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Neuroscience of inhibition for addiction medicine: From prediction of initiation to prediction of relapse

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Abstract

A core deficit in drug addiction is the inability to inhibit maladaptive drug-seeking behavior. Consistent with this deficit, drug-addicted individuals show reliable cross-sectional differences from healthy non-addicted controls during tasks of response inhibition accompanied by brain activation abnormalities as revealed by functional neuroimaging. However, it is less clear whether inhibition-related deficits predate the transition to problematic use, and, in turn, whether these deficits predict the transition out of problematic substance use. Here, we review longitudinal studies of response inhibition in children/adolescents with little substance experience and longitudinal studies of already-addicted individuals attempting to sustain abstinence. Results show that response inhibition, and its underlying neural correlates, predict both substance use outcomes (onset and abstinence). Neurally, key roles were observed for multiple regions of the frontal cortex (e.g., inferior frontal gyrus, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex). In general, less activation of these regions during response inhibition predicted not only the onset of substance use, but interestingly, also better abstinence-related outcomes among individuals already addicted. The role of subcortical areas, although potentially important, is less clear because of inconsistent results and because these regions are less classically reported in studies of healthy response inhibition. Overall, this review indicates that response inhibition is not simply a manifestation of current drug addiction, but rather a core neurocognitive dimension that predicts key substance use outcomes. Early intervention in inhibitory deficits could have high clinical and public health relevance.

Keywords

Response inhibition; inhibitory control; drug addiction; developmental trajectories; clinical outcome; fMRI; longitudinal designs

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None declared.

Introduction

Drug addiction is a chronically relapsing disorder marked by dysregulated inhibitory control, which may contribute to or exacerbate the addicted individual's ability to restrain drug-taking (Goldstein & Volkow, 2011; Kalivas & Volkow, 2005). Neuroimaging studies utilizing functional magnetic resonance imaging (fMRI) have consistently identified abnormalities in brain function during response inhibition in currently-addicted individuals across multiple drugs of abuse (Luijten et al., 2014; J. L. Smith, Mattick, Jamadar, & Iredale, 2014). Nevertheless, an enduring problem of such cross-sectional studies is the inability to infer the direction of association. Longitudinal studies offer an exciting opportunity to test whether core drug-relevant neurocognitive deficits (e.g., in response inhibition) predate the transition into and out of problematic drug use. In this way, one can evaluate whether such deficits in drug addiction represent an epiphenomenon or an actual predisposing factor.

Accordingly, the goal of the current review is to examine the extent to which performance- and/or neural-related decrements during tasks of inhibitory control precede the transition to drug use/addiction, and then whether such decrements predict clinical outcomes when already-addicted individuals seek treatment or attempt to abstain. In particular, we seek to evaluate the hypothesis that impaired response inhibition is not simply a concurrent symptom of drug addiction, but instead a core neurocognitive dimension that predicts key substance use outcomes. We concentrate on longitudinal studies, largely those reported within the last 10 years, which have examined prospective associations between inhibitory control and the dependent variable of interest (drug use initiation or escalation, dependence, relapse, or abstinence). Most of the fMRI studies reviewed here report the results of task-induced activations (e.g., activity that occurs during a condition of response inhibition contrasted with activity during a condition of prepotent response). Other studies used task-related functional connectivity (i.e., the covariation between the fMRI time courses of a given voxel and other voxels in the brain), which offers a promising complement to task-based activation studies. The main literature review itself is organized into two parts. Part 1 discusses adolescent longitudinal studies that use tasks of inhibitory control to predict future drug use or transition into drug dependence. Part 2 discusses adult longitudinal studies that use tasks of inhibitory control to predict clinical and treatment outcomes in already-addicted individuals. We conclude with a summary of findings and a discussion of future research directions.

We exclude from this review studies that involved passive exposure to drug-related stimuli, studies that used tasks associated with the receipt of reward, or studies that reported addiction-related abnormalities in brain structural integrity. Reviews that address these important topics can be found elsewhere [e.g., (Garavan, Brennan, Hester, & Whelan, 2013; Heitzeg, Cope, Martz, & Hardee, In Press; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014); note some overlap in currently included studies with those from (Heitzeg et al., In Press)]. This review also excludes behavioral addictions (e.g., gambling, food, sex, or video games) and studies that use event-related potentials (ERPs), as more longitudinal studies in these fields are needed before firm conclusions about prospective relationships can be drawn. Studies that focus on family history (or other risk factors) as the main grouping variable are also excluded [e.g., (Hardee et al., 2014)]. Finally, for brevity and focus, we also

exclude tasks of inhibition that measure related constructs [e.g., error awareness (Hester, Nestor, & Garavan, 2009)], or studies that incorporate pharmacological (Moeller et al., 2014; Schmaal et al., 2013) or genetic (Filbey, Claus, Morgan, Forester, & Hutchison, 2012) modulation.

Commonly-Used Response Inhibition Tasks in Drug Addiction

Three of the most commonly used inhibitory control tasks, in order from simplest to most cognitively complex, include go/no-go tasks (Chambers, Garavan, & Bellgrove, 2009), stop-signal tasks (Aron, Robbins, & Poldrack, 2014; Verbruggen & Logan, 2008), and Stroop tasks (MacLeod, 1991; D. G. Smith & Ersche, 2014). These tasks collectively measure a person's ability to modify or stop a behavior, particularly when the behavior may not be optimal or advantageous, or is perceived as incorrect. In go/no-go tasks, participants respond as quickly as possible to frequent go stimuli and inhibit responses to infrequent no-go stimuli. Correct non-responses on no-go trials reflect the ability to exert inhibitory control over behavior. In stop-signal tasks, the goal is to successfully inhibit (stop) an action that has already begun. Participants respond to an ongoing sequence of stimuli; on some (stop) trials, however, a signal is presented (e.g., a tone, a change in stimulus display) after the stimulus onset that instructs participants to halt their response on that trial. The paradigm is typically configured to find the inflection point in which 50% of stop trials are unsuccessful relative to the mean reaction time; the longer this stop-signal reaction time (SSRT), the worse the inhibitory control. In Stroop tasks, participants must override a more automatic response tendency (reading a word) and instead respond with a task-specific demand (responding to the ink color of the word). Stroop tasks can be purely cognitive: in the classical color-word Stroop, participants respond to the ink color of color words (e.g., "blue") presented in either the congruent font (blue font) or an interfering incongruent font (e.g., red font). Stroop tasks can also be emotional: interference can be introduced by attentional bias or current concerns of the individual. In the case of drug addiction, individuals can be instructed to ignore the semantic content of drug-related words (e.g., "pipe") and instead respond to their font color; typically, the reaction time to drug words is longer than for neutral words (e.g., "vase"), indicating impaired response inhibition (Cox, Fadardi, & Pothos, 2006). An important caveat is that these tasks, while tapping into inhibitory control, also depend on other executive, attentional, or emotional processing functions. For example, some have argued that Stroop tasks tap into different higher-order executive functions than go/no-go and stop signal tasks, such as compulsivity and impulsivity, respectively (Fineberg et al., 2014).

