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Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome

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1. ABSTRACT

Reward deficiency syndrome (RDS) was first proposed by Kenneth Blum in 1995 to provide a clinically relevant and predictive term for conditions involving deficits in mesocorticolimbic dopamine function. Genetic, molecular, and neuronal alterations in key components of this circuitry contribute to a reward deficit state that can drive drug-seeking, consumption, and relapse. Among the dysfunctions observed in RDS are dysregulated resting state networks, which recently have been assessed in detail in chronic drug users by, positron emission tomography, functional magnetic resonance imaging, and functional connectivity analysis. A growing number of studies are helping to determine the putative roles of dopamine and glutamatergic neurotransmission in the regulation of activity in resting state networks, particularly in brain reward circuitry affected in drug use disorders. Indeed, we hypothesize in the present review that loss of homeostasis of these systems may lead to 'unbalanced' functional networks that might be both cause and outcome of disrupted synaptic communication between cortical and subcortical systems essential for controlling reward, emotional control, sensation seeking, and chronic drug use.

2. INTRODUCTION

Drug use disorders continue to represent a major health and socioeconomic challenge affecting the lives of many in the U.S. and worldwide. In 2013, in the U.S. alone 24.6. million individuals aged 12 years or older reported illicit drug use, and among these, 1.5. million reported using the psychostimulant cocaine (1). An astounding 21.6. million adults 18 or older were reported that same year as having a substance use disorder, with 4.2. million showing abuse of dependence on marijuana, 1.9. million on pain relievers, 855,000 cocaine, and 517,000 heroin (1). These staggering numbers warrant more preclinical research, especially in novel directions that could ultimately help diagnose drug use disorders (through genetic testing) and offer effective treatments.

Reward Deficiency Syndrome (RDS) was first defined by K. Blum in 1995 as a putative predictor of impulsive and addictive behaviors related in large part to mesolimbic dopamine (DA) system dysfunction (see Table 1) (2-6). Binding of the neurotransmitter dopamine (DA) to the D2 DA receptor (DRD2), for example, has been linked to a variety of behaviors reflecting reward seeking (7-9), and the DRD2 has been referred to as a reward gene (10-14). The TaqI A1 allele of the DRD2

Table 1. Reward Deficiency Behaviors a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors (3)

Addictive Behaviors		Impulsive behaviors		Obsessive compulsive behaviors	Personality disorders
Substance Related	Non substance related	Spectrum disorders	Disruptive impulsive		
Alcohol	Thrill seeking (novelty)	Attention-deficit Hyperactivity	Anti-social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tourettes and Tic Syndrome	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Autism	Intermittent Explosive	Trichotillomania (hair pulling)	Borderline
Sedatives and Hypnotics	Hypersexual		Oppositional Defiant	Excoriation (skin picking)	Schizotypal
Stimulants	Gambling		Exhibitionistic	Non-suicidal Self-Injury	Histrionic
Tobacco	Internet Gaming				Narcissistic
Glucose					Avoidant
Food					Dependant
Modified according to DSM-5. Reproduced with permission from (2).					

gene has been most associated with neuropsychiatric disorders in general, and aggression (15), alcoholism, and chronic drug use conditions (16). Co-Morbid antisocial personality disorder symptoms and children and adults with attention deficit hyperactivity disorder (ADHD) or Tourette's Syndrome and high novelty seeking (17) and gambling and obesity (18, 19) have also been associated with the DRD2A1.

The brain reward circuitry, in particular, the DAergic system and the DA D1 and D2 receptors, have been implicated in reward mechanisms (10, 20). The net outcome of neurotransmitter interaction in mesolimbic brain regions is to produce "reward" when DA is released from afferent ventral tegmental area (VTA) synapses on GABAergic medium spiny neurons (MSNs) in the nucleus accumbens (NAc). This interaction involves D1 and D2 class of receptors among possibly nine total receptor subtypes (2, 21-23). Although initially dubbed the pleasure or anti-stress neurotransmitter DA may primarily be considered to be a "motivation molecule" (24-26) that when released into the synapse increases feelings of well-being and reduces stress (27, 28).

The mesocorticolimbic DA pathway plays an especially important role in mediating the reinforcement of natural reward-seeking behaviors, such as sex and eating, as well as non-natural reward-seeking behaviors mostly centered around chronic drug use (29). Completion of the consummatory phase of natural reward seeking involves the satisfaction of physiological (appetitive) drives (*e.g.,* hunger and reproduction). Seeking unnatural rewards not critical to survival tend to involve learning and habit formation, and thus entails satisfaction from acquired, pleasures like hedonic sensations derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors (30-33). Utilizing positron emission tomography (PET) others have found substantially lower levels of D2 receptors in obese, and alcohol and drug dependent subjects compared to non-dependent individuals (34-37). In animals, overexpression of the D2 receptor via viral vector-mediated delivery of the DRD2 gene directly into the NAc resulted in a significant reduction of alcohol and cocaine consumption (38-41). Also, there is clinical and preclinical evidence that obesity is inversely proportional to DRD2 levels in the brain, and that food restriction reversed this finding (36, 37, 42).

