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The Neurobiology of Successful Abstinence

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Abstract

This review focuses on the neurobiological processes involved in achieving successful abstinence from drugs of abuse. While there is clinical and public health value in knowing if the deficits associated with drug use correct with abstinence, studying the neurobiology that underlies successful abstinence can also illuminate the processes that enable drug-dependent individuals to successfully quit. Here, we review studies on human addicts that assess the neurobiological changes that arise with abstinence and the neurobiological predictors of successfully avoiding relapse. The literature, while modest in size, suggests that abstinence is associated with improvement in prefrontal structure and function, which may underscore the importance of prefrontally-mediated cognitive control processes in avoiding relapse. Given the implication that the prefrontal cortex may be an important target for therapeutic interventions, we also review evidence indicating the efficacy of cognitive control training for abstinence.

Overview

Neuroscience investigations of addiction typically focus on characterizing the addicted brain state and in understanding the etiology of addiction. In contrast, there is relatively little research in either human drug users or in animal models of drug abuse on the neurobiological processes involved in treatment despite the importance of questions such as what changes arise with treatment, what are the best predictors of treatment outcome, who responds to treatment and why? This disparity may be due, in part, to an assumption that the neurobiology of treatment is perhaps not much more than the undoing of the processes involved in becoming addicted. In contrast, in interpreting the neurobiological characteristics of successful abstinence, we propose that recovery be considered to consist of two distinct processes (Figure 1). The first is characterized by the restoration of function that arises from the brain's ability to repair itself once the neurotoxic influences of drugs of abuse desist. The second is the active process of abstaining from use. Minimally, relapse avoidance involves monitoring one's behavior and internal state to avert potential lapses and cognitive control and regulatory processes to suppress the desire for, or the actions to obtain, drugs.

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This review summarizes the neurobiology of successful abstinence by focusing on three related topics. First, what are the neurobiological changes that accompany abstinence in humans? Second, we address the neurobiological predictors of successful abstinence. In addition to their clinical utility, identifying predictors of treatment outcome can inform a fundamental understanding of what processes need to be intact to enable relapse to be avoided. These two summaries implicate the integrity of prefrontal functions as critical. If prefrontal abilities can causally contribute to successful abstinence then it should follow that interventions designed specifically to improve prefrontal abilities should aid abstinence. Thus, the third and final section of this review describes the cognitive training interventions that have been shown to facilitate abstinence.

1. Neurobiological Changes in Abstinence

Longitudinal studies of drug users that assess brain function before and after a period of abstinence are optimal for identifying the restoration of function. However, given attrition and relapse rates, these studies are expensive and the durations of abstinence tend to be relatively short. An alternative approach is a cross-sectional comparison of abstinent, former users and current users. Although there is an inherent ambiguity in determining if observed differences in former users preceded (and perhaps facilitated) abstinence or arose from abstinence, these studies can nonetheless identify the neurobiological characteristics of successful abstainers.

A body of research, employing both longitudinal and cross-sectional designs, suggests that brain volume deficits in alcoholics show evidence of recovery. First, with regard to the deficits, both cortical gray matter [1-3] and white matter in alcoholics sustain widespread volume loss [4], which is greatest in the frontal lobes [5,6]. Indeed, the frontal lobes appear to be more vulnerable to alcohol's effects than other brain regions/systems [6-9] although there is also evidence of caudate and putamen volume deficits [10,11]. Subsequent abstinence from alcohol has been associated with increased grey matter volumes and reduced ventricle size [7,10,12-15]. An MRI comparison of 56 alcohol abstainers and 45 controls [16] revealed somewhat contrary findings. At baseline, alcohol patients showed bilaterally decreased prefrontal lobes and increased lateral ventricles. The follow-up assessments conducted 6-9 months later showed decreases in ventricles but no change in the size of the prefrontal lobes. Age and the extent of initial impairment may be important moderating variables. For example, Trabert and colleagues [17] found significant reversibility of alcohol brain shrinkage within three weeks of abstinence in younger (<38 years), but not in older, subgroups of alcoholic men. Gazdzinski and colleagues [18] observed marked brain tissue volume recovery and concomitant CSF volume decreases in alcoholics who were abstinent for only one month. These tissue volume gains continued over 6-9 months of abstinence but at a much slower rate than during the first month. Importantly, the most rapid volume recovery was observed in those with the greatest baseline brain shrinkage and drinking severity. These volumetric effects may be accompanied by brain metabolic changes: Recovery of Positron Emission Tomography (PET) measures of brain metabolism (which are decreased during alcohol intake) can occur within 16-30 days of abstinence [9,13]. Conversely, hyper-excitability of the central nervous system has been suggested to persist during the first several months of sobriety before normalizing [19,20]. Indeed, there is evidence that elevated frontal lobe blood flow persists into abstinence and can take approximately four years to return to normal levels [21].