All three of these tasks have reliably yielded activations in regions of interest (ROIs)/networks known to be engaged during inhibitory control. These include the inferior frontal gyrus (IFG), anterior cingulate cortex (ACC) (especially its dorsal/motor subregion), middle frontal and superior frontal gyri (MFG/SFG) [which includes the dorsolateral prefrontal cortex (DLPFC)], parietal lobe, and pre-supplementary motor area (pre-SMA) (Bari & Robbins, 2013; Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015) (Figure 1). Importantly, some of these same regions are consistently identified as being disrupted in currently-addicted individuals performing the tasks [for recent, comprehensive reviews on this topic, see (Luijten et al., 2014; J. L. Smith et al., 2014)]. These studies and reviews in

current drug dependence suggest pertinent regions/networks to spotlight for longitudinal prediction (Figure 1), which is the focus of the remainder of this review.

Part 1: Progression into Addiction/Problematic Substance Use (Table 1)

Go/No-Go Studies

A moderately large sample of adolescents performed a go/no-go task during fMRI at baseline and then again 18 months later. More left angular/supramarginal gyrus activation and less ventromedial prefrontal cortex (vmPFC) activation to the no-go versus go trials at baseline predicted an increase in drug use occasions at follow-up (i.e., accounting for baseline drug use) – particularly in those who were already heavier users (Mahmood et al., 2013). Another longitudinal fMRI study tested for changes over the first year of college during an emotionally salient go/no-go task that instructed participants to respond to alcohol cues compared with non-alcohol cues; here, the dependent variable was task-related functional connectivity. Young adults were scanned three times (summer, first semester, second semester). At the second assessment (during which respondents reported an increase relative to the first assessment in the negative consequences of alcohol use, such as losing consciousness during drinking or performing poorly on an exam because of drinking), functional connectivity was increased among a network of regions implicated in response inhibition and cognitive control (e.g., bilateral DLPFC, rostral ACC, dorsal ACC) (Beltz et al., 2013).

Even more illuminating, however, are studies that begin tracking youth before they have begun experimenting with addictive substances. In one study, an fMRI go/no-go task was used at two study sessions to compare adolescents who were initially non-drinkers but later transitioned into heavy drinking against adolescents who remained non-drinkers during both assessments. Adolescents who later transitioned into heavy drinking showed less fMRI response to no-go versus go trials in the MFG, parietal cortex, putamen, and cerebellum. Interestingly, these effects were reversed at the second scanning session, such that the adolescent heavy drinkers showed increased fMRI activation in these regions (except in the putamen, where no group differences were observed in the second session) (Wetherill, Squeglia, Yang, & Tapert, 2013). Results were interpreted to indicate that the reduced fMRI activation before drinking could reflect vulnerability, whereas the increased fMRI activation after drinking could reflect compensation. Another fMRI study investigated adolescents again with initially very limited substance use experience, classifying them at follow-up into those who transitioned to heavy use of alcohol versus those who remained non-users. Similar results were reported, whereby youth who later transitioned into heavy alcohol use had less activation in multiple brain regions encompassing the IFG, DLPFC, putamen, middle temporal gyri, and inferior parietal lobules (Norman et al., 2011). More recently, preteens (9–12 years) performed an fMRI go/no-go task at baseline; four years later, participants completed assessments of substance use, which were used to create matched groups of substance users and non-substance users. In contrast to the other studies, there were no significant fMRI differences between the groups during successful no-go inhibition at baseline. Instead, non-users showed increased activation relative to users during unsuccessful inhibition versus successful inhibition in the left MFG (DLPFC); DLPFC

activation predicted outcome (group membership) over and above the effects of externalizing behavior (Heitzeg et al., 2014). This different pattern of effects could be due to the different fMRI contrast (error-related processing).

Stop-Signal Studies

Four hundred ninety-eight children from 275 families from a high-risk, prospectively-followed cohort completed executive function measures in early and late adolescence, with the goal of predicting lifetime drinking and drug-related ratings in late adolescence; multilevel models controlling for various potential confounds showed that poorer response inhibition (i.e., higher SSRT) predicted the onset of future drug and alcohol use (Nigg et al., 2006). Moreover, in the same high-risk sample, poorer response inhibition in late adolescence predicted alcohol-related problems in young adulthood (e.g., driving while intoxicated or experiencing an alcohol-induced blackout) (Wong, Brower, Nigg, & Zucker, 2010).

A different research group similarly used a multi-wave longitudinal study (five assessments over two years) to test associations between the behavioral stop-signal task and alcohol use in adolescents (Fernie et al., 2013). Data were analyzed using sophisticated cross-lagged analyses, which enable investigation of the relationships between response inhibition at time 1 and alcohol use at time 2 while controlling for cross-sectional associations between these variables at both time points and for their stability over time. Results showed that stop-signal performance prospectively predicted alcohol involvement, whereas the reverse association (alcohol involvement predicting response inhibition) did not reach significance. These analyses, which approximate causal relationships between variables in a non-experimental design, suggest that response inhibition in adolescence confers vulnerability toward future substance use.

In an elegant, recent fMRI study, machine learning techniques were used to integrate multimodal self-report, structural and functional imaging, and genetics data in service of predicting concurrent and future binge drinking in a large sample of adolescents. In the longitudinal arm, fMRI activation in the precentral gyrus to response inhibition failures predicted future binge drinking (Whelan et al., 2014).

