mode network (DMN), abstinent alcoholics show less resting state synchrony between the posterior cingulate and cerebellar regions compared to controls, but showed greater left posterior cingulate-cerebellar synchrony during a spatial working memory task, interpreted as suggesting that alcoholics need more integration of inputs from multiple brain regions to achieve the same task performance (Chanraud et al., 2011). In addition, higher connectivity among nodes of the DMN was associated with better task performance in both alcoholics and controls, and also associated with longer abstinence in the alcoholics.

In later work (Chanraud et al., 2013), it was observed that, compared to controls, recovering alcoholics recruited two additional fronto-cerebellar networks during a spatial working memory task. In another study, lower fronto-cerebellar fMRI synchrony during a motor task was also observed in chronic alcoholics abstinent 5-7 days versus controls (Rogers et al., 2012). These results reinforce the idea that synchronous brain activity from disparate regions is required to respond appropriately to a stimulus, that alcoholics may need to marshal more brain regions to complete a task, and also provides evidence for improved network communication with extended sobriety.

A study of 18 abstinent alcoholics and 17 healthy controls acquired fMRI during an attentional Stroop task (Schulte et al., 2012) and revealed abnormal synchrony in networks that may mediate between the top-down executive control and bottom-up appetitive drive networks. Using midbrain or posterior cingulate cortex (PCC) seeds (regions showing significant group x task activation contrasts in the fMRI analysis), they observed lower synchrony in alcoholics vs. controls between the PCC and middle cingulate cortex, interpreted as reflecting difficulty in adapting functional network activity to executive task demands. They also observed greater synchrony between the midbrain and the middle cingulate cortex and striatal regions, interpreted
as greater integration of inputs from multiple brain regions as a compensatory mechanism in alcoholics to support task performance.

A cue-reactivity fMRI experiment with alcohol-associated and neutral stimuli was used to study 46 detoxified alcohol dependent patients (19.74 ± 22.66 days abstinent) and 46 controls (Beck et al., 2012). Three months following scanning, 30 patients had relapsed and 16 had maintained alcohol abstinence. fMRI was compared between subsequent relapsers and abstainers. For alcohol-associated vs. neutral stimuli, abstainers demonstrated stronger functional connectivity between midbrain (including the ventral tegmental area and subthalamic nuclei) and left amygdala and between midbrain and left orbitofrontal cortex. These are brain regions associated with the processing of salient or aversive stimuli. The increased synchrony in abstainers between the midbrain and amygdala was interpreted as mediating an enhanced aversive reaction to alcohol stimuli, which may then act as a warning signal (through stronger midbrain-frontal cortex synchrony) to help maintain abstinence.

In summary, the totality of fMRI functional connectivity or synchrony work provides ample evidence that altered network synchrony exists in alcoholism, and that plastic changes in network synchrony occur with abstinence. However, from cross-sectional studies alone, one cannot determine whether the higher synchrony between executive control regions and lower synchrony in appetitive drive regions in LTAA (Camchong et al., 2013c) and to a lesser extent in STAA (Camchong et al., 2013d), both in comparison to NSAC, reflect changes with abstinence, selective survivorship (i.e. individuals with such synchrony differences are more likely to achieve abstinence, and individuals with greater differences from NSAC are more likely to achieve protracted abstinence), or a combination of changes with abstinence and selective
survivorship. Only longitudinal studies can determine whether the observed cross-sectional findings indeed reflect adaptive changes in network synchrony with extended abstinence.

**Treatment Implications**

Several behavioral and 12-Step treatments for alcoholism have documented clinical efficacy. Despite these successes, there is little understanding of how treatments work, or the mechanisms underlying reduction or cessation of drinking. In our studies of alcoholics in early through long-term abstinence, we identified brain network synchrony changes that were graded with abstinence duration, suggesting that achieving and maintaining abstinence is associated with adaptive brain network synchrony changes supporting reductions in bottom-up appetitive drive and increases in top-down executive inhibitory control. If it can be confirmed in longitudinal studies that the degree of these changes in the appetitive drive and executive control networks is associated with and predictive of successful abstinence, then interventions that directly augment these changes may have treatment potential for recovering alcoholics.