Turning to stimulants, Hanlon et al. [22] reported that one-month cocaine abstainers had significantly higher gray matter density than current cocaine users in neocortical areas, but subcortical gray matter density was lower in both the users and abstainers compared to non-using controls. Although not all studies test for cognitive correlates of brain changes, these authors found that cortical density was correlated with performance on memory and reaction

time tasks for both the current and one-month abstinent cocaine users. Within cocaine abstainers alone, subcortical tissue density was correlated with the ability to set-shift. Bolla et al. [23] reported that cocaine users abstinent for 23 days showed less PET activation than comparison subjects (non-drug using with the exception of moderate alcohol and marijuana use) in the left anterior cingulate (ACC) and the right dorsolateral prefrontal cortex (DLPFC) during a modified Stroop Task. Average amount of cocaine used per week was negatively correlated with activity in the rostral ACC and right DLPFC. Bell et al. [24] examined white matter integrity, by diffusion tensor imaging (DTI), in 43 cocaine-abstinent patients (abstinence range: 5 days to 102 weeks) and 43 non-using controls. Overall, abstainers had lower fractional anisotropy (FA) than controls, notably in callosal regions and in the lower superior corona radiata bilaterally, which may explain persistent behavioral deficits in executive and sensory functioning in abstinence. Within the abstainer group, FA value changed as a function of abstinence duration, increasing in some regions (e.g., right anterior thalamic radiation, right cingulum), but decreasing in others (all decreasing values fell on either the inferior or superior longitudinal fasciculus). Notably, the areas that changed with abstinence were different to those that differed to controls. In contrast to the functional hypoactivity that is characteristic of current cocaine users, Connolly et al. [25] found significantly greater activity in prefrontal, cingulate, cerebellar and inferior frontal gyri in cocaine abstainers performing a response inhibition Go-NoGo task relative to healthy controls. Short-term abstainers (1-5 weeks) had increased inhibition-related DLPFC and inferior frontal activity, indicative of the need for increased inhibitory control. Long-term abstainers (40-102 weeks) had increased error-related ACC activity, suggesting heightened behavioral monitoring.

Studies of abstinence from other drugs of abuse also show evidence of recovery. For example, Wang et al. [26] compared 20 heroin abstainers (at abstinence durations of three days and one month) to 20 non-using controls. At three-days abstinence heroin users had decreased gray matter density in the frontal cortex, cingulate, and occipital regions relative to controls. After one-month of abstinence, however, there was no longer a significant difference between abstainers and controls in the superior frontal gyrus, although differences remained in other regions (e.g., right middle frontal gyrus, left cingulate gyrus and left inferior occipital gyrus). Nestor et al. [27], using fMRI, found that both ex-smokers (minimum of 12-months abstinence) and never-smokers, versus current smokers, had significantly more cortical activity and significantly less subcortical activity in both a nicotine attentional bias paradigm and a Go-NoGo task. Similar to the previous observation on cocaine users [25], ex-smokers exhibited more neural activity than both never-smokers and current smokers in prefrontal cortical regions. Tapert et al. [28] found that abstinent adolescent marijuana users (abstinence duration of 28 days), versus non-using controls, had increased activity in frontal and parietal areas during a Go-NoGo task.

Discerning common threads from the research on abstinence-induced changes is challenging as the studies vary on abstinence duration, the substance being abused, whether or not abstainers were compared to non-using controls or to current users, and the type of brain measure or functional task employed. Tentatively, one might conclude that some brain changes occur relatively quickly with evidence of recovery by four weeks (e.g., [26,29]). Further, cortical and prefrontal improvements appear most pronounced although this may reflect the fact that these cortical areas are the ones that appear most adversely affected by abuse. That said, the evidence of brain changes in abstinence that are either qualitatively different (e.g., abstinence-related changes in different regions to those that show deficits in current users; [24]) or are quantitatively different (e.g., activity patterns in abstinent users that are greater than in either current users or non-users; [25,27]) suggest more than a restoration of function. We hypothesize that many of these changes reflect the increased cognitive control demands required to actively maintain abstinence (Figure 1). Although it

might be argued that the evidence of prefrontal changes with abstinence may reflect a bias in task selection (i.e., prefrontal changes are more likely to be detected as many studies employ cognitive control or working memory tests that engage prefrontal systems) this concern is mitigated somewhat by complementary evidence from whole-brain structural analyses. Consistent with the hypothesis that cognitive control is an important contributor to successful abstinence, research on the neural predictors of abstinence also tends to implicate prefrontal systems, the topic to which we turn next.

