Genetic Influences on Neural Circuitry for Human Reward Processing

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From the drunkard Noah of the Old Testament to the cannabis abusing hashishins of 12th century Persia and on to the present day, drug and alcohol addiction have been recognized as a scourge of mankind since the beginning of recorded history. Current estimates suggest that as many as 9% of Americans meet the DSM-IV criteria for substance use disorders[1,2], and the economic burden of substance abuse (including costs relating to crime, lost productivity, treatment, incarceration and law enforcement) has been assessed at approximately half a trillion dollars[3]. Thus, addiction is a highly prevalent and enormously costly public health issue. However, it is noteworthy that despite the fact that all drugs of abuse are highly reinforcing, only a relatively small percentage of individuals exposed to these drugs go on to develop the destructive pattern of compulsive drug seeking and use that is the hallmark of addiction[4]. Characterizing sources of individual differences in risk and elucidating their mechanisms of action will aid in the identification of novel therapeutic targets for addiction; as such, these research aims represent crucial next steps in advancing treatment options for individuals afflicted with substance use disorders.

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Family, adoption and twin studies have demonstrated that heritable influences account for a moderate-high proportion of population variance in risk for addiction, and therefore suggest that genetic mechanisms may predispose susceptibility[5-7]. In general, when attempting to identify etiopathophysiological pathways through which heritable factors might exert their effects on susceptibility for a given disorder, it is instructive to consider the core cognitive and behavioral domains that are disrupted in that disorder[8]. Addiction is fundamentally a disease of reward and motivation, and it is commonly accepted that addiction develops through the arrogation of evolutionarily conserved neural systems for processing survival-critical natural rewards (e.g. palatable food, sex) by drugs of abuse[9-13]. This singular fact raises the intriguing possibility that genetic risk factors may shape susceptibility by altering the functional properties of brain reward circuitry. The use of functional neuroimaging to characterize the impact of genetic variation on brain structure, function and connectivity is one experimental approach that offers the promise of confirming this hypothesis[8]. However, such an approach must be guided by a tenable conceptual model of reward, and girded by a comprehensive understanding of the genetic, pharmacological, anatomical, and functional architectures of brain reward systems. In what follows, we will outline a current influential conceptualization of reward; review the neurochemistry of "classic" mesolimbic and mesocortical dopaminergic reward circuitry; discuss the relationship between dopamine signaling and dissociable aspects of reward processing; detail findings from human functional imaging studies using reward paradigms; and present recent data implicating genetic variation in dopamine signaling as a source of individual differences in reward response.

A TRIPARTITE MODEL OF REWARD: LEARNING, MOTIVATION AND HEDONICS

A barely noticed television commercial cues a desire for ice cream. Anticipating the impending delights of a chocolate cone, you drive to Ben and Jerry's to obtain the desired treat. Consumption of the cone produces a subjective sense of pleasure. A moment's reflection on even the simplest of reward episodes reveals that reward is not a unitary construct, but rather comprised of several discrete constituent processes. Berridge and Robinson have outlined three basic psychological components: learning, motivation and affect[14]. Generally speaking, reward learning involves ascertaining predictive relationships among external stimuli, interoceptive sensations, and actions. For example, in a simple form of associative reward learning—pavlovian appetitive conditioning—reward-predicting conditioned stimuli (reward cues) energize behavioral responses appropriate to the facilitation of reward consumption. Reward learning mechanisms operate interactively and in parallel with neural systems involved in ascribing hedonic and motivational value to stimuli. These systems underpin