The idea of modifying brain network synchrony to promote abstinence is bolstered by the literature on using transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) to treat alcohol craving. These non-invasive treatments are thought to reduce craving by modulating the activity and connectivity of the brain. Boggio et al. (Boggio et al., 2008) showed that tDCS of the DLPFC decreased alcohol craving compared to sham treatment. In later work, Mishra et al. (Mishra et al., 2010) studied 45 alcohol dependent patients with rTMS of the DLPFC, and found significant decreases of a craving measure within the group that received rTMS compared to the sham group. One interpretation is that these treatments resulted in increased DLPFC activity and better executive control over craving. Most relevant is the case study by De Ridder et al. (De Ridder et al., 2011), who used rTMS targeting the anterior
cingulate cortex in an attempt to reduce craving and promote abstinence in a woman with a long
history of alcohol dependence and treatment. Before treatment, the patient showed increased
EEG synchrony between the ACC and posterior cingulate cortex (PCC), and fMRI showed that
cue-induced worsening of craving activated regions of the appetitive drive network (NAcc, ACC,
PCC). Following successful rTMS, fMRI activation of NAcc, ACC, and PCC disappeared and
the synchrony pattern normalized. When rTMS treatment became ineffective and relapse
occurred, fMRI activity and synchrony within the appetitive drive network returned. These
treatments appear to have altered network synchrony and reduced craving.

We suggest that neurofeedback that “feeds back” an auditory or visual signal that indexes
brain network synchrony may be another approach to promote network synchrony adaptations
that support abstinence. For example, a neurofeedback protocol may instruct a patient to try to
raise the pitch of a tone. A low-pitched tone is played when network synchrony is low, with pitch
increasing with network synchrony. Neurofeedback is a method built upon the idea that the mind
and body are one, and that by training the mind or brain to achieve particular states indexed by
some measured neurobiological signal (such as the BOLD response or EEG), the body will react
in a more optimal way in order to improve emotional, cognitive, physical, and behavioral
experiences.

Though technically possible, it is neither practical nor economically feasible to use
neurofeedback to directly modify fMRI network synchrony. Furthermore, although fMRI
provides high confidence in the identification of anatomical regions that contribute to the
executive control and appetitive drive networks, it is unable to reflect the sequential neural
activity underlying cognitive states of readiness or execution of a task due to the poor time
resolution of the BOLD response. Converging evidence suggests that the fMRI BOLD response
reflects the summed neural activity of several oscillatory EEG networks (see review, (Whitman et al., 2013)). These EEG networks may oscillate at multiple frequencies (e.g., theta, alpha, or gamma) and the activity of separate networks may vary as a function of cognitive states lasting only a few hundred ms. fMRI networks in response to task processing are likely to be comprised of multiple oscillatory EEG networks reflecting both induced and evoked EEG responses, including those that derive from frequency-dependent changes in phase alignment (Burgess, 2012). Therefore, the identification of EEG networks underlying executive control and appetitive drive could potentially reveal more about the mechanisms underlying the processing and inhibition of alcohol cues that contribute to the maintenance of abstinence, because of the more complex nature of EEG measures of brain activity that dynamically change at the same pace as cognitive processes.

**Neurofeedback of EEG network synchrony**

We propose that an effort should be made to identify EEG analogues of fMRI synchrony as possible neurofeedback targets. EEG network connectivity analysis is in its early stages, but pursuit of the identification of EEG networks that change with abstinence is crucial given the possibility of a neurofeedback intervention to facilitate abstinence. We have preliminary data showing that resting EEG coherency carries information that differs between LTAA and NSAC, and that correlates with resting state fMRI executive control network synchrony. However, much work is needed to identify reliable EEG executive control and appetitive drive network synchrony measures as neurofeedback targets.

