Review

COGNITIVE CONTROL AND THE DOPAMINE D$_2$-LIKE RECEPTOR: A DIMENSIONAL UNDERSTANDING OF ADDICTION

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The phenotypic complexity of psychiatric conditions is revealed by the dimensional nature of these disorders, which consist of multiple behavioral, affective, and cognitive dysfunctions that can result in substantial psychosocial impairment. The high degree of heterogeneity in symptomatology and comorbidity suggests that simple categorical diagnoses of "affected" or "unaffected" may fail to capture the true characteristics of the disorder in a manner relevant to individualized treatment. A particular dimension of interest is cognitive control ability because impairments in the capacity to control thoughts, feelings, and actions are key to several psychiatric disorders. Here, we describe evidence suggesting that cognitive control over behavior is a crucial dimension of function relevant to addictions. Moreover, dopamine (DA) D$_2$-receptor transmission is increasingly being identified as a point of convergence for these behavioral and cognitive processes. Consequently, we argue that measures of cognitive control and D$_2$ DA receptor function may be particularly informative markers of individual function and treatment response in addictions. Depression and Anxiety 0:1–12, 2011. © *2011 Wiley Periodicals, Inc.*

Key words: *cognitive control; mental disorders; addiction; impulsivity; dopamine; D$_2$ receptor*

INTRODUCTION

Mental disorders are multidimensional syndromes, characterized by a collection of symptoms that often span conceptually unrelated behavioral and cognitive domains. Though classification of these symptoms is typically categorical, with the symptom being "present" or "absent" in an individual, and the symptoms "summing" to a syndromal category, a dimensional analysis of symptomatology may provide advantages in understanding the biological basis of mental disorders.

Symptom dimensionality may be a fundamental link for understanding interindividual differences in response to treatment. Specifically, variation in symptom cluster and severity may explain why one intervention is highly beneficial for some individuals but with little-to-no therapeutic effect for others. The lack of correlation between treatment strategies and psychosocial outcomes is prevalent in individuals diagnosed with a variety of psychiatric disorders, such as schizophrenia, depression, or addiction.

The development of effective and targeted treatments relies on advancements in basic research directed at elucidating the neurochemical abnormalities that underlie these disorders in order to develop novel pharmacological agents. However, the translational of basic science results into pharmacological medicine and effective treatments has been fairly limited. This, too, may be a consequence of dichotomizing these

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disorders and symptoms, obfuscating the biological variability that exists within a disorder.

One potential strategy that has been proposed as a method to bridge the gap between basic scientific results, pharmacological development, and therapeutic strategies is to deconstruct disorder-specific symptoms into simpler and more refined phenotypes. There are numerous phenotypes that could be used to study specific dimensions of mental disorders (sensory-gating, feedback sensitivity, etc.); however, aberrant cognitive control processes have been consistently proposed as core features of several psychiatric disorders.

Here, we discuss the evidence that cognitive control represents an important dimension of mental disorders. Although this review focuses on the use of cognitive control to better understand addictions, the same principles can be extended to other mental disorders, including but not limited to anxiety, depression, and schizophrenia. In fact, deviations in cognitive control processes have been reported in individuals diagnosed with mood disorders, suggesting that cognitive control may be one important dimension of these disorders. We propose that investigating dimensions of disorders, such as cognitive control, can further our neural understanding of psychopathologies and assist in developing scientifically based individualized treatment strategies.

PHENOTYPIC OVERLAP BETWEEN ADDICTIONS, IMPULSIVITY, AND COGNITIVE CONTROL

Substance dependence is defined as compulsive and inflexible drug-seeking and -taking, despite the negative consequences associated with that behavior. This concept likely extends to so-called process addictions, as there is evidence that similar forms of compulsive behaviors can develop in response to nondrug reinforcers, including food[1] and sex.[2] Irrespective of the goal that drives the addiction, the behavioral sequela of addictions are similar, suggesting that a common set of biological substrates contribute to this set of psychiatric phenotypes.