the ability of a rewarding stimulus to induce a positively valenced affective state (pleasure) and elicit a motivational drive that prioritizes future (re)attainment of that state and organizes goal-directed behavior towards this end (desire). While these two reward components usually co-occur and are thus often experimentally conflated, Berridge and Robinson were among the first to argue in favor of a clear differentiation of these facets, which they term 'liking' and 'wanting,' respectively[15]. 'Liking' refers to the hedonic impact of a stimulus—the positively valenced sensory experience that immediately follows reward receipt. By contrast, 'wanting' or 'incentive salience' refers to the motivational value of that reward—that is, its ability to drive goal-directed behavior. The separation between 'wanting' and 'liking' echoes the distinction, first made by ethologists in the late 19th/early 20th century, between "appetitive" and "consummatory" phases of reward behavior. According to this classification scheme, goal-directed approach behavior aimed at obtaining a reward is considered to be part of the 'appetitive phase,' while consumptive (food reward) or copulative (sex reward) behaviors initiated upon reward receipt were considered part of the "consummatory" phase. Neurobiological discrimination of "liking" and "wanting" processes arose from the finding that experimental manipulation of the neurotransmitter dopamine (DA) appears to have a dissociable impact on behavioral measures of each. Namely, altering mesolimbic dopamine signaling has a specific and profound effect on reward 'wanting,' while reward 'liking' is unaltered by such changes[14]. Berridge and Robinson have hypothesized that dysregulation within mesolimbic dopamine circuitry for reward 'wanting' following exposure to drugs of abuse underlies compulsive drug seeking and drug taking behaviors in addiction. Prior to discussing these findings, I will review relevant anatomical and pharmacological aspects of dopaminergic neurotransmission.

DOPAMINE: ANATOMY AND PHARMACOLOGY

Dopaminergic cell bodies are localized to several discrete mesencephalic nuclei; forebrain innervation arises from two of these: the substantia nigra pars compacta (SN) and the ventral tegmental area (VTA). Ascending dopamine axons project via the median forebrain bundle (MFB) to form three relatively circumscribed pathways. The nigrostriatal system projects from SN to dorsal striatum (caudate and putamen); this system is involved in motor control, executive function and habit learning. The mesolimbic system originates in VTA and projects to ventral striatum (including nucleus accumbens; NAcc) and other limbic targets, such as amygdala and hippocampus. The mesocortical system emanates from the VTA as well and projects to cortical regions; cingulate, orbitofrontal and medial prefrontal cortices (PFC) receive particularly dense mesocortical innervation. Mesolimbic and mesocortical dopamine circuits are involved in diverse aspects of cognition and behavior, including motivation and associative learning (mesolimbic system; see below) and attention, working memory, and inhibitory control (mesocortical system).

Dopamine is synthesized in presynaptic nerve terminals from the essential amino acid L-tyrosine. Following the conversion of tyrosine to L-DOPA by tyrosine hydroxylase (TH)—the rate-limiting step of dopamine synthesis—L-DOPA is stripped of its carboxyl group by the enzyme amino acid decarboxylase (AADC) to form dopamine. After synthesis, dopamine is packaged into synaptic vesicles within the presynaptic terminal by the vesicular monoamine transporter (VMAT2). Excitatory stimulation of midbrain dopamine neurons causes dopamine release from axon terminal sites. Following release, extracellular dopamine is either cleared from the synaptic space or binds to a G-protein coupled receptor (GPCR) to initiate signal transduction. Clearance is accomplished by reuptake or enzymatic degradation. The presynaptic membrane-bound dopamine transporter (DAT) binds dopamine with high affinity and, under normal conditions, transports released neurotransmitter back into the presynaptic terminal for repackaging into vesicles or enzymatic breakdown. Dopamine is catabolized by monoamine oxidase (MAO) present in axon terminal mitochondria and in glia, and by catechol-o-methyltransferase (COMT), found extrasynaptically and postynaptically[16].

Alternatively, dopamine can bind to one of several GPCR subtypes. Dopamine receptors are classified into two families on the basis of sequence homology: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, D_4). D_1-like receptors (D_1Rs) are exclusively post-synaptic and are coupled to the G-protein $G_{\alpha s}$; stimulation of D_1Rs activates adenylyl cyclase (AC). D_2-like receptors (D_2Rs), which are located both pre- and post-synaptically, are $G_{\alpha i}$-linked and have an inhibitory effect on AC. Somatodendritic D_2 autoreceptors regulate dopamine nerve cell firing, while stimulation of presynaptic terminal D_2 autoreceptors attenuates dopamine synthesis and release. The downstream effects of postsynaptic dopamine receptor binding are mediated by the activation (by D_1Rs) or inhibition (by D_2Rs) of AC, which in turn influences production of cyclic adenosine monophosphate (cAMP) and thus the function of cAMP dependent protein kinase A (PKA). In the striatum, PKA governs the activity state of DARPP-32 (dopamine-and cyclic AMP-regulated

phosphoprotein with molecular weight 32 kDa), a "master molecular switch" that is known to regulate (by phosphorylation) the activity of a variety of cell-surface receptors and ion channels. In sum, dopaminergic signal transduction is a complex, multi-stage process that is highly regulated at each stage. Inter-individual variability (e.g. due to genetic variation) in the functionality or concentration of proteins involved in any of these stages—dopamine synthesis, vesicular sequestration, release, reuptake, enzymatic degradation, receptor binding or downstream messenger signaling—could be expected to influence individual differences in the functional characteristics of dopaminergic circuits outlined above, and by extension, aspects of cognition, emotion and behavior subserved by them[16].