Roberto Pascual-Marqui’s keynote address at the International Society for Neurofeedback and Research in 2011 presented a model for examining brain network synchrony from scalp-recorded EEGs. Using low-resolution electromagnetic tomography (LORETA)
(Pascual-Marqui, 2002, 2007) to estimate cortical EEG sources and ICA to identify synchronous source activity, he demonstrated EEG networks involving similar cortical regions to those of resting state fMRI networks from the literature. More recent work studied the effect of acute alcohol intake on the brain’s resting state network in social drinkers, by examining the magnitude squared coherence between the activity of cortical sources of EEG within different frequency bands (Lithari et al., 2012) to construct brain networks. Their work demonstrates that network synchrony changes occur over a short period of time (within 25 minutes of alcohol consumption) and are reflected in the scalp-recorded EEG, which can then be decomposed into neural sources for network analysis. These results support the idea that EEG brain network synchrony could be a neurofeedback target.

EEG neurofeedback in the treatment of substance use disorders dates to 1975 (for review, see (Sokhadze et al., 2008)), and was based on an alpha-theta training protocol, aimed at increasing the proportion of alpha (8-13 Hz) and theta (4-7 Hz) band activity in the ongoing EEG to promote a state of profound relaxation similar to a meditative state. Although early studies were uncontrolled and abstinence rates were not reported, results suggested that biofeedback-induced alpha/theta states promoted insight and attitude changes in alcoholics, and that these changes enhanced recovery (Twemlow and Bowen, 1976, 1977; Twemlow et al., 1977). Peniston and Kulkosky conducted the first randomized controlled studies of alpha-theta EEG neurofeedback (Peniston and Kulkosky, 1989). Of 10 alcoholic patients (who had formerly failed hospital treatment for alcoholism) that underwent neurofeedback training, 8 remained generally abstinent for at least 3 years, and they showed persistent changes in alcoholic personality variables. A case study (Fahrion et al., 1992) described neurofeedback treatment in an 18 month abstinent alcoholic who was experiencing craving and a fear of relapse, and concluded that
neurofeedback was a useful intervention for reducing craving even in abstinent alcoholics. Later work also reported sustained abstinence in a group of alcoholic depressed patients who were treated with alpha-theta neurofeedback (Saxby and Peniston, 1995). Critics suggest that alpha-theta neurofeedback is no more effective than suggestion or meditation techniques. We are encouraged that feedback of a single electrode measuring alpha and theta, which affords a limited view of the complex interaction of brain networks involved in alcohol abuse and dependence, works as well as it does. We speculate that feedback of EEG signals that reflect the functioning of the executive control and appetitive drive networks would yield even more impressive results.

With the idea that neurofeedback learning would be improved if activity from specific brain regions related to the desired outcome behavior was monitored, Congedo and colleagues pioneered neurofeedback using LORETA (Congedo et al., 2004). Alpha and beta band current densities were estimated for an anterior cingulate ROI using LORETA based on 19 scalp electrodes, and the power ratio between bands was used to drive feedback signals. They demonstrated that the current density power ratio increased over multiple neurofeedback sessions and that subjects could willfully increase that ratio. LORETA neurofeedback was subsequently used to train eight healthy individuals to increase their low-beta power activity (moving the EEG frequencies in a direction opposite to alpha/theta feedback) for an anterior cingulate ROI in an effort to improve alertness and attention (Cannon et al., 2007). Beta power was increased within the target ROI after neurofeedback, and changes were observed in psychometric testing suggesting that shifts in spectral power frequencies were associated with behavior change. Furthermore, beta power increases were also observed within ROIs that encompassed the left and right prefrontal cortex and the right post central gyrus, demonstrating parallel modifications in
regions of the executive control network, even though training occurred on a single anatomical node. Later work has explored the feasibility of neurofeedback of a LORETA-derived anatomical source in clinical populations (Cannon et al., 2008) and has estimated functional connectivity between LORETA-derived sources (Cannon et al., 2012; Coben et al., 2014).