3. "DOPAMINE HOMEOSTASIS": BRINGING FUNCTIONAL BALANCE TO THE DOPAMINE REWARD PATHWAY

Based on the notion that dysregulation of mesocorticolimbic DAergic activity promotes further drug use, a goal should be to regulate key components of this system to reduce abnormal craving, drug seeking, and other addictive behaviors included under the term RDS (43). Indeed, neuronal populations in the mesocorticolimbic system can be identified based on their unique gene expression patterns. Such information offers potential targets for the development of treatments to modulate deficient components of the reward circuit. Regarding therapeutic targets, it is believed that there

are many potential gene polymorphisms involved in the brain reward system and these known (and even unknown) polymorphisms will need to be identified across the central nervous system (CNS) especially along the brain reward circuitry (44, 45). Certainly, damage to DNA along this reward circuitry likely leads to altered, or even diminished, DAergic activity (46). Reduced dopaminergic activity has the effect of increasing sensitivity to stress, blunting reward sensation, and even impairing aspects of reward learning, especially in aged individuals (47-49).

There are numerous genes involved in regulating the activity of this system. The result of their patterns of expression, or their normal function, is to mediate a series of neurochemical mechanisms that have previously been described as the "brain reward cascade" (50). The brain reward cascade involves the release of serotonin, which has been shown to stimulate hypothalamic release of enkephalin in the substantia nigra. Enkephalin in turn inhibits GABA in the substantia nigra, which regulates the amount of DA released in the nucleus accumbens ("reward site"). The origin of the release of DA is the VTA. Various receptors (including 5HT2a receptors, μ-opiate receptors, GABA-A receptors, GABA-B receptors, and D1 and D2 like DA receptors) are critical in reward cascade. It is well known that under normal conditions DA in the nucleus accumbens works to maintain normal drives (51-56). Recent evidence postulates the role of dorsa raphe nuclei in the reward cascade.

For over forty years the Dorsal Raphe Nucleus (DRN) have been classified as a serotonergic structure and the VTA as a DAergic structure. These are two brain reward areas where electrical stimulation produces reinforcement responding at the highest rates and lowest thresholds (meaning increased reward sensitivity). Although multiple studies have examined the contributions of the DRN and VTA to reward most of these studies, have been focused on the serotonergic effects. As a result, these investigations have produced conflicting results, and the actual role of DRN-to-VTA circuitry in regulating motivated behaviors remains unclear. Contrary to the idea that the major input from DRN to VTA is serotonergic, Marisela Morales and her group (57) found that DRN neurons expressing the vesicular glutamate transporter-3 (GluT3) provide a major source of inputs from DRN to VTA. Within the VTA, these DRN-derived GlutT3 terminals synapse on DA neurons. Qi *et al*. (57) found that some of these VTA neurons innervated by DRN GluT3 synapses, in turn, innervate neurons in the NAc. By genetic approaches to specifically express channel rhodopsin 2 (ChR2) in DRN-GlutT3 neurons, it was also found that AMPA-mediated excitatory currents on DA-neurons that innervate the NAc can be elicited by intra-VTA light stimulation of the VGLUT3 -fibers. Such stimulation causes DA release in the NAc, reinforces instrumental behaviors, and established conditioned place preference. The Qi *et al.* (57) discovery of a rewarding excitatory glutamatergic synaptic input to the meso-accumbens DA neurons arising from DRN neurons containing VGLUT3, suggested that, new targets that may be important to improve deficits in motivation observed in RDS patients. Moreover, unpublished work from this research team at NIDA also found that GABA from the Substania Nigra regulates VGLUT3 synaptic inputs, and as a result may control VTA DA release in the NAc.

In RDS, reduced sensitivity and inefficiency of the reward system has been a theme considered by many investigators and has generated some controversy regarding the regulation of "liking" and "wanting" rewards, particularly drug reward (58-63). However, various genetic/epigenetic factors and neuroanatomical substrates converge upon the mesocorticolimbic DA reward system in mediating multiple ways in which addictions and related psychiatric conditions are expressed (64). Both genetic antecedents and environmental influences (epigenetic), may result in a deficiency of synaptic DA and predispose individuals to a high risk for multiple addictive, impulsive, and compulsive behaviors (65).