Stroop Studies

Few studies have used Stroop tasks to predict emerging substance use problems. One behavior-only study used a Stroop task to stratify adolescents into those with stronger or weaker response inhibition (incongruent>neutral response reaction time). The task itself was an approach-avoidance paradigm that used stimuli depicting alcohol or soda, and participants were instructed to either pull (approach) or push (avoid) a lever in response to the stimuli. Results showed that greater alcohol approach tendencies (i.e., faster reaction time to pull the lever toward than push the lever away) predicted alcohol use at 6-months follow-up only in the adolescents with weaker Stroop-assessed inhibition (Peeters et al., 2013).

Part 1 Summary

These studies suggest that performance on tasks of response inhibition in adolescence/young adulthood predict future initiation into substance use. Despite some exceptions (and although additional studies utilizing the Stroop task are needed), the general pattern of results suggests underactivations during the response inhibition trials in key inhibition-related regions in the individuals who would later become substance users; an opposite (hyperactivation) pattern seemed to occur when examining response failure. The most consistent neural correlate of response inhibition was the DLPFC, which is a core region in response inhibition but also in the implementation of cognitive control more generally (Egner, Etkin, Gale, & Hirsch, 2008; Kerns et al., 2004). Other regions identified in multiple studies included the parietal cortex and the putamen. The precentral gyrus also deserves mention, given this region's emergence in a well-powered and well-controlled study (Whelan et al., 2014). These neural underactivations during response inhibition in the individuals who would later develop problematic drug use were typically observed in the absence of behavioral differences between the groups (Table 1). Lack of group differences on task performance suggests that these fMRI differences are potentially marking abnormal neural activity (rather than, for example, an inability to perform the task). Taken together, inhibition problems and associated aberrant brain response during the exertion of inhibitory control appear to predate substance use.

Part 2: Prediction of Clinical Outcome in Already-Addicted Individuals (Table 2)

Go/No-Go Studies

In an interesting study of smokers motivated to quit, fMRI during a go/no-go task (successful no-go versus go events) was used to predict outcome via an experience sampling method (a unique contribution to this literature); as part of these assessments, participants responded eight times per day for three weeks about their craving and cigarettes smoked (Berkman, Falk, & Lieberman, 2011). The IFG, pre-SMA, and basal ganglia were selected as ROIs. Results revealed a positive correlation between craving at one time point and smoking at the next time point. Interestingly, this relationship was moderated by all three ROIs, such that individuals who had higher fMRI activations in these regions to the no-go stimuli had a blunted correlation between craving and smoking. This finding could suggest that enhanced neural response during response inhibition reflects a greater capacity to exert top-down control over impulses (e.g., craving) [although it should be noted that other studies have interpreted such enhanced activation as reflecting compensation (Wetherill et al., 2013)]. In a secondary analysis of this study, the basal ganglia ROI (but not the other two ROIs) predicted reduced smoking across 4 weeks (objectively measured by breath CO) (Berkman et al., 2011).

In another fMRI study (this one using a more standard analysis methodology), increased activation in a different region (the postcentral gyrus, to all no-go events versus all go events) predicted treatment outcome one week later (positive cocaine urine screen) (Prisciandaro, Myrick, Henderson, McRae-Clark, & Brady, 2013). Important caveats of this

study are that these participants were also included in a treatment trial that administered d-cycloserine, and they also completed a cue-reactivity task during the same scanning session.

Stop-Signal Studies

In an fMRI study, a moderately-sized cohort of treatment-seeking cocaine-dependent individuals completed the stop-signal task and was followed over 3 months to predict clinical outcome. Decreased activation in the dorsal ACC during error-related processing (stop error versus stop success) predicted relapse in males and females (note that males and females also exhibited some differential activations that predicted relapse: decreased thalamus activation in females; decreased insula activation in males) (Luo et al., 2013). In contrast, in a behavior-only study of treatment-seeking alcohol-dependent individuals, the stop-signal task administered at baseline did not predict 12-month outcome; instead, 12-month outcome was predicted by genetic variation (type 2A serotonin receptor polymorphism) (Jakubczyk et al., 2013). Notable differences between these studies include the use of fMRI and the length of the follow-up period (3- versus 12 months).

Stroop Studies

In a behavior-only study examining the variables that predict treatment retention in a therapeutic community, participants completed a battery of neuropsychological measures including the color-word Stroop task. Better Stroop task performance (both the standard inhibition measure and a second measure assessing switching) significantly predicted better 3-month outcome, but these results did not survive the authors' correction for multiple comparisons (Verdejo-Garcia et al., 2012). Other behavioral studies used emotional (drug) Stroop tasks. In an early study of alcohol abusers, participants completed an alcohol Stroop task at baseline and then again four weeks later. Compared with control participants and alcohol abusers who completed treatment, alcohol abusers who did not complete treatment had alcohol-related interference scores that increased from baseline to follow-up (Cox, Hogan, Kristian, & Race, 2002). A caveat of this study is the small sample sizes in each group (n=5 participants who remained abstinent or had a small lapse; n=9 participants who relapsed or failed to maintain contact with a counselor). In another earlier study, treatment-seeking drug-addicted individuals performed a drug Stroop task, with the stimuli content matched to the participants' particular substance problem (e.g., cocaine stimuli for individuals addicted to cocaine) (Carpenter, Schreiber, Church, & McDowell, 2006). Results showed that cocaine Stroop interference scores predicted more cocaine positive urines and shorter treatment duration in the cocaine participants, but similar substance-specific analyses were not significant in individuals in treatment for marijuana or heroin (but note smaller sample sizes in these latter two groups compared with the cocaine group). In contrast, another study from the same lead author showed that drug Stroop interference scores were *positively* correlated with a greater likelihood of continuing with treatment (entering a Phase II, which included providing negative cocaine urine screens) (Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012). This latter result could indicate that the interference scores in this case were tapping into a hypervigilance toward the cocaine cues to sustain commitment to the treatment process (Moeller & Goldstein, 2014). These conflicting findings remain to be reconciled, but could include variability in the characteristics of the

participants (e.g., abstinence lengths) and/or the therapeutic context (e.g., presence of a voucher system) (Carpenter et al., 2012).