Key to our concepts of drug abuse and dependence are impulsive and compulsive patterns of drug seeking. For example, persistent use of a substance despite knowledge of the long-term detrimental consequences may mirror the myopic characteristics of impulsivity (wherein immediate gratification outweighs delayed negative consequences). Furthermore, reduced ability to voluntarily cease drug use can be viewed as failed ability to exert inhibitory control over compulsive behaviors. Indeed, several lines of evidence have implicated dimensions of

impulsivity and cognitive control as core features of addictions.[3,4]

Impulsivity is a construct that describes a set of behaviors that, in extreme forms, have the potential to be maladaptive, including difficulty resisting urges, hasty or risk-prone decision making, and reduced sensitivity to delayed outcomes.[5] There are several studies that implicate aspects of impulsivity in addictions.[6–10] Specifically, higher levels of trait impulsiveness are present in individuals dependent upon substances[7,11–14] or individuals who are affected by other addictions.[15,16]

Chronic exposure to drugs of abuse has been reported to produce an enhancement in impulsive-like responding in animals,[17–19] implicating drug use as one mechanism by which high impulsivity manifests. However, high-trait impulsivity prior to drug use has been proposed as a risk factor for the development of substance dependence.[20–22] Variability in impulsive-like behaviors in rodents has been found to predict future self-administration of drugs[23–26] and is associated with a punishment-resistant, drug-taking phenotype.[27] Therefore, high impulsivity may be a consequence of substance use as well as an indicator of susceptibility for developing substance dependence.

Individual differences in impulsive temperament are likely related to variation in cognitive control, which is defined as the ability to exert volitional control over one's thoughts, feelings, and actions.[28] It is itself a multidimensional construct, involving several psychological processes and neural systems. Because cognitive control involves the utilization of representations of goals and/or abstract rules to guide behavior, it necessarily implicates several higher order processes, such as working memory, cognitive flexibility, response inhibition, and goal-directed attention. Relatively poor function in any of these domains can contribute to inflexible behaviors and/or mental states, and consequently underlie dimensions of a number of psychiatric disorders, including (but certainly not limited to) addictions.[29–33] Indeed, there is growing evidence that impulsivity and cognitive control are directly related,[34–36] suggesting that impulsivity may represent a higher order phenotypic consequence of extreme deficits in multiple dimensions of cognitive control.

As predicted, cognitive control deficits have been observed in individuals dependent upon a variety of substances,[29–33] as well as in animals chronically exposed to drugs of abuse,[37–39] indicating that the materialization of these deficits may, in part, be due to chronic drug use/exposure. However, deficits in cognitive control processes that precede drug use may themselves influence the development of dependence. Children who are at high risk for the development of substance abuse, based upon familial patterns of alcoholism,[40] have purported cognitive control impairments prior to any drug use.[41,42] Furthermore, variation in cognitive control processes correlates with behavioral predictors of substance abuse, such as

severity of drug use and quantity of drug experimentation,[42] and preclinical predictors of drug reinforcement.[43]

Although cognitive control deficits are not part of the current diagnostic criteria for addictions or other psychiatric disorder, they have been proposed to be defining characteristics of addictions and to be both an indicator of susceptibility to the condition and a target of effective treatment that reduce cognitive impairments.[3,44,45] Indeed, pharmacological treatments that are known to enhance cognitive control have also been reported to reduce symptoms in individuals affected by addictions,[46–48] and performance on tasks of cognitive control correlates with predictors of sobriety,[49–51] implicating impulsivity and cognitive control as important dimensions that directly influence the ability of individuals to cease substance use.[3]

The high degree of overlap between cognitive control, impulsivity, and behavior addictions suggest that these processes are governed by similar overlapping mechanisms. Indeed, there is substantial evidence that implicates the dopaminergic system within the corticostriatal circuit as the point of convergence for these behavioral and cognitive processes.

CORTICOSTRIATAL CIRCUIT AS A COMMON NEURAL PATHWAY

Anatomical and biochemical studies examining the anatomical basis of cognitive control, impulsivity, and behavior addictions have independently and convergently implicated brain nuclei within the corticostriatal circuit as critical brain regions of these phenotypes. The corticostriatal circuit is composed of a series of segregated loops between cortical, striatal, and midbrain structures that are topographically organized: limbic and associative information arising from the prefrontal cortex innervates the medial portion of the striatum, whereas sensory and motor information from the premotor and motor cortex innervate the lateral portion of the dorsal striatum.[52] The topographical organization is retained in the striatal projections to the pallidum and substantia nigra, which finally relay back to the cortex via the thalamus.[53] Because of these parallel looping projections, neural signals embedded in this circuit are susceptible to modulation at any of these points and alterations, biochemically and anatomically, in any of these brain regions influence the circuit, and therefore the signal as a whole.