2. Baseline Predictors of Relapse

Supporting evidence for the hypothesis that prefrontal control systems are central to successful abstinence comes from studies that have investigated pre-quit neurobiological predictors of treatment outcome. These studies build on a cognitive literature demonstrating, for example, that attentional biases to drugs and drug-related cues are particularly good indicators of treatment outcome and have been shown to predict relapse better than other standard dependence measures such as self-reports of dependence or drug use histories [30,31]. Similarly, scores on self-report measures of impulsivity have been shown to predict poorer treatment outcome [32,33]. As neuroimaging measures can sometimes prove to be better predictors of future abstinence than subjective measures such as self-reported craving [34,35], there have been a number of longitudinal studies assessing if baseline imaging (either prior to or early in cessation) can predict outcome. One important caveat is that this literature tends to test retrospectively for neuroimaging predictors. Here, the analyses tend to be predicated on the known outcome (abstainer vs. relapser), which, due to overfitting with multi-voxel multivariate analyses (i.e., lots of predictor variables relative to the numbers of participants), can inflate the predictive power of the observed results. This is an important qualification as the true predictive value of these observed “postdicted” effects are rarely quantified in independent samples.

With that caveat in mind, the relevant neuroimaging literature, though small, does identify prefrontal systems, amongst other regions, as effective predictors of treatment outcome. With regards to alcohol, treatment outcome has been predicted by frontal blood flow, cognitive inhibition and working memory measures obtained at the end of detoxification [36], by brain metabolite levels in the DLPFC, ACC, insula, cerebellum and superior corona radiata as measured by spectroscopy [37], by gray matter volume in the parietal-occipital sulcus, medial and right lateral prefrontal cortex [3], by morphometry in numerous control and reward areas [38,39] and by white matter integrity in the frontal lobes [40]. Task activation can also predict outcome. For example, alcohol intake over six months was predicted by activation in response to positive pictures relative to neutral pictures in the thalamus and ventral striatum [41]. In one of the first studies to predict outcome using baseline activation measures, Grüsser and colleagues [34] reported that relapse in alcoholics could be predicted by pre-treatment activity in response to alcohol-related stimuli in the ACC, putamen, and medial prefrontal cortex.

Task activation has also been shown to predict outcome in smokers. Janes et al. [42] reported that reactivity to smoking cues in numerous cortical and subcortical areas assessed before quitting smoking in 21 nicotine-dependent women discriminated abstainers from relapsers over the following eight weeks. Similarly, grey matter volumes in cortical and subcortical areas also predicted smoking cessation treatment outcome [43]. Numerous tasks yielding a diverse set of results have identified predictors of treatment outcome in stimulant users. For example, Paulus and colleagues [44] showed activation levels in prefrontal, temporal and posterior cingulate regions early in abstinence to predict subsequent relapse for methamphetamine users. Brewer et al. [45] identified prefrontal regions in addition to other subcortical and posterior cingulate regions as being the best predictors of treatment outcome in a treatment-receiving sample of cocaine users. Task activation on monetary reward, cue-

reactivity and oddball attentional tasks have identified activity levels in numerous brain areas, including the thalamus, basal ganglia, amygdala, hippocampus, insula, posterior cingulate, precentral, temporal and lingual cortices as predictors of subsequent abstinence [35,46,47]. Finally, preliminary evidence suggests that D2 receptor levels were lower in the dorsal striatum of methamphetamine users who subsequently relapsed [48].