A growing number of fMRI studies have used Stroop tasks to predict clinical outcome in already-addicted individuals. In one of the first studies of its kind, 20 treatment-seeking cocaine-dependent individuals performed an fMRI color-word Stroop task prior to initiating treatment. Interestingly, *higher* behavioral Stroop interference predicted better clinical outcomes (more weeks in treatment). Analysis of the fMRI data showed that during interference trials (incongruent versus congruent), higher activation of the vmPFC, posterior cingulate, and striatum predicted a longer duration of self-reported abstinence (the striatum additionally predicted percent of negative urine screens); and reduced activation of the DLPFC predicted treatment retention (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008). In another study, a drug (cocaine) Stroop task was administered to cocaine-dependent patients during their first week in detoxification treatment and was used to predict cocaine use at 3-month follow-up. Dorsal ACC activation to cocaine versus neutral words positively predicted future cocaine use (i.e., relapse) (Marhe, Luijten, van de Wetering, Smits, & Franken, 2013). Interestingly, the direction of correlation was opposite to the previous study, perhaps attributable to the task valence (emotionally neutral in the former versus emotionally salient in the latter).

Other fMRI studies instead examined the predictive effects of task-related connectivity during neutral Stroop tasks. In one study, 16 treatment-seeking cocaine-dependent individuals and matched healthy controls completed an fMRI color-word Stroop task (Mitchell et al., 2013). In addition to the behavioral Stroop predicting abstinence [i.e., more interference at pretreatment correlated with better outcome, supporting the study above (Brewer et al., 2008)], less functional connectivity among the ventral striatum, thalamus, substantia nigra, right insula, and left hippocampus predicted better clinical outcome (longer abstinence) (Mitchell et al., 2013). This finding is somewhat difficult to interpret considering that the addicted individuals had less connectivity among these regions overall than healthy controls. Nevertheless, this prospective finding within the addicted group is consistent with other work showing that subcortical pathways in drug addiction are hyperconnected during resting-state in association with a greater severity of dependence (Konova, Moeller, Tomasi, Volkow, & Goldstein, 2013); less hyperconnectivity of these subcortical structures, then, could be driving the better treatment outcomes observed in this study. In contrast, however, in a second connectivity study of treatment-seeking cocaine-addicted individuals, independent component analysis (ICA) was applied to fMRI data during color-word Stroop interference (Worhunsky et al., 2013). Here, better clinical outcome (higher numbers of negative cocaine urine screens) was predicted by greater engagement of a subcortical network (encompassing the thalamus, striatum, amygdala, and hippocampus) and a ‘ventral fronto-striatal’ network (encompassing vmPFC, ventral striatum, and subgenual/rostral components of the ACC). In contrast, more weeks in treatment were associated with reduced engagement of a ‘fronto-cingular’ network (encompassing ACC, medial PFC, and insula). Thus, additional research is needed to reconcile inconsistencies among the studies, especially with respect to the contribution of subcortical structures.

Other studies have used bookend (pre-post) fMRI sessions to examine neural changes as a function of treatment and/or abstinence. In one study, substance-dependent individuals underwent fMRI during a color-word Stroop task at baseline and follow-up, with 8 weeks of computer-assisted cognitive behavioral therapy (CBT) for substance abuse in between the two scanning sessions; non-substance-using control participants also completed the Stroop task following a similar time interval. At follow-up, the treatment-seekers showed decreased interference-related fMRI signal in multiple brain regions including the DLPFC, ACC, IFG, and a subcortical cluster that encompassed the midbrain and subthalamic nucleus (Devito et al., 2012). In another study, treatment-seeking cocaine-addicted individuals completed a drug Stroop task at baseline and then again at a 6-month follow-up. Results showed that midbrain fMRI signal increased during the entire task (to drug and neutral words) from baseline to follow-up, and this enhanced midbrain response correlated with reduced cocaine-related choice on a simulated drug-choice paradigm (Moeller, Tomasi, Woicik, et al., 2012).

Part 2 Summary

Here, many of the behavior-only studies used drug Stroop tasks, which yielded somewhat mixed/contradictory results in predicting clinical outcome in treatment-seeking drug-addicted individuals. When inhibition tasks were combined with neuroimaging, prediction was generally improved. Similarly to the initiation literature, these neuroimaging effects generally emerged in the absence of behavioral task effects (particularly for go/no-go and stop signal tasks) (Table 2). In contrast, the Stroop tasks were often associated with behavioral differences (between groups, assessment time points, etc.) (Table 2), and therefore one cannot rule out the possibility that differential fMRI activations are attributable to differential ability of individuals to perform the task. Despite this potential uncertainty, however, these imaging studies were fairly consistent in showing that clinical outcome was prospectively predicted by the DLPFC, dorsal ACC, IFG, and regions of the basal ganglia such as the striatum and midbrain. In general, although with multiple exceptions, better clinical outcome was predicted by decreased PFC activation but enhanced subcortical activation. The predictive effect of subcortical activation could be attributable to recovery of dopaminergic integrity with abstinence (Volkow et al., 2001). Nevertheless, it is important to replicate this subcortical effect in future work, both because of the inconsistent direction of activation in these studies and because subcortical activations are not as reliably reported during inhibitory control tasks in healthy individuals.

Overall, better response inhibition and less activation during the exertion of inhibitory control predicted a better clinical outcome. As there is no *a priori* reason to suspect that individuals with better response inhibition had a less severe addiction, these studies suggest that better response inhibition helps individuals to refrain from drug-taking when they are motivated to do so. An interesting variable to examine in this regard, which was not routinely reported in these studies, is the number of quit attempts during the course of the addiction. One could anticipate that individuals with better response inhibition would have fewer quit attempts.

Conclusion and Future Directions

Paradigm Considerations

An important future direction is to test whether there are unique neural mechanisms underlying the ability to exert inhibitory control in a drug-related context versus a neutral context. Insofar as inhibitory control in drug-addicted individuals is anticipated to be lowest upon being confronted with drugs or drug-associated stimuli (Goldstein & Volkow, 2011), such task designs could potentially explain unique variance in drug use outcomes – particularly since neuropsychological impairments in drug addiction, while pervasive, are generally mild in magnitude and may require more sensitive neuropsychological probes for their detection (Goldstein et al., 2004; Goldstein, Woicik, Lukasik, Maloney, & Volkow, 2007; Moeller et al., 2009; Woicik et al., 2009). Although drug Stroop tasks have been deployed to predict clinical outcome in addicted individuals as reviewed above, these studies generally have not concurrently administered a standard color-word Stroop task for direct comparisons (e.g., drug task minus matched neutral task).