Anatomical, biochemical, and functional alterations within the corticostriatal circuitry have been implicated in both substance and process addictions. Specifically, prefrontal gray matter density is lower in substance-dependent individuals[54–62] and morbidly obese individuals.[63,64] Functional and metabolic studies have also reported reduced connectivity between prefrontal and subcortical structures[65,66] and altered glucose metabolism in prefrontal[67–70] and striatal regions[70,71] in substance-dependent individuals. Similar abnormalities in morphology and glucose metabolism have been reported in animals exposed to drugs,[72–76] implicating drug use as the mechanism by which the neural alterations observed in substance-dependent individuals manifest.

Although no studies to date have directly examined whether variation in corticostriatal integrity is predictive of future addictions, reduced gray matter in cortical and subcortical brain nuclei are present in alcohol-naïve adolescents at high risk for substance dependence.[77] Additionally, animal studies have provided evidence that experimentally induced damage to the prefrontal cortex, prior to drug exposure, enhances the acquisition and performance of drug self-administration.[78] Therefore, preexisting variation in corticostriatal integrity may directly influence drug reinforcement, which may eventually develop into substance dependence.

Similar brain regions within the corticostriatal circuit have been implicated in impulsivity and impulsive-like behaviors: individuals with damage to the ventral and orbital frontal regions consistently report higher levels of impulsivity,[79,80] with analogous results being observed in animals with lesions to the prefrontal cortex[81] and striatal regions.[82,83] Further, more relatively small deviations in corticostriatal integrity have been reported to associate with impulsivity. Specifically, gray matter density within the prefrontal cortex and ventral striatum correlates with self-report levels of impulsivity[84,85] and delay discounting functions[86] in unaffected individuals, implicating corticostriatal integrity as the anatomical mechanism for explaining impulsivity.

The prefrontal cortex has been well established as being essential for several dimensions of cognitive control, as damage to this region is associated with impairments in response inhibition,[87–90] working memory,[91–93] attention,[94] and behavioral/cognitive flexibility.[95–98] However, similar deficits have been reported in animals following lesions to the striatum,[82,99–101] indicating that these processes depend upon the coordinated activity of linked corticostriatal network. Indeed, functional imaging studies have reported activation of several corticostriatal–brain nuclei during tasks of working memory[102] and behavioral flexibility,[103,104] providing evidence that these processes rely on a large network of corticostriatal brain nuclei.

Deficits in cognitive control processes are not unique to addictions. Individuals diagnosed with mood disorders, such as depression, bipolar, or anxiety, have deficits in several domains of cognitive control[105–108] and abnormalities in corticostriatal-related nuclei.[109–113] Therefore, abnormalities in structure and/or function of the corticostriatal circuit may be the mechanism by which phenotypic variation in cognitive processes, such as response inhibition or behavioral flexibility, arise in a number of psychiatric disorders.

DOPAMINE AS THE COMMON NEURAL SUBSTRATE

Brain nuclei of the corticostriatal circuit receive dopaminergic innervation from midbrain dopamine (DA) neurons. Specifically, the prefrontal cortex receives direct dopaminergic projections from mesencephalic dopaminergic neurons and projects back to DA and GABAergic interneurons within the midbrain.[114] In addition to this direct feedback pathway, the prefrontal cortex also sends excitatory projections to the striatum, enabling direct control over midbrain-mediated DA release in the ventral striatum.[115] Depletion of DA content in the prefrontal cortex increases extracellular DA levels in the basal ganglia[116–119] and DA release in response to reinforcing stimuli,[120] demonstrating the involvement of prefrontal DA in modulating baseline and stimulus-elicited striatal DA efflux. These neural systems are thought to contribute to top-down control of the prefrontal cortex over subcortical DA projections, and dysfunction within any one of these brain regions alters dopaminergic tone in the nuclei that comprise the corticostriatal circuit.[115,121] Because of the relationships between corticostriatal-related nuclei and cognitive control, impulsivity, and behavior addictions, dopaminergic dysfunction within this circuitry is believed to underlie these phenotypes.