We propose that EEG neurofeedback promoting increased inhibitory control network synchrony and reduced appetitive drive network synchrony would result in a “resting state brain” that can more appropriately deal with the challenges of maintaining abstinence. The design of such an EEG neurofeedback protocol requires identification of EEG networks that change with abstinence and correspond to the appetitive drive and executive control networks previously identified using fMRI. Given the success of LORETA for estimating EEG network synchrony (Cannon et al., 2012; Coben et al., 2014; De Ridder et al., 2011) and the active research in the estimation of EEG sources and source synchrony (Chiang et al., 2009; Cook and Koles, 2006; Gramfort et al., 2013; Sekihara et al., 2001), we are confident that these networks can be identified and used as neurofeedback treatment targets for abstinence maintenance.

We acknowledge that there are technical challenges inherent in a real-time EEG brain network synchrony neurofeedback system. However, we have developed a prototype for an EEG neurofeedback system using a quad-core Intel i5 computer to acquire and estimate network synchrony using an EEG coherency independent components analysis, and a second computer to display a movie as the feedback signal. Although we believe the best estimates of EEG network synchrony will be derived from intracranial source estimates, our prototype has computational demands greater than those required to estimate intracranial source connectivity, and thus are more than adequate to establish the feasibility of a future EEG network synchrony neurofeedback system. In the prototype, 64 channels of scalp EEG are recorded, pairwise cross-
coherencies are estimated, and the contribution of the independent components (IC) that index executive control or appetitive drive network synchrony are computed, and the subject’s baseline network synchrony is estimated for use during training. During neurofeedback training, 64 channels of scalp EEG are continuously recorded and the EEG is analyzed to estimate network synchrony in real-time. The real-time synchrony is compared to the subject’s baseline synchrony and the target distributions of synchrony for NSAC, STAA, and LTAA. A degraded video stimulus is fed back to the subject if there is a large difference between the real-time estimate of synchrony and the target synchrony, while clear feedback is presented when the real-time synchrony estimate approaches the target synchrony. Our prototype is fast enough to update the neurofeedback to the patient 10 times per second despite a computationally intensive method of reflecting EEG network synchrony. It is likely that a much simpler algorithm will sufficiently index EEG network synchrony (e.g., cross-correlation of selected electrode pairs within one or two frequency bands, correlation of estimated source activity or power between a small number of anatomical sources). The central research task to develop an EEG neurofeedback system for treatment of alcoholism is identifying the EEG measures of network function that change with abstinence and that correspond to the appetitive drive and inhibitory control fMRI networks.

Conclusions

Alcoholism is characterized by a lack of control over impulsive and compulsive excessive alcohol consumption despite significant negative consequences, a pattern of behavior that implies weak “top-down” executive control over impulsive and compulsive urges to consume alcohol, and a strong “bottom-up” appetitive drive to impulsively and compulsively consume alcohol. fMRI studies have identified multiple brain regions that contribute to the poor decision making and risky behaviors seen in alcoholism. This chapter reviews fMRI network
synchrony or “functional connectivity” studies which suggest that faulty co-activation or synchrony of multiple brain regions comprising “networks,” or an imbalance between opposing brain networks, is important in alcoholism. fMRI network studies in active alcoholics suggest that these impulsive and compulsive behaviors are related to the ineffectiveness of brain networks, characterized by decreased synchrony in top-down executive control network and increased synchrony in the bottom-up appetitive drive network. Repeated high level alcohol exposure may compromise network integrity, as suggested by the relationship between synchrony and the severity and duration of alcohol use. A series of studies in short- and long-term abstinent alcoholics observed decreased synchrony in appetitive drive networks and increased synchrony in inhibitory control networks, suggesting that the alcohol-induced imbalances in brain networks are reversed, helping to achieve and maintain abstinence by inhibiting behavior and reducing appetitive drive. Longitudinal studies of abstinent alcoholics at rest and during task performance are warranted to definitively establish whether plastic changes in the synchronous activity in brain networks reflects a crucial brain mechanism underlying the behavior changes in alcoholics that result in extended abstinence. Furthermore, the identification of measures of EEG network synchrony analogous to the fMRI executive control and appetitive drive networks could potentially reveal the mechanisms underlying the processing and inhibition of the brain response to alcohol cues that contribute to the maintenance of abstinence, because the EEG dynamically changes at the same pace as cognitive processing. Confirmation of the progressive network synchrony changes in longitudinal studies of abstinent alcoholics, together with the identification of EEG networks, would support the treatment potential of interventions to augment these network changes. Neurofeedback of EEG alpha and theta rhythms has been a successful component of alcoholism treatment in some subjects, and feedback of a signal that
indexes brain network synchrony holds great promise as an alcoholism treatment. A prototype for neurofeedback to alter measures of EEG network synchrony is described and feasibility of this treatment approach is demonstrated. In summary, if longitudinal studies confirm that the adaptive changes in brain functional organization summarized in this chapter support ongoing abstinence, then EEG treatment interventions to augment these changes is feasible and should be pursued.
**Figure captions**