Response inhibition paradigms could also benefit from designs that enable the parametric correlation of trial-by-trial behavioral responses with the associated neural signals for each individual. This type of design could help reduce concerns about interpretation of the fMRI effects when there are also behavioral differences between groups or longitudinal assessments. More broadly, another interesting direction would be to directly contrast an inhibitory control task with another demanding cognitive task (e.g., working memory) that engages similar neural circuitry (e.g., the DLPFC). In this way, one could test whether any cognitively demanding task predicts future drug use, or whether there are uniquely predictive aspects of response inhibition.

Expand Study into More Addictions

Another important direction is to expand the present literature into different drug classes. Alcohol is overrepresented in studies examining the prediction of drug use initiation, and cocaine is overrepresented in studies examining prediction of clinical outcome. For the former (prediction of initiation), the decision to focus on alcohol use is justified, given the focus of these studies on adolescents and young adults. Nevertheless, it will be important to expand this young adult longitudinal literature into the misuse of opioid prescription medication, which has become a paramount public health concern in recent years (Schrager et al., 2014). Moreover, the recent legalization of marijuana in several states (e.g., Colorado and Washington) has increased concerns about underage use and misuse (Monte, Zane, & Heard, 2015). For the latter (prediction of outcome), it will be important to increase the number of studies examining how response inhibition impacts clinical outcomes in other addictions that have high public health implications (e.g., nicotine, alcohol, heroin, methamphetamine). Beyond drug addiction, there is scant inhibitory control longitudinal research on behavioral addictions, such as gambling or internet/video game addiction.

Individual Differences

It is imperative to study addicted individuals with psychiatric comorbidities. Individuals with comorbidities represent a majority of addicted individuals and are more likely to have unmet

treatment needs (Melchior, Prokofyeva, Younes, Surkan, & Martins, 2014). Another potential modulatory variable is the presence of comorbid attention deficit/hyperactivity disorder (ADHD), which is associated with both the initiation of substance abuse and impaired response inhibition (Lee, Humphreys, Flory, Liu, & Glass, 2011); other externalizing symptomatology, such as anger, could also be important to examine (Aharonovich, Nguyen, & Nunes, 2001). Finally, sex differences may modulate response inhibition in drug addiction, as indicated by one of the studies reviewed above (Luo et al., 2013). In further support, in a study examining sex by substance dependence interactions on self-reported impulsivity, female drug-addicted individuals exhibited the highest impulsivity of all participant groupings (Perry et al., 2013). Women may also have greater difficulty inhibiting drug use (e.g., smoking) following cue exposure (Doran, 2014).

Underlying Neurochemistry

The neurochemistry of these effects also remains to be uncovered, especially if these results are to aid the development of innovative pharmacotherapies to treat drug addiction. Dopamine is likely to play an important role, given its reported contribution to higher-order cognitive functions that bear on self-regulation/response inhibition inclusive of cognitive flexibility (Kehagia, Murray, & Robbins, 2010), exertion/sustaining effort (Niv, Daw, Joel, & Dayan, 2007; Satoh, Nakai, Sato, & Kimura, 2003), and motivation (Moeller, Tomasi, Honorio, Volkow, & Goldstein, 2012). For example, in a preliminary sample of cocaine-addicted individuals and healthy controls, we showed that dopamine D2 receptor availability, measured by positron emission tomography (PET) with [^{11}C]raclopride, correlated with fMRI midbrain response to errors during the color-word Stroop task when cognitive resources were presumably most depleted (during the final versus the first task repetition) (Moeller, Tomasi, Honorio, et al., 2012). In addition, studies administering the stop-signal tasks during PET with [^{18}F]fallypride in healthy individuals revealed correlations between SSRT and D2/D3 receptor availability in the left OFC, right MFG, and right precentral gyrus (Albrecht, Kareken, Christian, Dzemidzic, & Yoder, 2014) and the striatum (Ghahremani et al., 2012). Accordingly, therapeutic agents that act on this system, such as the indirect dopamine agonist methylphenidate, could be used to modulate the neural correlates of response inhibition in drug addiction as indeed previously demonstrated (Goldstein et al., 2010; Li et al., 2010; Moeller et al., 2014; Sofuoglu, Devito, Waters, & Carroll, 2013).

Summary, Limitations, and Clinical Implications

We reviewed behavioral and neuroimaging studies of response inhibition aiming to predict longitudinal outcomes in substance abuse. We identified a larger number of studies relevant to the prediction of clinical outcome than to the prediction of transition into substance abuse, underscoring a need for more studies that can detect at-risk individuals before they transition to addiction. In particular, needed are large-scale, comprehensive studies that can integrate and/or disentangle the influences of multiple and multimodal predictors related to response inhibition; the creation of several collaborative imaging consortiums has begun to address this crucial gap (Paus, 2010) [see results in the current review reported by (Whelan et al., 2014)]. These big data initiatives can also help resolve some of the inconsistencies between studies, as small sample sizes are likely to represent a source of increased variation; this concern is accentuated for the relapse prediction studies, which as a whole had smaller

sample sizes than the drug use initiation studies. Another concern for these relapse prediction studies is the abstinence length at the time of scanning: abstinence length was variable between the studies (ranging from hours to weeks), and in many studies this information was not reported (Table 2). This variable could have crucial bearing on the capacity to exert inhibitory control (e.g., if one is studying participants who are experiencing acute withdrawal symptoms and/or intense craving), or alternatively could be evidence of individuals having already exerted inhibitory control (e.g., if one is studying participants who have sustained abstinence for several weeks). Moreover, one needs also to exercise a degree of caution when interpreting the results of studies that retrospectively test for neuroimaging predictors (e.g., using the outcome, such as relapse versus abstinence, as the basis of creating groups for a baseline neuroimaging analysis). This type of analysis can lead to overfitting that can inflate the magnitude of the observed differences, a problem that has been well-articulated elsewhere (Garavan et al., 2013).

Despite these concerns, results generally support the hypothesis that these tasks, and their underlying neural correlates, predict important prospective outcomes. Behaviorally, better response inhibition generally predicted better outcomes. Neurally, the general pattern of results was that frontal regions were less activated during the exertion of inhibitory control in the individuals who would later become problematic substance users. This finding of blunted frontal activation during response inhibition is also consistent with other externalizing psychopathologies, including ADHD (Rubia et al., 2011) and intermittent explosive disorder (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Interestingly, however, less activation of similar frontal regions generally predicted better clinical outcomes when the context was sustaining abstinence.