It is well known that alcohol and other drugs of abuse, as well as sex, food, gambling, aggressive thrills and other positive reinforcers, cause activation and neuronal release of brain DA and involvement of the Na(+)/K(+)-ATPase (66). Increases in DA release, particularly in NAc, can decrease negative feelings and satisfy abnormal feelings like cravings for substances like alcohol, cocaine, heroin, and nicotine, which among others are linked to low DA activity (67). Therefore, a formidable challenge to both scientists and clinicians in the field of substance and non-substance compulsive seeking behaviors is the development of compounds that can induce "dopamine homeostasis". In other words, rather than tilting the dopamine-mediated brain reward balance to either extreme (too high or too low), a balance needs to be maintained within a limited functional range. Assessing such functional limits within mesocorticolimbic circuitry requires *in vivo* brain functional biomarkers of activity, which are only possible through functional magnetic resonance imaging (fMRI) and potentially functional connectivity analysis of brain network activity. Emerging evidence strongly suggests that cognitive, emotional and behavioral disturbances observed in some psychiatric illnesses are associated with functional deficits in widespread brain networks (68-72). The same principle of dysregulated functional circuitry may hold true for drug addiction (73). However, the cellular mechanisms mediating resting state functional connectivity, and in particular the role of dopamine, serotonin, and glutamate in mediating specific patterns of functional connectivity remain unclear. In the following sections, we summarize some of the work that has been done, specifically focusing on studies examining changes in functional connectivity and drug use disorders.

4. UNDERSTANDING RESTING STATE BRAIN FUNCTIONAL CONNECTIVITY

Recently, there has been controversy concerning the role of brain DA in reward and addiction. David Nutt and associates eloquently proposed that DA may be central to psychostimulant dependence, and somewhat relevant for alcohol, but not important for opiates, nicotine, or even cannabis (74). Others have also argued that surfeit theories can explain cocaine-seeking behavior and non-substance-related addictive behaviors. It seems prudent to make a distinction between, what constitutes "surfeit" as compared to "deficit" regarding short-term (acute), and long-term (chronic), brain reward circuit responsivity. In an attempt to resolve the controversy regarding the contributions of mesolimbic DA systems to reward, we cite the three most important competing explanatory categories: "liking," "learning," and "wanting." They are (a) the hedonic impact (liking reward), (b) the ability to predict rewarding effects (learning) and (c) rewarding stimuli incentive salience (wanting).

Regarding acute effects, RDS behaviors, and most drugs of abuse have been linked to hyperdopaminergic states and heightened feelings of well-being due to the preferential DA release at mesolimbic-VTA-caudate-accumbens loci. Also, most of the evidence seems to favor the "surfeit theory" (59, 75) in the acute phase of the experience. The "dopamine hypotheses", is now known to be complex and involves encoding attention, reward expectancy, incentive motivation and the set point of hedonic tone.

In terms of chronic effects, the work of Willuhn's group provides impetus to develop anti-RDS compounds that can modulate dopamine function. They demonstrated, in an extended access cocaine self-administration paradigm, that excessive use of cocaine is caused by decreased phasic DA signaling in the striatum (76). Also regarding chronic addictions, others have shown a blunted responsivity at brain reward sites with food, nicotine, and even gambling behavior. Being cognizant that there are differences in DAergic function as addictions progress, relapse may involve a prolonged state of DA deficiency. Vulnerability to compulsive drug use and relapse may be the cumulative effects of genetic reward polymorphisms and elevated sensitivity to stress. The preferred goal to combat relapse may be DA homeostasis and with this aim functional connectivity in both animal and human models is an emerging area of interest.

Compulsive drug use can affect widely distributed regions of the brain and evidence is accumulating that the functional interactions between brain regions change throughout the stages of cocaine use, abstinence, and relapse (77-88). Identifying neural circuits affected by cocaine use disorders, and understanding their association with compulsive drug seeking behavior, remains a challenge (73). Some researchers have addressed this matter by applying novel optogenetic approaches to investigate the causal role of individual neuronal groups in driving drug self-administration and reinstatement (89-96).

The brain of humans and rodents show a high degree of intrinsic synchronous activity measured by blood oxygen level-dependent (BOLD) fMRI during rest (97, 98). Functional connectivity analysis of these synchronous BOLD signals may provide insight into network-level changes associated with cocaine and other RDS behaviors during self-administration, withdrawal, and reinstatement. BOLD signal oscillations have neurobiological and behavioral significance (99-101) in human subjects and animal models (97, 98). Changes in functional connectivity in humans are associated with dysfunctional cognitive and behavioral states (68) that might contribute to addiction severity and relapse (81, 85, 88, 102). For example, it has been reported that cocaine users show a reduction in resting state activity along specific neural pathways, also significantly increased connectivity has been cited (81). In cocaine users, shorter withdrawal lengths mostly involve increased or altered connectivity, in cortical, striatal and midbrain regions, while, longer duration withdrawal times mostly involve significant reductions in functional connectivity in comparison to controls. However, changes in functional connectivity can vary according to factors such as length of abstinence, propensity to relapse, response to treatment (81, 85, 103). For example, impulsivity and loss of control over recent cocaine use are associated with increased functional connectivity between prefrontal cortex and striatum (104). Subjects with cocaine use disorders that were stabilized for 4-8 days in inpatient clinics (short-term abstinence) showed hyperconnectivity between structures involved in memory, visuospatial processing, and motivation (105). This novel approach can reflect the integrity of functional circuits that mediate aspects of neural communication between CNS regions (106). This method is an informative biomarker that may be used to examining the effects of drugs of abuse on mesocorticolimbic regions.