DOPAMINE, WANTING AND LIKING

Interest in dopamine as a neurochemical substrate for reward developed from research into the neural basis of reinforcement motivation. In their seminal work, Olds and Milner used intracranial electrical self-stimulation to identify brain regions where animals would work for continued electrical stimulation. They found that self-stimulation behavior was most robustly elicited when electrodes were placed in sites along the MFB; Olds termed these sites "pleasure centers[17]." Subsequent work by Roy Wise and others implicated the involvement of SN and VTA dopamine neurons in electrical self-stimulation[18], detailed the sensitivity of MFB stimulation reward to pharmacological intervention with dopaminergic drugs[19], demonstrated that all drugs of abuse increase synaptic dopamine in the NAcc[20], showed that animals will work for the opportunity to self-administer dopamine potentiating drugs[21-23], and appeared to suggest that such drugs reinforce instrumental behavior only to the extent that they elevate dopamine[24]. These and related findings led Wise to develop the hedonia hypothesis of dopamine, which held that "dopamine junctions represent a synaptic way station…where sensory inputs are translated into the hedonic messages we experience as pleasure, euphoria or "yumminess[25]." This hypothesis is the conceptual foundation for many of the dominant neurobiological theories of drug addiction (e.g. the reward allostasis model of Koob and LeMoal[11]), which share the view that addiction is a disorder of meso-accumbens dopamine "pleasure" systems. Wise's formulation of reward neurochemistry was premised on the assumption that the hedonic and motivational values of a stimulus are so inextricably linked as to be indistinguishable. It was presumed that if a food or drug is pleasurable, an animal will work to obtain it, and conversely, that the degree to which an animal works to obtain a reward is in direct proportion to its hedonic value. Thus, for Wise, evidence that dopaminergic manipulations affected drug-seeking and consumption was considered confirmation that dopamine was necessary for producing the hedonic effects presumed to drive such goal-directed behaviors. However, Berridge and colleagues challenged this assumption by using experimental measures that allowed them tease apart hedonic and motivational responses to rewards. Such designs permitted the demonstration of dissociable neural substrates for reward 'wanting' and reward 'liking'.

Utilizing affective facial expressions as an objective and quantifiable measure of hedonic response to gustatory reward stimuli (e.g. sucrose), a range of dopaminergic interventions have been found to have little to no impact on hedonic 'liking' reactions despite profound effects on behavioral indices of motivation. For example, 6-hydroxy-dopamine (6-OHDA) lesions of ascending dopaminergic projections have no effect on hedonic responses to sucrose, despite almost completely depleting dopamine levels in NAcc and dorsal striatum[26-27]. In addition, D_2R blockade does not alter 'liking' responses (to sucrose) or 'disliking' responses (to quinine)[28]. Similarly, neither systemic administration of amphetamine[29], amphetamine microinjections into NAcc[30], or electrical stimulation of the MFB[31] affect liking reactions to sucrose reward, although all three of these manipulations significantly potentiate manifestations of reward 'wanting,' such as food seeking and ingestive behaviors. Notably, genetically hyperdopaminergic and hypodopaminergic mice (DAT and TH knockouts, respectively) show striking and directionally consistent alterations in reward 'wanting' behavior (DAT knockouts increased, TH knockouts decreased) in the absence of corresponding changes in hedonic response[32-36]. In aggregate, these findings strongly suggests dissociable neural mechanisms for ascribing motivational and hedonic value to rewards, with dopamine selectively mediating reward 'wanting' but not reward 'liking'. Berridge and Robinson's Incentive Salience model and Incentive Sensitization hypothesis developed directly from these observations.