Despite the diverse pharmacological targets of stimuli with reinforcing and/or rewarding properties, all have been found to increase DA levels within the ventral striatum.[122–125] Therefore, DA is believed to be involved in the incentive value and motivational properties of rewards,[126] and is implicated in the neural circuitry of disorders involving abnormal reward seeking and taking. Although acute administration of drugs with abuse liability increase striatal DA tone, lower levels of DA have been found in postmortem tissue of cocaine- and heroin-dependent individuals[127–129] as well as in animals chronically exposed to drugs.[130–135] Studies utilizing *in vivo* imaging techniques have found similar dopaminergic alterations, specifically with lower levels of DA, rates of DA synthesis, and drug-induced DA release being observed in cocaine-[136–138] and alcohol-dependent individuals.[139,140]

Although a hypodopaminergic striatal system may be a consequence of chronic drug use,[135,141] low DA tone existing *before* drug use may directly influence drug taking as well as the progression of dependence. ADHD patients, who are at a substantially greater risk for developing substance dependence,[142,143] have reduced drug-induced striatal DA release.[144,145] These findings parallel earlier work providing causal evidence for this relationship in high alcohol-preferring rats.[146–148] Therefore, low levels of DA may drive individuals to seek out and obtain rewards that increase DA levels as a way to compensate for their preexisting hypodopaminergic state.

Several recent studies have demonstrated that variation in the DA system underlies impulsivity, such that individuals that report greater levels of impulsiveness have greater amphetamine-induced DA release in the ventral striatum.[149] Furthermore, administration of the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA) can induce impulsive responding in healthy subjects[150] and in Parkinson's disease patients.[151] Preclinical evidence indicates that impulsivity may be, in part, be mediated by DA's actions in the striatum: amphetamine-induced increases in impulsive-like responding are attenuated following focal DA depletion within ventral and dorsal striatal regions.[152,153] Thus, the enhanced DA release in the striatum in high impulsive individuals may be a neurochemical consequence of prefrontal-mediated dysfunction over control of DA release within the striatum.

The DA system has been broadly implicated in modulating cognitive control processes. Targeted DA depletion of the prefrontal cortex and striatum has been reported to impair performance in several tasks of cognitive control,[121,154–158] and variation in striatal DA synthesis has been reported to correlate with performance on tasks of working memory and behavioral flexibility.[159–162] Although several linear monotonic relationships between DA and cognitive control have been reported, greater DA tone in prefrontal and striatal regions can also produce cognitive control deficits similar to those associated with low DA tone,[163–165] indicating that the relationship between DA levels and cognitive control may be nonlinear.[162,164,165] Therefore, deviations in dopaminergic tone within the corticostriatal circuitry may explain individual variation in cognitive control processes amongst both clinical and nonclinical populations.[161]

Although a hypodopaminergic state may drive individuals to seek out and/or obtain rewards that neurochemically elevate DA levels, cognitive control may directly modulate this relationship. Rigid or inflexible behaviors present prior to drug use may influence the developmental time course of addictions, predisposing individuals to develop habitual compulsive behaviors at a rate much faster than individuals with normal or high cognitive control function. This may be due, specifically, to DAs influence on both these processes, whereby low dopaminergic tone results in an enhanced drive to obtain rewards as well as impairing the ability to exert egocentric control over the very same behaviors that are reinforced by the persistent use of rewards.

DA D_2/D_3 RECEPTOR SYSTEM AS A COMMON BIOCHEMICAL MECHANISM

The functional effects of DA are mediated by two classes of metabotropic receptors known as the D_1- and D_2-like families. D_1-like receptors, comprised of the D_1 and D_5 receptor subtypes, are G_s coupled and, when activated, increase adenylate cyclase levels.

D$_2$-like receptors, comprised of the D$_2$, D$_3$, and D$_4$ receptor subtypes, are G$_i$ coupled and when stimulated, formation of adenylate cyclase is either decreased or is unaltered.[166] Both D$_1$- and D$_2$-like receptors are expressed on postsynaptic terminals in brain nuclei that receive dopaminergic input; however, D$_{2/3}$ receptors are also found presynaptically where they act as autoreceptors, regulating both DA release and synthesis. Because D$_2$-like receptors convey the DA signal postsynaptically as well as regulate overall dopaminergic tone, alterations to this receptor can have both profound as well as variable effects on the signaling profile of this DA. Therefore, the D$_2$-like receptor is of particular interest in disorders that are believed to be a result of dopaminergic dysfunction, such as, but not limited to, addictions.