This review of neurobiological patterns of prediction reveals a broad and varied set of results. Note that sample sizes are often very small (occasionally fewer than ten subjects in a group), the tasks and measures are varied, and the timing of testing varies (e.g., before treatment, during treatment, after detoxification). The wide range of results implicating numerous brain systems may suggest that the analysis concerns raised earlier regarding data overfitting may compromise the reliability and generalizability of reported effects and suggest that larger prospective studies that, ideally, survey activity in numerous brain systems and test the reliability of effects in independent samples, are still required. A recent paper has taken an important step in this direction [49]. Luo and colleagues used cross-validation approaches (i.e., separating the dataset into model training and testing subsets) to identify and quantify the true predictors of treatment outcome in a sample of cocaine users. They observed better outcomes to be associated with greater baseline error-related activity in the anterior cingulate, suggesting that this monitoring process may be very important for successful abstinence and echoing the cross-sectional evidence that also identifies increased error-related cingulate activation with longer abstinence [25]. In passing, it should be appreciated that the ability to predict treatment outcome will likely be substantially reduced relative to the inflated estimates in the extant literature: Using the retrospective prediction methods that are typical of the field, Luo et al report an area under the receiver operating characteristic curve (which plots specificity of a test against its sensitivity) of .85 but show with subsequent analyses using cross-validation techniques that the true prediction on independent samples is closer to .60 (where chance = .5).

3. Training for Abstinence

The efficacy of pharmacological [50] and behavioral therapies [51,52] for drug dependence have been reviewed thoroughly elsewhere, and in light of the preceding review indicating the importance of cognitive control network integrity to abstinence, we limit our focus to cognitive interventions. Cognitive training interventions have typically been based on the repeated practice of a cognitive task, with the aim of benefitting both the task's specific cognitive domain and generalizing benefit to other cognitive domains. For example, a growing literature has focused on the use of working memory (WM) training to improve cognition in a range of clinical groups [53], most notably attention-deficit hyperactivity disorder [54]. Repeated practice of WM tasks has demonstrated both improvement in WM performance and generalization to other domains such as increased fluid intelligence and cognitive control. Bickel and colleagues [55] found that WM training in stimulant-dependent patients improved cognitive control over reward (as measured by a delayed discounting task which assesses the degree to which the subjective value of rewards are discounted as a function of the time to their receipt). To date, however, no study has examined WM training efficacy for improving treatment outcomes in a dependent sample. The findings of increased prefrontal activity associated with improved WM capacity [56,57] hold promise for addiction treatment through both their potential generalization to cognitive control and through the role of WM in craving and impulse control [58,59]. The viability of WM training in drug-abusing cohorts will require further evidence of its reliability [60] and durability [53], particularly given the intensity and duration of the training intervention.

Practicing self-control directly (i.e., small acts of impulse control such as avoiding sweets, which were practiced over two weeks before quitting) significantly improved abstinence rates in cigarette smokers; 27% of participants assigned to a self-control training condition

relative to 12% of participants in a control condition were still abstinent one month after quitting [61]. Practicing the withholding of a response to an alcohol-related stimulus was associated with a reduction of alcohol consumption in binge-drinking adolescents, without positively influencing performance on a cognitive control task (Stop-signal task) [62]. Successful training of cognitive control over cravings, for example, with a CBT-like strategy of thinking of the long-term consequences of drug-related visual cues, has also been shown to both increase prefrontal cortical activity and down regulate striatal activity [63,64].

Attentional bias to drug-related cues has consistently been associated with subjective craving and relapse rate [65,66]. New behavioral interventions to reduce either attentional bias [67,68] or approach bias (i.e., the tendency to approach rather than avoid drug-related cues) [69], have consistently reduced the level of bias in various drug-dependent groups (nicotine, alcohol), though the preliminary nature of these studies has provided only limited (but generally positive) effects on treatment and relapse outcomes in addiction (see [70] for a review of other psychiatric conditions).

Conclusions

The cortical and behavioral changes that arise during abstinence, that precede and predict abstinence, and that might improve with training and thereby forestall relapse all appear to implicate, *inter alia*, the prefrontal cortex. The literature is relatively small and uses a wide range of measures and task probes, rendering it difficult to conclude with certainty which prefrontal regions and which prefrontally-mediated processes are most relevant to successful abstinence. In addition to requiring more prospective studies, a number of outstanding issues remain to be resolved. First, a difficult challenge is to determine if observed abstinence-related changes causally contribute to avoiding relapse. Studies that experimentally manipulate prefrontal systems (either by cognitive training as described here or through other interventions) are especially important to resolve this. Second, it is well understood that a propensity to relapse is characteristic of dependence. This raises the important challenge to understand the neurobiology of relapse risk and understand how relapse vulnerabilities might co-exist with the processes that maintain abstinence (Figure 1). Perhaps the brain systems that are implicated in the development of dependence and, critically, that do not change with abstinence, may constitute relapse risk while those that do change with abstinence may reflect the critical processes for avoiding relapse? One further avenue of research lies in determining if our understanding of relapse avoidance can be informed by studies that characterize resilient individuals who do not become addicted in the first instance.