4.1. Functional connectivity and addiction: neurobiological underpinnings

Understand functional connectivity changes, particularly in the context of well-studied intrinsically active networks such as Salience, Executive, and Default networks, is key to being able to address widespread neuroadaptations involved in and/or contributing to addictive behaviors. Activity in these and other previously described networks, in turn, may relate to underlying cellular adaptations in the biophysical properties of neuronal membranes. These adaptations include changes in electrical excitability of select neurons within a broader network and the occurrence of synaptic plasticity that can modify the responsiveness of mesocorticolimbic

DA and glutamate neurons to subsequent drug reward challenges (107-113). For example, in rats, repeated cocaine or amphetamine administration alters the number of dendritic spines, their morphology, and hinders structural plasticity in NAc, prefrontal cortex, and other neocortical regions (114-118).

A single exposure or repeated administration of cocaine and other drugs of abuse increases the ability to elicit long-term potentiation (LTP) and long-term depression (LTD) in VTA DA neurons (109, 110, 119-121). Repeated cocaine also alters these forms of synaptic plasticity in NAc, amygdala, and forebrain (109, 110), and effect biophysical parameters leading to changes in excitability of NAc MSNs (122, 123). Altered synaptic plasticity may impact subsequent excitability and plasticity within these regions (110, 122), with the consequence of altering the activity of downstream and upstream structures (124-126). For example, changes in excitability of NAc MSNs (123) may affect activity in both the VTA directly, or through the ventral pallidum (91), and this circuitry is influential for reinstatement of drug seeking behavior (127). Moreover, NAc neurons are also influenced by changes in prefrontal cortical (PFC) (128, 129) and ventral hippocampal (125, 130) activity via incoming glutamatergic synapses, which may elicit reinstatement (89, 93, 131). Given the extensive connectivity these neurons share with other structures, it is likely that the effects of repeated cocaine on their activity significantly impacts activity in broadly distributed regions of the brain. Thus, in the cocaine-addicted brain, a wider network of structures may show altered functional connectivity through synaptic changes in PFC, NAc, and VTA neurons. Connectivity is likely to involve ventral hippocampus, amygdala, pallidal areas, substantia nigra, anterior thalamus, and other higher cortical centers integrating sensory and spatial information, and long-term memory. A critically important aspect of the mentioned *in vivo* functional neurocircuitry of cocaine use is that key players in the circuitry vary through distinct stages of addiction (78).

4.2. Are glutaminergic and dopaminergic pathways therapeutic targets for reward homeostasis?

Glutamate and DA represent potential targets for novel treatments that modulate not only cocaine seeking behavior, but also other RDS behaviors, and there is growing evidence that these neurotransmitters are necessary for the establishment of resting state functional connectivity networks. Both substrates are affected by chronic psychostimulant administration (111, 112). In cocaine self-administering rats, basal extracellular glutamate concentrations are reduced in the core of NAc (128), which also receives heightened PFC-evoked glutamate release (94, 123). Evidence supports this heightened release and reduced tonic extracellular glutamate in reinstatement (123, 132). Elevating extrasynaptic glutamate by stimulating the cystine-glutamate exchanger using the pro-cystine drug, N-acetylcysteine (NAC), has been found to reduce cue- and cocaine-prompted reinstatement (123, 132-135). This outcome supports its development as a treatment for cocaine craving and addiction (136). N-acetylcysteine restores synaptic plasticity in NAc, normalizes neuronal excitability, and glutamate transport (122, 133). Additionally, it was recently shown that as cocaine intake escalates, phasic DA signaling in the ventromedial striatum is reduced (76). The DA precursor L-3,4-dihydrophenylalanine (L-DOPA) was found to reduce escalated cocaine intake and restore striatal DA (76). Consistent with this result, in human subjects, L-DOPA was observed to increase functional connectivity between midbrain and striatal regions (72). In this regard, Febo and Blum (unpublished) have examined the effects of a DA precursor complex (KB220Z) on functional connectivity and have observed that there is a significant increase in functional connectivity strength in PFC and NAc of the rat (Figure 1).