D$_2$-like receptor availability has been consistently reported as being lower in individuals dependent on a variety of substances, such as cocaine,[67] methamphetamine,[12,167] nicotine,[168] opiates,[169] and alcohol,[170–172] as well as in morbidly obese individuals.[173] The alterations in D$_2$-like receptor levels seem to, in part, be mediated by chronic exposure to rewards, as similar reductions in D$_2$-like receptor levels have been reported in animals following chronic exposure to cocaine,[174] alcohol,[175,176] and high caloric food.[177]

However, animals with preexisting low levels of the D$_2$-like receptor have greater cocaine self-administration,[25,174] and viral vector-mediated knock down of D$_2$ receptors has been reported to produce compulsive eating in mice.[177] Based upon this evidence, low levels of the D$_2$-like receptor have been proposed to be a consequence as well as a risk factor for substance use, and pharmacological manipulations that increase D$_2$-like receptor function have been proposed as a possible treatment for substance dependence. Indeed, there is evidence that increasing levels of D$_2$-like receptors attenuates alcohol consumption[175] and cocaine self-administration[178] and that supranormal levels of the D$_2$-like receptor may act as neuroprotective factor for individuals with familial alcoholism.[179]

Recent evidence has highlighted the involvement of the D$_2$-like receptor system in impulsivity and impulsive-like behaviors. D$_2$-like receptor availability in the striatum[12] and midbrain[149] negatively correlate with self-report levels of impulsiveness. Genetic studies examining the DRD2 gene have found that individuals that carry the TaqIA allele, a variant associated with reduced striatal D$_2$-like receptor availability,[180] report higher levels of impulsivity[181] and exhibit steeper discounting of delayed rewards.[182]

The DA D$_2$-like receptor system is involved in several cognitive processes, most notably behavioral and/or cognitive flexibility[183–187] and working memory.[188–190] Pharmacological blockade of D$_2$-like receptors impairs reversal-learning performance[183,191] and working memory,[190] with similar results being found in mice lacking the D$_2$ receptor gene[192,193] and carriers of the DRD2 TaqIA allele.[194] Although the

mechanism by which the D$_2$-like receptor system modulates cognitive control processes is unknown, striatal D$_2$-like receptor availability positively correlates with glucose metabolism in prefrontal regions.[138] Therefore, improving DA D$_2$-mediated transmission may directly modulate prefrontal dependent activity, improving aspects of cognitive control.

A recent study has provided evidence that ties these behavioral and biochemical processes together, demonstrating that administration of a D$_2$-like receptor agonist improves reversal-learning deficits in stimulant-dependent individuals.[195] Therefore, the cognitive control impairments present in individuals with an addiction may be a behavioral manifestation of abnormal D$_2$-mediated DA transmission.

D$_2$-LIKE RECEPTOR DYSFUNCTION: A COMMON SUBSTRATE FOR COGNITIVE CONTROL, IMPULSIVITY, AND SUBSTANCE DEPENDENCE

Dysfunction of the D$_2$-like receptor system represents a common biochemical mechanism underlying cognitive control, impulsivity, and addictions. Based upon the presented evidence, we propose that reductions in D$_2$-like receptor function contribute to the development of addictions through two primary mechanisms that are interrelated (see Fig. 1).

First, low D$_2$-like receptor function prior to drug use results in aberrant positive feedback processing,[187] resulting in inflexible habitual behaviors. Impairments in the ability of individuals to exert control over their behaviors manifests as heightened levels of impulsivity that promote compulsive consumption of rewards,[25,27] and eventually, if reward use is continued, lead to the
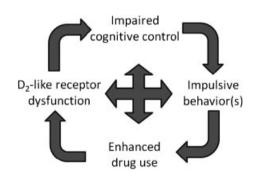

Figure 1. A theoretical model, based upon the available evidence, illustrating the relationship between cognitive control, impulsivity, substance use, and the dopamine D$_2$-like receptor. This model highlights the circular nature of the relationship as well as the cross-directional influences that these behavioral and biochemical phenotypes can have on one and other. The D$_2$-like receptor system represents the biochemical point of convergence for cognitive control, impulsivity, and substance dependence; therefore, we propose that dysfunction of this receptor system can act as both an antecedent as well as a consequence of drug use that directly influences the development of dependence by altering cognitive control processes.

development of dependence. Second, chronic intake of rewards can reduce D_2-like receptor function,[174,177] resulting in aberrant positive feedback integration which promotes the rapid development of habitual behaviors and heightened levels of impulsivity that enhances substance use and, eventually, the development of dependence.