INCENTIVE SALIENCE AND INCENTIVE SENSITIZATION

Based on the findings outlined above, Berridge and Robinson have argued that mesolimbic dopamine mediates the dynamic attribution of "incentive salience." This value, when ascribed to a reinforcing stimulus, "transforms mere sensory information about rewards and their cues…into attractive, desired, riveting incentives…to make [them] a 'wanted' target of motivation[14]." Incentive salience "tags" a stimulus as a target for goal-directed behavior and ensures that

an organism will prioritize resources towards obtaining that stimulus over others. Noting that that the key neurobiological nexus for the actions of drugs of abuse—meso-accumbens dopamine circuitry—is critically involved in ascribing incentive salience to environmental stimuli, Berridge and Robinson have hypothesized that drug addiction involves a dysregulation of incentive salience processing. Their "Incentive Sensitization" hypothesis is based on the observation that drugs of abuse induce a profound and long-term hypersensitivity of this system to rewards and to reward-predicting cues. Repeated administration of a wide range of addictive drugs causes animals to become sensitized to their psychomotor effects (e.g. elevated locomotor, exploratory and approach behavior). Strikingly, repeated exposure to psychoactive drugs induces sensitization to their incentive motivational effects, even as tolerance develops to their hedonic effects. For example, pre-exposure to amphetamine decreases the dose and the time required for an animal to subsequently learn to self-administer the drug, and increases the amount of work they will expend to gain access to it[23,37-38]. The expression of sensitization is strongly influenced by associative learning mechanisms, with drug associated cues promoting excessive 'wanting' behavior long after the last drug exposure[39]. The development of sensitization is paralleled by structural adaptations in NAcc dendritic spines, and by cellular alterations within the VTA and at NAcc/PFC synapses[40-42]. In sum, the Incentive Sensitization hypothesis posits that repeated exposure to an addictive drug sensitizes meso-accumbens circuitry for incentive motivation, leading to an excessive attribution of incentive salience to the drug and to drug-related stimuli, even in the face of diminished hedonic responses to the drug over time. In this way, meso-accumbens sensitization by drugs of abuse causes addicted individuals to 'want' the drug more and more, engaging in increasingly compulsive and destructive behaviors to obtain these drugs, even as they may come to 'like' the drugs less and less.

INCENTIVE SALIENCE AND THE HUMAN NAcc: FUNCTIONAL IMAGING STUDIES

Human functional neuroimaging studies recapitulate the distinction between wanting and liking by elucidating distinct neuroanatomical substrates for each, and suggest that reward-related NAcc activity in humans is specific to incentive salience. Several early fMRI studies demonstrated that monetary reward and drugs of abuse robustly activate mesolimbic and mesocortical dopamine terminal fields in humans[43-47]. In addition, monkey electrophysiological work by Schultz revealed differences in the response patterns of NAcc and orbitofrontal neurons to the expectation and delivery of rewards, suggesting a neuroanatomical basis for the distinction between appetitive and consummatory phases of reward recognized by ethologists[48]. Drawing on this body of work, as well as its conceptual links to Berridge and Robinson's incentive salience model of reward, Knutson and colleagues have found that anticipating and receiving monetary rewards activate distinct neural circuits. NAcc is active following the presentation of cues that signal the opportunity to emit an instrumental response to obtain reward, but not during the receipt of that reward; by contrast, medial prefrontal cortex is active following the attainment of monetary reward, but not during the anticipatory period preceding reward receipt[49-52]. Similar results have been observed during the anticipation and receipt of taste reward[53]. Further support for the notion that human NAcc is sensitive to the motivational aspects of reward, rather than reward hedonics, is offered by data showing that NAcc response to monetary reward is contingent on stimulus saliency[54] and dependent on the production of an instrumental response[55-56]. Finally, NAcc activity is associated with cue-induced craving (wanting) in abstinent substance abusers[57-59], and a recent fMRI study found that NAcc activation following acute cocaine administration was positively correlated with subjective ratings of drug craving, but negatively correlated with subjective ratings of drug "high" (liking)[60]. These findings imply a specific and circumscribed role for NAcc in human reward processing: the attribution of incentive salience ('wanting') to reinforcing stimuli.