Key ingredients in this complex act synergistically to replenish the pool of L-DOPA and facilitate its conversion to DA. The formulation is directed at re-establishing baseline connectivity through the DA biosynthetic pathway amongst other ingredients (L-Tyrosine and pyridoxine, which provide the enzymatic co-factor pyridoxal-5'-phosphate for L-amino acid decarboxylase conversion of L-DOPA to DA) (6, 137). A KB220 variant has been tested in abstinent psychostimulant abusers and found to normalize quantitative electroencephalographic (qEEG) abnormalities (137). Moreover, a preliminary double-blind cross-over study in heroin-dependent participants shows increases in ventral striatal functional connectivity (Figure 2).

Understanding how DA and glutamate systems modulate resting state functional connectivity in mesocorticolimbic structures increases the utility of this functional mapping strategy as a biomarker for drug use disorders. Research in this regard is limited but has recently been approached indirectly through examination of the effects of, DA depletion (like Parkinsonism and related conditions), DA replacement therapies (like L-DOPA), DAergic agonists and N-methyl-D-aspartate (NMDA) receptor blockers, on resting state functional connectivity (138-141).

The role of DA in the brain at rest is an important and an emerging area of research interest especially in Parkinsonism (142). Piray *et al*. (143) using systematic pharmacological manipulation of dopamine D2-receptors and resting-state functional imaging in humans, found that DA modulates interactions between motivational and cognitive regions, as well cognitive and motor regions of the striatum. Specifically, stimulation and blockade of the dopamine D2-receptor had opposite (increasing and

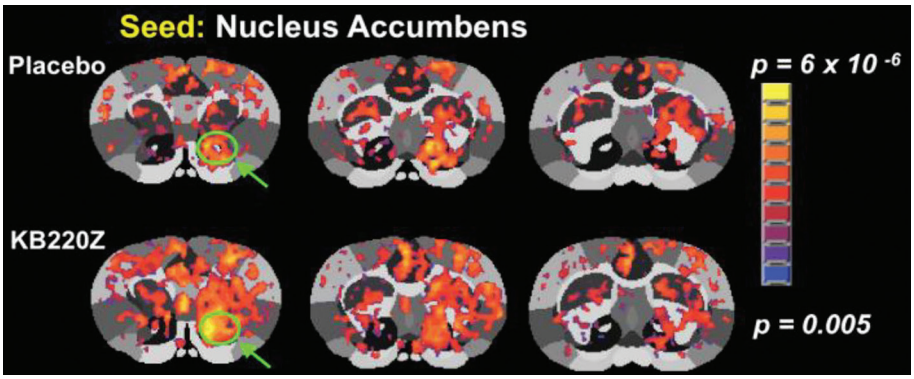

Figure 1. Administration of a complex (KB220Z) increases connectivity with the NAc and PFC. This effect would presumably benefit cocaine-addicted individuals showing reduced functional connectivity in mesocorticolimbic circuitry. Reproduced with permission from (79).

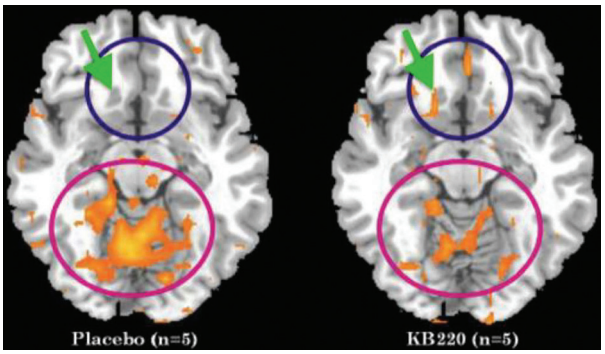

Figure 2. A double-blind cross-over study in abstinent heroin-dependent participants of KB220Z, a DA precursor complex one hour following delivery of neurotransmitter precursors, functional connectivity between regions of the accumbens and the medial orbital cortex is enhanced. Arrow and blue circle are shown to emphasize increases in functional connectivity in NAc with oral KB220Z. Reproduced with permission from (6).

decreasing) effects on the efficacy of those interactions. In fact, trait impulsivity was specifically associated with DAergic modulation of ventral-to-dorsal striatal connectivity. Ventral-to-dorsal striatal connectivity in individuals with high trait impulsivity exhibited greater drug-induced increases (after stimulation) and decreases (after blockade) of than those with low trait impulsivity.