REFERENCES

1. Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcohol Clin Exp Res*. 2002; 26:558–564. [PubMed: 11981133]
2. Jernigan TL, Butters N, Ditraglia G, Schafer K, Smith T, Riwin M, Grant I, Schuckit M, Cermak LS. Reduced cerebral gray matter observed in alcoholics using magnetic resonance imaging. *Alcohol Clin Exp Res*. 1991; 15:418–427. [PubMed: 1877728]
3. Rando K, Hong K-I, Bhagwagar Z, Li C-SR, Bergquist K, Guarnaccia J, Sinha R. Association of Frontal and Posterior Cortical Gray Matter Volume With Time to Alcohol Relapse: A Prospective Study. *Am J Psychiatry*. 2011; 168:183–192. [PubMed: 21078704]
4. Pfefferbaum A, Lim KO, Zipursky RB, Mathalon DH, Rosenbloom MJ, Lane B, Chung NH, Sullivan EV. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: A Quantitative MRI Study. *Alcohol Clin Exp Res*. 1992; 16:1078–1089. [PubMed: 1471762]

5. Kubota M, Nakazaki S, Hirai S, Saeki N, Yamaura A, Kusaka T. Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *J Neurol Neurosurg Psychiatry*. 2001; 71:104–106. [PubMed: 11413273]
6. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol Clin Exp Res*. 1997; 21:521–529. [PubMed: 9161613]
7. Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Structural brain alterations associated with alcoholism. *Alcohol Health Res World*. 1995; 19:266–272.
8. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon H, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry*. 1998; 55:905–912. [PubMed: 9783561]
9. Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience*. 1997; 79:983–998. [PubMed: 9219961]
10. Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. *Neuroimage*. 2007; 34:879–887. [PubMed: 17127079]
11. Sullivan EV, Deshmukh A, De Rosa E, Rosenbloom MJ, Pfefferbaum A. Striatal and forebrain nuclei volumes: Contribution to motor function and working memory deficits in alcoholism. *Biol Psychiatry*. 2005; 57:768–776. [PubMed: 15820234]
12. OscarBerman M, Shagrin B, Evert DL, Epstein C. Impairments of brain and behavior - The neurological effects of alcohol. *Alcohol Health Res World*. 1997; 21:65–75. [PubMed: 15706764]
13. Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcohol Clin Exp Res*. 1995; 19:1177–1191. [PubMed: 8561288]
14. Shear PK, Jernigan TL, Butters N. Volumetric magnetic resonance imaging quantification of longitudinal brain changes in abstinent alcoholics. *Alcohol Clin Exp Res*. 1994; 18:172–176. [PubMed: 8198216]
15. Zipursky RB, Lim KO, Pfefferbaum A. MRI study of brain changes with short term abstinence from alcohol. *Alcohol Clin Exp Res*. 1989; 13:664–666. [PubMed: 2688465]
16. Wobrock T, Falkai P, Schneider-Axmann T, Frommann N, Wolwer W, Gaebel W. Effects of abstinence on brain morphology in alcoholism. *Eur Arch Psychiatry Clin Neurosci*. 2009; 259:143–150. [PubMed: 19165528]
17. Trabert W, Betz T, Niewald M, Huber G. Significant reversibility of alcoholic brain shrinkage within 3 weeks of abstinence. *Acta Psychiatr Scand*. 1995; 92:87–90. [PubMed: 7572265]
- 18*. Gazdzinski S, Durazzo TC, Meyerhoff DJ. Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. *Drug Alcohol Depend*. 2005; 78:263–273. [PubMed: 15893157] This study used an automated three-dimensional whole brain MRI to measure brain changes over a 12-month interval in 23 alcohol-dependent individuals. Brain volume recovery occurred rapidly following abstinence onset, suggesting that studies in which brain structure was measured after several weeks of abstinence may have underestimated abstinence-induced changes.
19. Roberts AJ, Koob GF. The neurobiology of addiction. *Alcohol Health Res World*. 1997; 21:101–106. [PubMed: 15704343]
20. Stephens DN, Duka T. Cognitive and emotional consequences of binge drinking: role of amygdala and prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3169–3179. [PubMed: 18640918]
21. Gansler DA, Harris GJ, Oscar-Berman M, Streeter C, Lewis RF, Ahmed I, Achong D. Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: A pilot SPECT study. *J Stud Alcohol*. 2000; 61:32–37. [PubMed: 10627094]
22. Hanlon CA, Dufault DL, Wesley MJ, Porrino LJ. Elevated gray and white matter densities in cocaine abstainers compared to current users. *Psychopharmacology*. 2011; 218:681–692. [PubMed: 21691942]