These results have important clinical implications. Although results cannot illuminate causal relationships between variables, longitudinal prediction constitutes an improvement over cross-sectional studies and can support the important conclusion that response inhibition deficits could be targeted for intervention to improve future outcomes. These could include targeted cognitive-behavioral exercises, possibly in combination with pharmacotherapy and/or individualized neurofeedback. These types of interventions can help address the vital public health goals of identifying the young individuals most likely to progress from recreational to problematic substance use, and identifying the addicted individuals most likely to relapse after beginning treatment or abstinence. Individuals with reduced inhibitory control could be selected for additional therapeutic/interventional resources to produce better drug-related outcomes.

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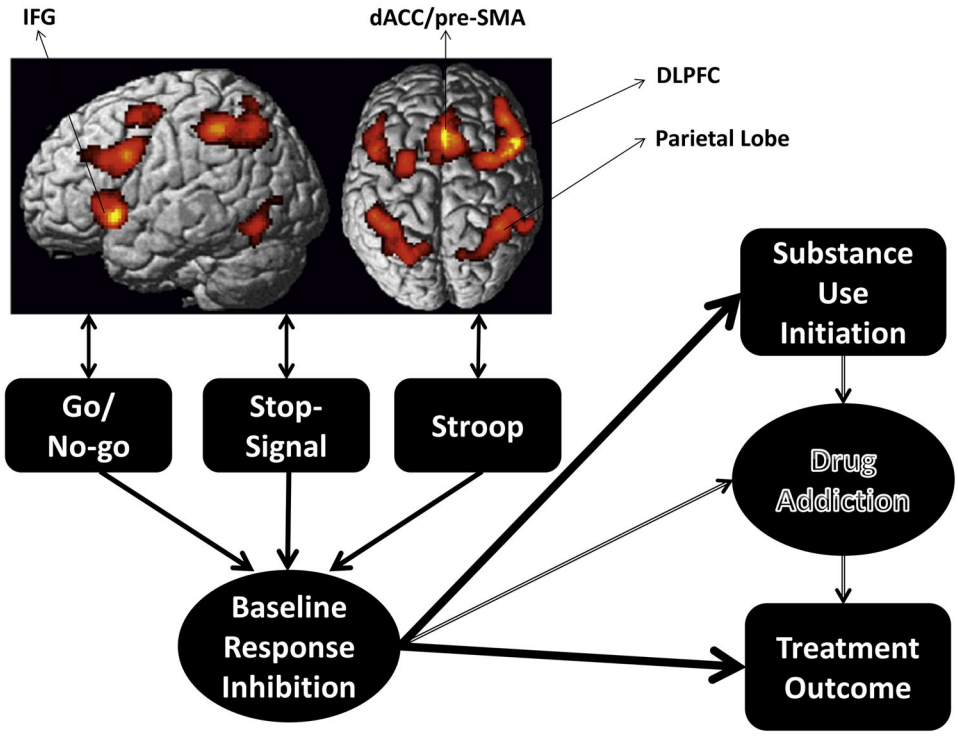

Figure 1.

Schematic of the current review. Response inhibition is associated with performance- and neural correlates of response inhibition [regions/networks include IFG, dACC/pre-SMA, DLPFC, and parietal lobe], which together prospectively predict substance use initiation and clinical/treatment outcomes. Blue arrows reflect concurrent associations; red arrows reflect longitudinal predictions; skinny black arrows are descriptive. Rectangles reflect measured variables; circles reflect latent variables (i.e., variables defined by other measured variables, whether explicitly included in the schematic or not). The broken text and arrows of the addiction circle signify implied relationships (i.e., not the focus of the current review). IFG = inferior frontal gyrus, dACC = dorsal anterior cingulate cortex, pre-SMA = pre-supplementary motor area, DLPFC = dorsolateral prefrontal cortex. Brain activation maps are adapted from a previous meta-analysis of response inhibition in health (Cieslik et al., 2015) (with permission from Elsevier).

Table 1

Prediction of drug use initiation.

Study	Participants (Retention Rate)	Mean Age (SD)	Sex: M/F	Race	Disorder Status	RI Task	Time Between Assessments	Main Results, Behavioral	Main Results, Imaging
Go/No-go Tasks									
(Beltz et al., 2013)	**N = 11** (91.01%)	18–19	5/6	NR	NR	Go/no-go fMRI	T1 – T2: 2 mo T2 – T3: 3 mo	NS	Task functional interconnectivity: ↑ B dlPFC, ACC over time
(Heitzeg et al., 2014)	**N = 45** HC, n=19 NU, n=13 PU, n=13	 10.9 (1.1) 10.9 (0.9) 11.0 (1.0)	 15/4 10/3 10/3	100% C	*Externalizing*: CBCL &YSR	Go/no-go fMRI	T1 –T2: ~4 yr	RT: PU ↓ NU	*Contrast: failed RI>correct RI;* NU ↑ PU: L MFG; L MFG neg corr Externalizing
(Norman et al., 2011)	**N= 38** HU: n=21 HC: n= 17	 13.9 (0.9) 13.4 (0.7)	 11/10 8/9	~80% C	*Substance Use*: CDDR & DSM-IV *Externalizing*: CBCL	Go/no-go fMRI	T1 – T2: 4.2 yr	NS	*Contrast: HU no-go < HC no-go*: ↑ L DLPFC, L supMFG, R IFG, B MedialFG, B paracentral lobules, pre-SMA, L ACC, L Put, L MTG, R MTG, B IPL; ↑ R IFG, L ACC, R MTG, L IPL neg corr T2 CBCL Attention Problems
(Mahmood et al., 2013)	**N= 80** HF, n=39 LF, n=41	 17.4 (0.9) 17.6 (1.0)	 28/11 30/11	 76% C 79% C	CDDR	Go/no-go fMRI	T1 – T2: 18 mo	NS	*Contrast: no-go > go* HF users: ↓ vmPFC pos corr T2 Drug & Alc Sx
(Wetherill, Squeglia, Yang, & Tapert, 2013)	**N= 40** HU, n=20 HC, n=20	 14.7 (1.1) 14.1 (1.2)	 11/9 11/9	55% C, 20% H, 15% multi, 5% As 5% A	*Substance Use*: CDDR and DSM-IV; *Psychopathology/Externalizing:* CBCL, YSR, & ASR	Go/no-go fMRI	T1 – T2: 3+ yr	NS group difference; RI ↑ with age	*Contrast: HU no-go < HC no-go;* T1: ↑ B MFG, IPL, L Put, L cerebellum; T2: ↓B MFG, R inferior parietal lobule, L cerebellum; HU: ↑ R MFG pos corr T2 drinking
Stop-Signal Tasks									
(Fernie et al., 2013)	**N= 287** (94.4%)	12 – 13	NR	NR	NR	Stop-signal behavior	T1 – T2: 6 mo T2 – T3: 6 mo T3 – T4: 6 mo T4 – T5: 6 mo	↑ SSRT pos corr T2 Drinking	NA
(Nigg et al., 2006)	**N= 498**	12–14	362/136	100% C	*Alc/Drug Use*: DDHQ	Stop-Signal behavior	T1 – T2:~ 3yr	↑ SSRT pos corr T2 Drinking & Drug Problems	NA