Individuals with early stage Parkinsonism, which have some initial level of DA depletion in basal ganglia structures, showed decreased connectivity of the left dorsolateral prefrontal cortex and right insular cortex, right superior frontal gyrus and anterior cingulate compared to unaffected subjects (138). Others have reported reduced connectivity (specifically, node degree) in left putamen, right globus pallidus (139). Interestingly, Nagano-Saito and colleagues used a transient DA depletion strategy by administering an amino acid solution deficient of D-Phenylalanine/L-Tyrosine to healthy participants and found that performance on set shifting tasks and frontal-striatal connectivity were both reduced in comparison to administering a more balanced amino acid solution (140). Thus, deficits in cognitive flexibility caused by acute reductions in DA may be associated with a reduction in functional connectivity between prefrontal cortex and striatum.

There is also building evidence that enhancement of DA synthesis and increasing the releasable pool of this catecholamine adjusts functional connectivity in mesocorticolimbic areas. Thus, administering (L-DOPA; which is a precursor for DA synthesis) to healthy participants reduced connectivity between the amygdala and bilateral inferior frontal gyri and areas of the default mode network (DMN) (141). Another group showed that L-DOPA increased functional connectivity between midbrain and DMN, between caudate and frontal-parietal areas, and ventral striatum and a frontoinsular network (72). On the other hand, blocking DA receptors with haloperidol exerted opposite effects on functional connectivity between these regions (144). L-DOPA has also been shown to increase functional connectivity areas of the putamen, cerebellum, and brainstem, and between inferior ventral striatum and ventrolateral prefrontal cortex (145). Interestingly, it was observed to disrupt connectivity between striatal areas and the DMN (145). In further support that DA replacement therapies may correct deficits in functional connectivity, recently it was shown that Parkinson's patients without medication showed significant impairments in connectivity with striatal divisions, which was improved by upon administering DA medications to patients (142). The above-cited effects of DA depletion and replenishment with L-DOPA illustrate the important role of DA in modulating resting state networks. Consistent with the role of DA in regulating activity in basal ganglia, most effects are observed in ventral and dorsal striatal regions and their connectivity with cortical structures known to receive DA inputs. However, it is important to note that in the case of RDS, the networks impacted by deficient DA activity may vary from DA pathways affected in Parkinsonism due to the source of DA being VTA in the mesolimbic pathway rather than through Substantia Nigra (nigrostriatal pathway).

Importantly, a caveat to focusing on L-DOPA as a treatment strategy is that it omits other components of the Brain Reward Cascade.

Administering the DA and norepinephrine transporter blocker methylphenidate to healthy subjects has been shown to exert varied effects across a number of studies, which include increased motor-memory circuit connectivity and reduced prefrontal cortical connectivity (146). Others have reported that methylphenidate, mostly reduced functional connectivity between NAc and ventral pallidum and subthalamic nucleus, and reduced connectivity between NAc and prefrontal and temporal cortices (147). However, in another study methylphenidate at the same dose (40 mg) was mostly found to increase connectivity between dorsal attentional networks and thalamus, increase connectivity between association areas and primary sensorimotor regions, and decrease connectivity with striatothalamocortical circuits (148). These above-mentioned effects of methylphenidate, are mediated, in part, by elevated extracellular levels DA and norepinephrine. However, the effect of DA receptor stimulation on functional connectivity is unclear. Subjects administered the DA agonist, bromocriptine show changes in frontal-striatum functional connectivity, which specifically correlated with working memory performance (149). In consideration of the functional connectivity changes affected in drug use disorders (summarized in the preceding sections); it makes much less sense to use drugs that bind to DA receptors or transporter. That is to say, the results of such studies do not seem to be well aligned with outcomes, that would benefit or correct deficits in functional connectivity. However, based on the effects of L-DOPA and our preliminary results with KB220, we argue that enhancement of DAergic biochemical pathways would instead be an improved strategy adjusting or balancing resting state networks, particularly in frontal and striatal regions (Figures 1 and 2).

The role of glutamate in functional connectivity has largely been assessed by studies seeking to understand the effects of ketamine on functional connectivity. Ketamine, which has antidepressant properties, is a NMDA receptor blocker. Based on the excitatory neurotransmission mediated through NMDA receptors (activation leading to neuronal depolarization), one would expect significant reductions in functional connectivity (because such depolarizations would be prevented in the presence of the drug). However, some studies have shown hyperconnectivity instead. Ketamine increased prefrontal connectivity in healthy participants (150) and corticothalamic circuitry (151). Positive symptoms of ketamine are associated with increased cortical paracentral lobule and left precentral gyral connectivity, whereas increased connectivity in prefrontal and striatal areas was surprisingly associated with negative symptoms (152). Interestingly, NMDA blockade reduced functional connectivity between the DMN and dorsomedial prefrontal cortex, and DMN to prefrontal, anterior and posterior cingulate cortical areas (153). Regulating extracellular levels of glutamate and increasing glutamate transmission (which are both disrupted in drug use disorders) with N-acetylcysteine (NAC) increases functional connectivity between major mesocorticolimbic areas including the ventral striatum, prefrontal cortex, precuneus, and areas of the DMN (154). This increased functional connectivity correlates with improved affective scores and less craving (154).