23. Bolla K, Ernst M, Kiehl K, Mouratidis M, Eldreth D, Contoreggi C, Matochik J, Kurian V, Cadet J, Kimes A, et al. Prefrontal cortical dysfunction in abstinent cocaine abusers. *J Neuropsychiatry Clin Neurosci.* 2004; 16:456–464. [PubMed: 15616172]
24. Bell RP, Foxe JJ, Nierenberg J, Hoptman MJ, Garavan H. Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. *Drug Alcohol Depend.* 2011; 114:159–168. [PubMed: 21075564]
25. Connolly CG, Foxe JJ, Nierenberg J, Shpaner M, Garavan H. The neurobiology of cognitive control in successful cocaine abstinence. *Drug Alcohol Depend.* 2012; 121:45–53. [PubMed: 21885214]
26. Wang X, Li B, Zhou X, Liao Y, Tang J, Liu T, Hu D, Hao W. Changes in brain gray matter in abstinent heroin addicts. *Drug Alcohol Depend.* 2012; 126:304–308. [PubMed: 22717339]
- 27*. Nestor L, McCabe E, Jones J, Clancy L, Garavan H. 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. *Neuroimage.* 2011; 56:2258–2275. [PubMed: 21440645] This study demonstrated that abstinent smokers were characterized by having levels of activity related to cognitive control that was greater than current smokers and non-smoker controls. Similar to the findings in reference 25, the result stands in contrast to the typical hypoactivity of current users and suggests that abstinence may require (or produce) increased levels of activity in prefrontal systems that underlie the Abstinence Maintenance processes indicated in Figure 1.
28. Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, Frank LR. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology.* 2007; 194:173–183. [PubMed: 17558500]
29. Mon A, Durazzo TC, Meyerhoff DJ. Glutamate, GABA, and other cortical metabolite concentrations during early abstinence from alcohol and their associations with neurocognitive changes. *Drug Alcohol Depend.* 2012; 125:27–36. [PubMed: 22503310]
30. Cox WM, Hogan LM, Kristian MR, Race JH. Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug Alcohol Depend.* 2002; 68:237–243. [PubMed: 12393218]
31. Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. Attentional bias predicts outcome in smoking cessation. *Health Psychol.* 2003; 22:378–387. [PubMed: 12940394]
32. Moeller FG, Dougherty DM, Barratt ES, Schmitz JM, Swann AC, Grabowski J. The impact of impulsivity on cocaine use and retention in treatment. *J Subst Abuse Treat.* 2001; 21:193–198. [PubMed: 11777668]
33. Patkar AA, Murray HW, Mannelli P, Gottheil E, Weinstein SP, Vergare MJ. Pre-treatment measures of impulsivity, aggression and sensation seeking are associated with treatment outcome for African-American cocaine-dependent patients. *J Addict Dis.* 2004; 23:109–122. [PubMed: 15132346]
34. Grusser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology.* 2004; 175:296–302. [PubMed: 15127179]
35. Kosten TR, Scanley BE, Tucker KA, Oliveto A, Prince C, Sinha R, Potenza MN, Skudlarski P, Wexler BE. Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology.* 2006; 31:644–650. [PubMed: 16123763]
36. Noel X, Sferrazza R, Van der Linden M, Paternot J, Verhas M, Hanak C, Pelc I, Verbanck P. Contribution of frontal cerebral blood flow measured by Tc-99m-bicisate spect and executive function deficits to predicting treatment outcome in alcohol-dependent patients. *Alcohol Alcohol.* 2002; 37:347–354. [PubMed: 12107037]
37. Durazzo TC, Pathak V, Gazdzinski S, Mon A, Meyerhoff DJ. Metabolite Levels in the Brain Reward Pathway Discriminate Those Who Remain Abstinent From Those Who Resume Hazardous Alcohol Consumption After Treatment for Alcohol Dependence. *J Stud Alcohol Drugs.* 2010; 71:278–289. [PubMed: 20230726]
38. Cardenas VA, Durazzo TC, Gazdzinski S, Mon A, Studholme C, Meyerhoff DJ. Brain Morphology at Entry into Treatment for Alcohol Dependence Is Related to Relapse Propensity. *Biol Psychiatry.* 2011; 70:561–567. [PubMed: 21601177]