Study	Participants (Retention Rate)	Mean Age (SD)	Sex: M/F	Race	Disorder Status	RI Task	Time Between Assessments	Main Results, Behavioral	Main Results, Imaging
(Wong, Brower, Nigg, & Zucker, 2010)	**N= 386**	15–17	292/94	100% C	DDHQ-Y & DISC	Stop-Signal behavior	T1 – T2: ~3 yr T2 – T3: ~3 yr T3 – T4: ~3 yr T4 – T5: ~3 yr	↑ SSRT pos corr T2 Alc Sx	NA
(Whelan et al., 2014)	**N= 2650**			NR	ESPAD	Stop-Signal fMRI	T1 – T2: ~2yr	NR	*Contrast: failed RI*:↑R precentral gyrus pos corr with T2 binge drinking
	BD, n=115	14.62(.39)	4/66						
	FBD, n=121	14.45(.40)	69/52						
	HC, n=150	14.53(.43)	70/80						
Stroop Tasks									
(Peeters et al., 2013)	**N= 347** (72.0%)	13.6 (0.9)	330/44	~75% Dutch ~25 non-Dutch	Alc Quantity: 14-item Scale; Severity: CRAFFT	cwStroop behavior; approach-avoidance behavior	T1 – T2: 6 mo	Poor RI: Alc approach pos corr T2 Alc use	NA

Notes. As=Asian, A=African American, Alc = alcohol, ASR= Adult Self Report, B = bilateral, C=Caucasian, CBCL=Child Behavioral Checklist, CDDR= Customary Drinking and Drug Use Record, cwStroop = Stroop with Classical Color-Word Stimuli, DDHQ= Drinking and other Drug Use History Questionnaire, DDHQ-Y= Drinking and other Drug Use History Questionnaire—Youth Version, DISC= Diagnostic Interview Schedule for Children, DLPFC= Dorsolateral Prefrontal Cortex, ESPAD= European School Survey Project on Alcohol and Drugs, FBD=Future Binge Drinker, FH+= Family History AUD Positive, Fas= False Alarms, FH-= Family History AUD negative, H=Hispanic, HC= Healthy Control, HF= High Frequency, HU= Heavy User, IFG= Inferior Frontal Gyrus, IPL –Inferior Parietal Lobe, L= left, LF= Low Frequency, MFG= Middle Frontal Gyrus, MTG= Middle Temporal Gyrus, neg corr = Negative Correlation, NA= Not Applicable, NR= Not Reported, NS= Not Significant, NU= Non-user, PFC= Prefrontal Cortex, pos corr = Positive Correlation, PU= Problem-User, Put = Putamen, Pre-SMA = Pre-Supplementary Motor Area, SSRT = Stop Signal Reaction Time, R = right, RI = Response Inhibition, Sx = Symptoms, T= time, TRF=Teacher's report Form YAAPST= Young Adult Problems Screening Test, vmPFC = Ventromedial Prefrontal Cortex, YSR= Youth Self Report.

Table 2

Prediction of clinical outcome.

Study	Participants (retention rate)	Mean Age (SD)	Sex: M/F	Race	Abst Length	Disorder Status	Treatment Status	RI Task	Time Between Assessments	Main results, Behavioral	Main Results, Imaging
Go/No-Go Tasks											
(Berkman, Falk, & Lieberman, 2011)	N= 31	46 (9.7)	16/15	52% C, 26% H, 19% A, 3% O	NR	> 10 cig/day	Cessation program	Go/no-go fMRI	T1 –T2: 4 wk	NS	*Contrast: no-go > go:* ↑ IFG, BG, & pre-SMA poss corr with attenuation of craving-smoking link
(Prisciandaro, Myrick, Henderson, McRae-Clark, & Brady, 2013)	CD: N= 30 (ReL: n= 6; No-ReL: n=24)	41.2 (8.3) 48.4 (8.7)	5/1 20/4	83% A 83% A	≥ 72 hr	DSM-IV for CD	Outpatient	Drug no/no-go fMRI	T1 – T2: 1 wk	NS	*Contrast: No-go > Go;* ↑ B postcentral gyri poss corr with urine+
Stop-Signal Tasks											
(Jakubczyk et al., 2013)	AD: N= 254	44.2 (10.2)	189/65			DSM-IV for AD	Inpatient	Stop-signal behavior	T1 –T2: 12 mo	NS	NA
(Luo et al., 2013)	CD: N=97 ReL: n=80 No-ReL: n=17	 39.1 (7.5) 43.0 (7.3)	 27/53 7/10	29% C 67% A 4% O	2–4 wk	DSM-IV for CD	Inpatient	Stop-Signal fMRI	T1—T2: 14 d T1 – T3: 30 d T1 – T4: 60 d T1 – T5: 90 d	NS	*Contrast: stop error>stop correct*: In female CD, ↓ thalamus & dACC pos corr relapse; In male CD, ↓ L insula & dACC pos corr relapse
Stroop Tasks											
(Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008)	CD: N= 20	38.6 (9.3)	12/8	30% C 50% A 20% H	28 d	DSM-IV for CD	Outpatient	cwStroop fMRI	NR	RT: ↑ incong > cong pos corr Tx retention	*Contrast: incong< cong;* ↑ R Put pos corr urine- & longest abst; R putamen, L vmPFC & left PCC pos corr longest abst; ↓DLPFC pos corr Tx retention
(Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012)	CD: N= 25	37 (7.1)	22/3	36% C 28% A 24% H 3% O	14 d	DSM-IV for CD	Outpatient	dStroop behavior	24 wk	RT: ↑ drug > neutral pos corr Phase II Tx and urine-	NA
(Carpenter, Schreiber, Church, & McDowell, 2006)	**N= 80** CD: n= 45 MJ: n=25	 38.6 (8.1) 32.4(8.9)	 33/12 20/5	31% C 24% A 33% H	NR	DSM-IV for CD/MJ	Outpatient	(substance-matched) dStroop behavior	NR	RT: In CD, ↑ cocaine > neutral pos corr urine+ and	NA