**Figure 1:** Resting-state fMRI synchrony within the appetitive drive network and group differences in synchrony are shown. a) The voxels with activity synchronous to the subgenual anterior cingulate cortex (sgACC) and nucleus accumbens (NAcc) seeds are overlaid in red/yellow. These regions of the thalamus and caudate are crucial in bottom-up appetitive drive. b) The average Z-scores indexing synchrony between the seeds and the colored regions shown in the left panel are shown for non-substance abusing controls (NSAC), short-term abstinent alcoholics (STAA), long-term abstinent alcoholics (LTAA), and stimulus-dependent long-term abstinent alcoholics (LTAAS). The LTAA show significantly less synchrony than NSAC, STAA, and LTAAS, with STAA and LTAA synchrony midway between NSAC and LTAA.

**Figure 2:** Resting-state fMRI synchrony within the executive control network and group differences in synchrony are shown. a) The voxels with activity synchronous with the subgenual anterior cingulate cortex (sgACC, shown in green on the left brain image) are located in the right dorsolateral prefrontal cortex (DLPFC) and are overlaid in red on the right brain image. The voxels with activity synchronous with the bilateral nucleus accumbens (NAcc, show in yellow) are located in the left DLPFC and are overlaid in red on the right brain image. The right DLPFC is associated with emotion regulation, and the left DLPFC is associated with inhibitory control. b) The average Z-scores indexing synchrony between the NAcc and left DLPFC (top) and between the sgACC and right DLPFC (bottom) are shown for non-substance abusing controls (NSAC), short-term abstinent alcoholics (STAA), long-term abstinent alcoholics (LTAA), and stimulus-dependent long-term abstinent alcoholics (LTAAS). The LTAA show significantly greater synchrony than NSAC and STAA, with STAA and LTAAS synchrony values slightly greater than NSAC, between inhibitory control brain regions. Both LTAA and LTAAS show
significantly greater synchrony than NSAC, with STAA values midway between NSAC and LTAA, between emotion regulation brain regions.

**Figure 3:** Alcohol-cue Stroop task. During the fixation (Fix) blocks, subjects keep their eyes fixated on the cross. During the neutral (Neu) and alcohol (Alc) blocks, subjects are instructed to keep looking at the fixation cross in the middle, while they notice the color of the pictures border and respond by pressing the corresponding colored button on the response pad.
References


Nestor, L.; McCabe, E.; Jones, J. et al. Differences in" bottom-up" and" top-down" neural activity in current and former cigarette smokers: Evidence for neural substrates
which may promote nicotine abstinence through increased cognitive control.


Weiland, B. J.; Sabbineni, A.; Calhoun, V. D. et al. Reduced left executive control network functional connectivity is associated with alcohol use disorders. *Alcoholism, clinical and experimental research*, in press.


Figure 1
Figure 2
Figure 3