INCENTIVE SALIENCE AND THE HUMAN NAcc: BEHAVIORAL PHARMACOLOGY AND RECEPTOR IMAGING

fMRI signal is dependent on task-driven hemodynamic changes that are correlated with changes in local field potentials; as such, it is thus a fundamentally indirect measure of brain activity[61]. In addition, while preclinical research is increasingly supportive of the notion that NAcc fMRI reward signal is driven by dopamine signaling[62], this has yet to be definitively confirmed. Therefore, a series of behavioral pharmacology and radioligand PET studies provide a critical complement to the fMRI work outlined above by demonstrating that dopaminergic activity in the NAcc is necessary and sufficient for human reward wanting. Using a dietary manipulation that acutely depletes catecholamine levels (acute catecholamine depletion; ACD), Leyton and colleagues demonstrated that ACD significantly attenuates stimulated dopamine release in the NAcc[63], selectively decreases subjective "wanting" ratings following intranasal cocaine without affecting ratings of cocaine-induced pleasure[64], and impairs motivated

responding to reward predicting cues without altering hedonic responses to amphetamine[65]. This same group found that the magnitude of amphetamine induced dopamine release in the NAcc is strongly correlated with self-reported 'drug wanting'—and with individual differences in "novelty seeking" trait scores—but not with amphetamine-linked changes in positive affect[66]. Similarly, elevated stimulated NAcc dopamine release has been linked to compulsive drug wanting, but not drug liking, in patients with Parkinsons disease who abuse L-DOPA[67]. In the gustatory domain, methylphenidate-induced striatal dopamine release increases non-hedonic ratings of appetitive motivation for food[68]. Of note, it has been shown that amphetamine-associated conditioned cues increase NAcc dopamine release to an extent that is comparable to the drug itself[69], mirroring fMRI data (vide supra) that implicate NAcc in cue-induced craving. Furthermore, building on the results of prior behavioral experiments [70-72], Boileau and colleagues have established a relationship between stimulant-induced sensitization and NAcc dopamine in humans. They administered a constant dose of amphetamine to participants on three occasions; the second and third exposures were 14 and 365 days after the first exposure, respectively. Relative to first exposure, they found that psychomotor responses and amphetamine-induced dopamine release in NAcc were markedly potentiated on the second and third exposures. Remarkably, the magnitude of sensitized response was strongly correlated with individual differences in "novelty seeking" trait scores and self-report impulsivity measures related to addiction risk[73]. Taken together, these data suggest that NAcc dopamine function is associated with incentive salience, mediates a conditioned 'wanting' response, and is sensitized by exposure to drugs of abuse—all of which are predicted by the Incentive Sensitization hypothesis of addiction.

GENETIC VARIATION IN MESOLIMBIC DA SIGNALING AS A RISK FACTOR FOR ADDICTION

As outlined above, converging evidence identifies NAcc dopamine signaling as a core neurobiological substrate for reward 'wanting,' a reward component process that is putatively dysfunctional in addiction. Supporting a role for NAcc DA in addiction, substance abusers consistently show alterations in mesolimbic DA function, including decreased NAcc D2R availability[74-76] and increased NAcc fMRI activation to drug cues[77-79]. Further, the personality traits predicted by individual differences in mesolimbic DA function—novelty seeking, sensation seeking and impulsive temperament—are strongly linked to substance abuse risk[66,73,80-84]. Considering the high genetic liability to addiction, these findings imply that some of the variance in addiction risk may be explained by heritable individual variation in DA function. It is thus worth noting that polymorphic markers in dopamine signaling pathway genes have been associated with both addiction-linked temperament factors and to substance abuse diagnosis. Specifically, allelic variants in genes encoding MAOA, COMT, DAT, TH, AADC, VMAT2, and dopamine receptor subtypes 1-5 have been linked to high novelty seeking and impulsivity and to drug and alcohol addiction[85-108].