Study	Participants (retention rate)	Mean Age (SD)	Sex: M/F	Race	Abst Length	Disorder Status	Treatment Status	RI Task	Time Between Assessments	Main results, Behavioral	Main Results, Imaging
	HD: n=10	32.4 (6.6)	9/1							shorter Tx; in MJ and HD, NS	
(Cox, Hogan, Kristian, & Race, 2002)	**N= 30** AD: n=14 (ReL: n=9; No-ReL: n=5) HC: n= 16	41.9 (10.6) 37.3 (10.3)	11/3 4/12	NR	NR	DSM-IV for AD	Inpatient	dStroop behavior	AD: ~24 d HC: ~28 d	RT: in AD ReL but not Non-ReL, ↑ alcohol > neutral	NA
(Devito et al., 2012)	SUD: n=12 HC: n=12	37.2 (9.5) 31.0 (8.6)	7/5 5/7	NR	NR	DSM-IV for SUD	RCT	cwStroop fMRI	T1 – T2: 8 wk	RT: SUD < HC, but ↓ incong RT in SUD at T2	*Contrast: incong > cong T2 < T1 SUD < HC*: ↓ STN/VTA, GP, thal & hypothal
(Marhe, Luijten, van de Wetering, Smits, & Franken, 2013)	CD: N=26	38.7 (9.2)	22/4	NR	NR	DSM-IV for CD	Inpatient	dStroop fMRI	T1 – T2: 3 mo	RT: cocaine > neutral	*Contrast: cocaine > neutral*:↑ R dACC ROI pos corr cocaine use days
(Mitchell et al., 2013)	CD: N= 15 HC: N= 15	39.0 (10.4) 40.0 (7.4)	6/9 7/8	CD: 40% C: 66.7% A HC: 53% C: 47% A	NR	DSM-IV for CD	Outpatient	cwStroop fMRI	T1 – T2: 8 – 12 wk	NS	*Measure: intrinsic connectivity:* CD < HC: R caudate, B OFC, IFG, insula, thal, SN and VS; ↑ connectivity in B thalamus, VS, & SN neg corr abst during Tx & pos corr urine+
(Moeller et al., 2012)	CD: N= 15 (tx – seeking) CD: N= 13 (active users) HC: N= 13	41.4 (9.1)	11/4	NR	≥ 3 wk	DSM-IV for CD	Mix Inpatient/Outpatient	dStroop fMRI	T1 – T2: 6.4 (1) mo	RT: T2 < T1 neutral	*Contrast: T2 > T1*; ↑B midbrain (VTA/SN) & R thal, neg corr simulated drug-seeking
(Verdejo-Garcia et al., 2012)	CD: N= 131	33.9 (21.6)	120/11	NR	≥ 15 d	DSM-IV for CD	Therapeutic Community	cwStroop behavior	T1 – T2: 15–30 d	RT incong > cong: cocaine + heroin comorbid < cocaine only; RT trend pos corr Tx retention	NA
(Worhunsky et al., 2013)	CD: N= 20 HC: N=20	38.6 (9.3) 36.8 (8.9)	12/8 12/8	CD: 30% C, 50% A, 20% O HC: 70% C, 30% A	NR	DSM-IV for CD	Outpatient	cwStroop fMRI	8 wk treatment	RT: NS; Errors: CD > HC	Measure: ICA: ↑ subcortical- & ventral fronto-striatal' networks pos corr urine-; ↓ fronto-cingular' network pos corr Tx wks

Notes. As=Asian, A=African American, Abst = abstinence, ACC= Anterior Cingulate, AD= Alcohol Use Disorder, ASR= Adult Self Report, B= Bilateral, BG =basal ganglia, C=Caucasian, CBCL= Child Behavior Checklist, CD= cocaine Dependence, Cong = Congruent, CDDR= Customary Drinking and Drug Use Record, cwStroop = Stroop with Classical Color-Word Stimuli, DDHQ-Y= Drinking and other Drug Use History Questionnaire—Youth Version, DISC= Diagnostic Interview Schedule for Children, DLPFC= Dorsolateral Prefrontal Cortex, DMFC= Dorsomedial Frontal Cortex, dStroop = Stroop with Drug-Associated Stimuli, GP = globus pallidus H=Hispanic, HC= Healthy Control, HD= Heroin Dependence, ICA = Independent Components Analysis, IFG= Inferior Frontal Gyrus, Incong = Incongruent, ITC= Inferior temporal cortex, IRAP= Implicit Relational Assessment Procedure, L= Left, Lent Nucl = Lentiform Nucleus, MFG= Middle Frontal Gyrus, MedFG= Medial Frontal Gyrus, MJ= Cannabis Dependence MTG= Middle Temporal Gyrus, NA= Not Applicable, NR=Not Reported, No-ReL= Non-relapsers, NS= Not Significant, O = other race, PFC= Prefrontal Cortex, Pre-SMA = Pre-Supplementary Motor Area, Put = Putamen, R= Right, ReL=Relapsers, RCT = Randomized Clinical Trial, RI = Response Inhibition, ROI = Region of Interest, R-SAT = regulation—Revised Strategy Application Test, SFG = Superior Frontal Gyrus, STG = Superior Temporal Gyrus, SN = Substantia Nigra, STN = Subthalamic Nucleus, SUD= Substance Use Disorder, T= time, Thal = Thalamus, Tx = Treatment, Urine+ = Positive Urine Result, Urine- = Negative Urine Result, vmPFC = Ventromedial Prefrontal Cortex, VS = Ventral Striatum, VTA = Ventral Tegmental Area, YSR= Youth Self Report