Overall, the above results bring us a step closer to understanding the contributions of DA and glutamate in modulating resting state networks. An important aspect of these studies that should be considered in light of the varied results is the potential for baseline connectivity to differ across individual subjects. Moreover, regarding treatment strategies, it appears that treatments directed at balancing biochemical functioning in mesocorticolimbic areas, like L-DOPA, KB220, and NAC, might provide a better strategy for correcting the deficiencies present in these regions and a better and more consistent readout in functional connectivity studies.

To summarize, Willuhn's group (76) reported that dopaminergic function is reduced as substance (cocaine) and non-substance-related addictive behavior increases. Decreases in D2/D3 receptors and lower activation of cues in occipital cortex and cerebellum were associated with chronic cocaine exposure by Volkow *et al*. in a recent PET study (155). Therefore, treatment strategies, directed towards dopamine homeostasis like less powerful pro-dopamine regulators (unable to induce DA receptor down –regulation), along with glutaminergic optimization using NAC that might conserve DA function and may be an attractive approach to relapse prevention in psychoactive drug and behavioral addictions. However, we caution against the sole use of L-DOPA because of known side effects as seen with Parkinson patients (156).

4.3. Dopamine and brain functional connectivity: Psychiatric genetic links

Arvid Carlsson, Paul Greengard, Eric Kandel equally shared the 2000 Nobel Prize in Physiology or Medicine for their outstanding work concerning signal transduction in the nervous system and the role of DA as a neurotransmitter. Now fifteen years later neuroscientists and clinicians have seen some amazing advances concerning DA and brain functional connectivity and genetic risk factors affecting psychiatric conditions. With advances in neuroimaging techniques such as fMRI, single-photon emission computerized tomography (SPECT), PET, and now optogenetics, understanding of DA's role in the brain will change. Keeping within this narrow perspective some studies that further enhance our knowledge related to DA and potential DA regulation will briefly be discussed.

It is important to acknowledge the seminal findings of Blum *et al.* (10) published in JAMA on the first association of the DRD2 A1 allele as a risk factor for severe alcoholism. The role of the A1 allele of the DRD2 gene and other reward genes like Mu-Opiate Receptor, MOA-A, GABAA, COMT, 5-HTTLPR, DRD4, and associated risk alleels, have been confirmed in RDS behaviors (157-170). There is also evidence of an association of the DRD2 *Taq* A1 polymorphisms with addiction relapse (171), increased hospitalization (172), and even mortality (173). However, much less is known about the actual role of DA *per se* in brain functional connectivity and potential allelic risk factors in developing deficits.

As of 06-29-2016 a word Pubmed search "Psychiatric Genetics" revealed 17,433 articles. However, a word search using the terms, "Psychiatric Genetics" and "Brain Functional Connectivity" revealed only 74 articles suggesting the relatively new area of research. The following section provides a brief snapshot of this emerging area of psychiatry.

In one experiment, Zhou *et al*. (174) found significant COMT (rs4680)×DRD2(rs1076560) interaction in intra-network connectivity. The network included the left medial prefrontal cortex of the anterior DMN, the right dorsal attention network at the right dorsolateral frontal cortex, and the left dorsal anterior cingulate cortex in the salience network. Moreover, they also found that DRD2 genotypes exerted differential effects on intra-network connectivity in subgroups of COMT genotypes. Zhou *et al*. concluded that "These findings suggest a network-dependent modulation of the DA-related genetic variations on intra-network connectivity." Regarding clinical relevance, (175) a set of structured multimodal activities (Combination Training; CT), revealed that cognitive/occupational performances and reorganization of functional connectivity benefited from greater functional connectivity and cortical thickness in a group of healthy elderly individuals. This effect was most pronounced in carriers of polymorphisms of both COMT (Val158Met) and DAergic genes (DRD3 ser9gly).

Work by Tian *et al*. (176) suggested that COMT and DRD2 genotypes may associate with brain functional connectivity and dopamine signaling. In support, Xu *et al*. (177) evaluated different genotypic combinations of COMT and DRD2 in healthy humans and found a non-additive COMT x DRD2 interaction in rsFC in the right dorsal anterior cingulate cortex (dACC) exhibiting a U-shape modulation by DA signaling. Interestingly, the authors suggest "healthy young adults without optimal DA signaling may maintain their normal behavioral performance via a functional compensatory mechanism in response to structural deficit due to genetic variation."