The relationship between addiction, reward 'wanting,' and mesolimbic DA suggests that risk-variants in dopaminergic genes may influence the development of addiction by affecting the sensitivity of meso-accumbens 'wanting' circuitry to reward-related stimuli. Data from several recent "imaging genetic" studies appear to confirm this hypothesis by linking such variants to individual differences in the NAcc response to reward. Forbes and colleagues examined the impact of four common functional polymorphisms in the COMT, SLC6A3 (DAT1), DRD4 and DRD2 genes on reward-related brain activity: a variable number tandem repeat (VNTR) polymorphism in the 3' region of the DAT1 gene, a non-synonymous (val158met) coding single nucleotide polymorphism (SNP) in exon 4 of the COMT gene, an insertion/deletion (ins/del) polymorphism in the 5' promoter region of the DRD2 gene, and a VNTR in exon four of the DRD4 gene. These variants have been linked to elevated synaptic dopamine and attenuated postsynaptic inhibition via decreased DA clearance (DAT1 and COMT)[109-111], reduced receptor expression (DRD2 and DRD4)[112-113] and diminished agonist-stimulated signaling (DRD4)[114-115]. Carriers of alleles in DAT, DRD2 and DRD4 associated with increased striatal DA release, increased synaptic DA availability, and decreased postsynaptic inhibition exhibited significantly larger NAcc responses to monetary reward[116]. Further, the magnitude of NAcc response positively predicted impulsive temperament, an important risk factor for substance abuse[117-119]. Of note, the same DRD4 allele (the 7-repeat allele) associated with increased NAcc sensitivity to monetary reward is enriched in substance abusing individuals[88,120-121] and DRD4 7-repeat carriers show exaggerated NAcc engagement to alcohol-associated cues. Moreover, the magnitude of increased NAcc response as a function of DRD4 genotype predicts self-report measures of alcohol use, such as frequency and amount[122].

Despite positive findings for variants in DAT1, DRD2 and DRD4, Forbes and colleagues found no effect of the COMT val158met polymorphism on NAcc reward-related activity. However, the task design in that study conflated reward anticipation and reward feedback—an important behavioral distinction

with clear implications for NAcc reward function, as outlined above. Using tasks designed to isolate brain activity associated with reward anticipation[50], two studies have found that COMT genotype is significantly associated with NAcc activity[123-124]. In both studies, the low-activity 158Met allele, linked to increased DA availability and overtransmitted in alcoholism[96,125-126], predicts increased NAcc response to the anticipation of monetary reward. The discordance between these findings and those of Forbes and colleagues suggests that the manifestation of genetic effects on NAcc function critically depends on task characteristics. It remains to be seen if the impact of other DA genetic variants on NAcc reward-related activity is specific to reward anticipation/'wanting'. Of note, allelic variants in downstream dopamine signaling elements, including PPP1R1B (DARPP-32), RGS4, and AKT1, have also been shown to affect striatal structure, frontostriatal connectivity and striatal activity in non-reward paradigms[127-129]. On the whole, these findings imply that addiction-associated genetic variation at multiple nodes within the DA signaling pathway converges to increase the sensitivity of mesolimbic DA circuitry to rewarding stimuli. That these genetic influences on NAcc function are related to clinically relevant behavioral phenotypes (such as impulsive temperament and alcohol use frequency) strengthens the notion that genetically mediated NAcc hypersensitivity may be an important aspect of the neurobiological risk architecture of addiction.

CONCLUSIONS

Herein, we have detailed findings that identify mesolimbic dopamine signaling as a core neurobiological mediator of incentive salience or reward 'wanting', a psychobehavioral process that may be disrupted in addiction. Preliminary functional imaging evidence indicates that heritable variation in dopamine pathway genes may regulate the sensitivity of mesolimbic DA circuitry to rewarding stimuli. Risk-associated genetic variants may exert their deleterious effects by sensitizing NAcc response to such stimuli, perhaps resulting in the hyperattribution of incentive salience in genetically susceptible individuals following exposure to drugs of abuse. In addition, genetically influenced alterations in mesolimbic DA signaling may hasten the development of incentive sensitization by reducing the number drug exposures required to induce sensitization of drug seeking and consumptive behavior. Such changes could lead to an acceleration of the process by which drug use behaviors shift from "recreational" to "compulsive." Future imaging studies might endeavor to examine the impact of known functional variants on specific aspects of reward processing, particularly reward anticipation/'wanting', and on the neural correlates of psychostimulant sensitization (cf. Boileau *et al*). In addition, using individual differences in NAcc reward response or amphetamine-sensitized stimulated DA release as a quantitative trait, novel susceptibility alleles could potentially be identified by genome-wide screens, a strategy that has yielded significant findings in other cognitive domains (e.g. memory[130]). A combination of top-down (neuroimaging phenotype to genotype) and bottom-up (genotype to neuroimaging phenotype) approaches is one promising investigative strategy for finding new pathophysiological pathways in addiction; one or more of these may prove amenable to therapeutic intervention.

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FURTHER INFORMATION

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