Although this review focuses on the vast body of work that links D_2-like receptor dysfunction and cognitive control with addictions, a large amount of data indicates the D_1-like receptors also play a critical role in cognitive processes, such as working memory.[196] Specifically, activation of D_1-like receptors, and not D_2-like receptors, is necessary for the delay-dependent firing of prefrontal neurons during tasks of working memory.[197] Despite the profound working memory deficits that are present in substance-dependent populations,[198,199] there is limited evidence that D_1-like receptors are altered in these individuals.[200,201] Inconsistent results have been found in animal studies examining the effects of chronic drug exposure on D_1-like receptors.[202–204] Nevertheless, D_1-like receptors are most likely involved in the rewarding and reinforcing properties of drugs, as animals with full loss of this receptor fail to self-administer cocaine.[205] Future studies are needed to clarify the role of the D_1-like receptor with respect to drug addiction and to determine the distinct and collective contributions of D_1- and D_2-like receptors to addictive-related behaviors.

IMPLICATIONS FOR TREATMENT

Increasing D_2-mediated DA transmission represents a primary target for addiction, acting as a potential intervention for at-risk individuals as well as a treatment for those with a debilitating addiction. In fact, several clinical trials have examined the efficacy of D_2-like receptor agonists for cocaine dependence,[206–208] with most finding little-to-no improvements in short- and long-term measures of sobriety relative to placebo. Although these results may seem disheartening, the lack of findings may be due to the pharmacological profile of D_2-like receptor agonists and/or the symptom heterogeneity that is present in addictions.

First, pharmacological agonists have tonic or sustained activity at receptors which differs from the phasic stimulation that occurs under normal physiological conditions. It is possible that sustained activation of receptors by the agonist disrupts neurotransmission to the same extent that antagonists do, resulting in behavioral and cognitive impairments commonly reported with D_2-like receptor antagonists.

Second, cognitive control deficits and substance dependence are not completely overlapping; in fact, cognitive performance of some dependent individuals is at the level of controls.[30] It may be that individuals with normal-to-high cognitive abilities show little

or no therapeutic benefit from D_2-like receptor agonists because cognitive deficits do not represent the principal impairment driving their addiction.

This may, in part, be due to the D_2-like receptor. The efficacy of methadone-replacement therapy for opiate dependence is mediated by the DRD2 gene, such that carriers of the TaqIA polymorphism are more likely to have poorer treatment outcomes compared to individuals that do not carry the A1 allele.[209] Furthermore, smokers that have a 141 base-pair deletion in the promoter region of the DRD2 gene, which is known to decrease transcriptional efficiency of the D_2 receptor,[210] are more likely to benefit from nicotine replacement therapies than pharmacological treatment with buproprion, with the opposite being true for individuals homozygous for 141 bp insertion.[211]

Based on these studies, the D_2-like receptor represents a potential genetic and biochemical factor in predicting the efficacy of pharmacological interventions and outcomes for a particular individual. We suggest that this is driven by the relationship between D_2-like receptors and cognitive control,[187] whereby individuals with low levels of the D_2-like receptor obtain the greatest therapeutic benefit from pharmacological agents that enhance cognitive control and individuals with levels of D_2-like receptors comparable to those of nondependent controls and normal-to-high levels of cognitive control would not. Although this theory remains to be tested, there is evidence that individuals with better reversal-learning performance have performance decrements in response to D_2-like receptor agonists, whereas those with poorer reversal learning have performance improvements.[162] These studies highlight the potential benefits that biological factors have in the development of individualized therapeutic strategies for mental disorders.

SUMMARY

The evidence presented above provides a biological mechanism for explaining the discordance between treatment strategies and efficacy in addiction as it relates to the dimension of cognitive control. Utilizing similar dimensional analyses for other psychiatric conditions may provide insight into the neural determinants that predict treatment efficacy in addition to improving our conceptual understanding of the biological basis of mental disorders.

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