39. Durazzo TC, Tosun D, Buckley S, Gazdzinski S, Mon A, Fryer SL, Meyerhoff DJ. Cortical Thickness, Surface Area, and Volume of the Brain Reward System in Alcohol Dependence: Relationships to Relapse and Extended Abstinence. *Alcohol Clin Exp Res.* 2011; 35:1187–1200. [PubMed: 21410483]
40. Sorg SF, Taylor MJ, Alhassoon OM, Gongvatana A, Theilmann RJ, Frank LR, Grant I. Frontal white matter integrity predictors of adult alcohol treatment outcome. *Biol Psychiatry.* 2012; 71:262–268. [PubMed: 22047719]
41. Heinz A, Wrase J, Kahnt T, Beck A, Bromand Z, Grusser SM, Kienast T, Smolka MN, Flor H, Mann K. Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in detoxified alcoholic subjects. *Alcohol Clin Exp Res.* 2007; 31:1138–1147. [PubMed: 17488322]
42. Janes AC, Pizzagalli DA, Richardt S, Frederick BD, Chuzy S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, et al. Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence (vol 67, pg 722, 2010). *Biol Psychiatry.* 2010; 67:1002–1002.
43. Froeliger B, Kozink RV, Rose JE, Behm FM, Salley AN, McClernon FJ. Hippocampal and striatal gray matter volume are associated with a smoking cessation treatment outcome: results of an exploratory voxel-based morphometric analysis. *Psychopharmacology.* 2010; 210:577–583. [PubMed: 20424827]
44. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry.* 2005; 62:761–768. [PubMed: 15997017]
45. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment Brain Activation During Stroop Task Is Associated with Outcomes in Cocaine-Dependent Patients. *Biol Psychiatry.* 2008; 64:998–1004. [PubMed: 18635157]
46. Clark VP, Beatty GK, Anderson RE, Kodituwakku P, Phillips JP, Lane TD, Kiehl KA, Calhoun VD. Reduced fMRI activity predicts relapse in patients recovering from stimulant dependence. *Hum Brain Mapp.* 2012
47. Jia ZR, Worhunsky PD, Carroll KM, Rounsaville BJ, Stevens MC, Pearlson GD, Potenza MN. An Initial Study of Neural Responses to Monetary Incentives as Related to Treatment Outcome in Cocaine Dependence. *Biol Psychiatry.* 2011; 70:553–560. [PubMed: 21704307]
48. Wang GJ, Smith L, Volkow ND, Telang F, Logan J, Tomasi D, Wong CT, Hoffman W, Jayne M, Alia-Klein N, et al. Decreased dopamine activity predicts relapse in methamphetamine abusers. *Mol Psychiatry.* 2012; 17:918–925. [PubMed: 21747399]
49. Luo X, Zhang S, Hu S, Bednarski S, Erdman E, Farr O, Hong K-I, Sinha R, Mazure C, Li C-s. Error processing and gender shared and specific neural predictors of relapse in cocaine dependence. *Brain.* In Press.
50. Castells X, Casas M, Perez-Mana C, Roncero C, Vidal X, Capella D. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev.* 2010:CD007380. [PubMed: 20166094]
51. Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology.* 2013; 64:452–463. [PubMed: 22735770]
52. Zgierska A, Rabago D, Chawla N, Kushner K, Koehler R, Marlatt A. Mindfulness meditation for substance use disorders: a systematic review. *Subst Abus.* 2009; 30:266–294. [PubMed: 19904664]
- 53*. Morrison AB, Chein JM. Does working memory training work? The promise and challenges of enhancing cognition by training working memory. *Psychon Bull Rev.* 2011; 18:46–60. [PubMed: 21327348] This paper provides a broad summary of the empirical literature on working memory training, highlights the methodological and conceptual issues that are most relevant to that literature and suggests future directions for assessing the efficacy of working memory training.
54. Melby-Lervag M, Hulme C. Is Working Memory Training Effective? A Meta-Analytic Review. *Dev Psychol.* 2012

55. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: working memory training decreases delay discounting among stimulant addicts. *Biol Psychiatry*. 2011; 69:260–265. [PubMed: 20965498]
56. Jaeggi SM, Buschkuhl M, Jonides J, Perrig WJ. Improving fluid intelligence with training on working memory. *Proc Natl Acad Sci U S A*. 2008; 105:6829–6833. [PubMed: 18443283]
57. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci*. 2004; 7:75–79. [PubMed: 14699419]
58. Bickel WK, Jarmolowicz DP, Mueller ET, Gatchalian KM, McClure SM. Are executive function and impulsivity antipodes? A conceptual reconstruction with special reference to addiction. *Psychopharmacology*. 2012; 221:361–387. [PubMed: 22441659]
59. Hester R, Garavan H. Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacol Biochem Behav*. 2009; 93:270–277. [PubMed: 19135471]
60. Chooi WT, Thompson LA. Working memory training does not improve intelligence in healthy young adults. *Intelligence*. 2012; 40:531–542.
61. Muraven M. Practicing Self-Control Lowers the Risk of Smoking Lapse. *Psychol Addict Behav*. 2010; 24:446–452. [PubMed: 20853930]
62. Houben K, Havermans RC, Nederkoorn C, Jansen A. Beer a no-go: learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increased response inhibition. *Addiction*. 2012; 107:1280–1287. [PubMed: 22296168]
- 63*. Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci U S A*. 2010; 107:14811–14816. [PubMed: 20679212] This paper demonstrates that upregulation of prefrontal cognitive control regions was associated with down-regulation of emotion processing cortices and subsequent drug (cigarette) craving. It provides a neurobiological mechanism for successful suppression of craving, which might assist treatment outcomes.
64. Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *NeuroImage*. 2010; 49:2536–2543. [PubMed: 19913102]
65. Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend*. 2008; 97:1–20. [PubMed: 18479844]
- 66*. Field M, Munafo MR, Franken IH. A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. *Psychol Bull*. 2009; 135:589–607. [PubMed: 19586163] This paper shows a significant, but small, relationship between attentional bias and craving, which is moderated by a number of factors including the legality of the drug and the method for assessing attention. The ramifications of being able to objectively measure self-reported cravings for treatment are critically discussed.
67. Field M, Duka T, Tyler E, Schoenmakers T. Attentional bias modification in tobacco smokers. *Nicotine Tob Res*. 2009; 11:812–822. [PubMed: 19474181]
68. Schoenmakers TM, de Bruin M, Lux IF, Goertz AG, Van Kerkhof DH, Wiers RW. Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug Alcohol Depend*. 2010; 109:30–36. [PubMed: 20064698]
69. Wiers RW, Eberl C, Rinck M, Becker ES, Lindenmeyer J. Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. *Psychol Sci*. 2011; 22:490–497. [PubMed: 21389338]
70. Macleod C, Holmes EA. Cognitive bias modification: an intervention approach worth attending to. *Am J Psychiatry*. 2012; 169:118–120. [PubMed: 22318791]

Highlights

- We review the changes in brain structure and function that arise with abstinence.
- We review the pre-treatment neurobiological predictors of abstinence.
- We discuss the potential of cognitive training of frontal systems for abstinence.

Figure 1.

The figure depicts three processes that are hypothesized to characterize the neurobiology of abstinence. The first two are involved in the recovery process. Restoration refers to the return of brain function and structure over time (red columns) to premorbid levels comparable to non-addicted comparison participants (blue column) and which arises from the discontinuity of drug use. Abstinence Maintenance refers to those processes hypothesized to actively resist relapse by monitoring the external and internal cues to relapse and by regulating drug urges. The functions and structures associated with this process are hypothesized to contribute in a causal manner to maintaining abstinence and may, with prolonged abstinence, increase beyond the levels observed in healthy controls. Finally, Relapse Risk reflects the long-lasting vulnerability to relapse that characterizes drug dependence. The dynamic between the integrity of the Maintenance and Relapse Risk processes and how the relationship between the two is affected by relapse precipitants such as exposure to drugs, drug cues, and stress may determine the likelihood of successful abstinence.