Interestingly, Meyer *et al*. (178) pointed out that prefrontal DA levels are relatively increased in adolescence compared to adulthood. It is well known that carriers of the MET variant of COMT result in lower enzymatic activity and higher DA availability. Oppositional effects were observed in prefrontal brain networks at rest, of adolescents and adults, in areas of the brain including anterior medial PFC and ventrolateral as well as the dorsolateral PFC, and parahippocampal gyrus. They also observed an age-dependent and significant reversal of COMT Val158Met effects on resting state functional connectivity between the anterior medial PFC and ventrolateral and the dorsolateral PFC, and parahippocampal gyrus. Val homozygous adults exhibited increased and adolescents decreased connectivity compared to Met homozygotes for all reported regions. This finding is somewhat surprising given the understanding that carriers of the Val variant results in a lower availability of synaptic DA. As such, one would expect a decrease in rsFC and not an increase as seen in adults compared to adolescents (179). Nevertheless, it does suggest that adolescent and adult resting state networks are dose-dependent and diametrically affected by COMT genotypes when a hypothetical model of DA function that follows an inverted U-shaped curve is followed.

It is well known that DA signaling through D2 and other DA receptors has been implicated in reward processing, regulation of cognition and the effects of drugs of abuse, and also has significant effects on responses to stressors and salient aversive stimuli (180). In fact, Peciña *et al*. (181) found that a haplotype block comprised of two SNPs, rs4274224, and rs4581480, had an effect on the hemodynamic responses of the subgenual anterior cingulate cortices (sgACC) during implicit emotional processing and the dorsolateral PFC during reward expectation. The authors suggest that these findings may be normal variation and contribute to potential vulnerability to psychopathology associated with functions, such as risk for mood and substance use disorders (or RDS behaviors).

Recent evidence supports the notion that the DMN consists of brain regions which relative to cognitive processing have "increased" activity during rest. Moreover, this activity in the DMN is associated with functional connectivity with the striatum, a DA-enriched brain region (182). Specifically, it was found a lowered DA state caused the following network changes: reduced global and local efficiency of the whole brain network, reduced regional efficiency in limbic areas, reduced modularity of brain networks, and greater connectivity between the normally anti-correlated task-positive and DMN. In support of the work, earlier studies by Sambataro *et al*. (183) evaluated a functional SNP within the dopamine D2 receptor gene (DRD2, rs1076560 G > T) shifts splicing of the 2 D2 isoforms, D2 short and D2 long. Within the anterior DMN, the variant GG subjects had relatively greater connectivity in medial PFC, which was directly correlated with striatal DA transporter (DAT)

binding. However, within the posterior DMN, GG subjects had reduced connectivity in posterior cingulate relative to T carriers. Additionally, rs1076560 genotype predicted connectivity differences within a striatal network, and these changes were correlated with connectivity in medial PFC and posterior cingulate within the DMN. Sambataro *et al*. (183), proposed that that genetically determined D2 receptor signaling is associated with DMN connectivity and that these changes are correlated with striatal function and presynaptic DA signaling. Moreover, regarding cognitive processing, non-carriers of the A1 allele of the DRD2/ANKK1-*Taq* A1 polymorphism associated with higher DRD2 density show increased task-switching costs, increased prefrontal switching activity in the inferior frontal junction area, and increased functional connectivity in dorsal frontostriatal circuits relative to A1 allele carriers (184). Also, Stelzel *et al*. (184) found a DRD2 haplotype analysis confirmed an association between high D2 density and increased switching effort. Accordingly, these results emphasize the importance of individual differences in striatal D2 signaling in healthy humans, leads to individual differences in switching intentionally to newly relevant behaviors.

Finally, understanding that personality traits linked to emotion processing are, in part, heritable and genetically based, Blasi *et al*. (185), evaluated the role of the DRD2 (intronic single nucleotide polymorphism within the DRD2 (rs1076560, guanine > thymine or G > T). They found greater amygdala activity during implicit processing and dorsolateral PFC response during explicit processing of facial emotional stimuli in GG subjects compared with GT. They also discovered that rs1076560 genotype is associated with differential relationships between amygdala/dorsolateral PFC functional connectivity and emotion control scores.

5. SUMMARY AND PERSPECTIVES

Based on the above-cited literature, we predict that a feeling of well-being can be achieved only when DA is released in the nucleus accumbens at balanced “dopamine homeostatic” levels. Any deviation causes “dopamine resistance” and as such could result in increased aberrant cravings. Accordingly, there is a need for a compound that can target and achieve DA regulation, *i.e.* DA homeostasis. There is further need for a compound that can be administered to normalize such brain functional impairments by activating the release of brain DA at the reward site and thus reduce excessive craving behaviors.

It is now known that drug addiction is characterized by widespread abnormalities in brain function and neurochemistry, including drug-associated effects on concentrations of the excitatory and inhibitory neurotransmitters glutamate and gamma-aminobutyric acid (GABA), respectively. In healthy individuals, these neurotransmitters may drive the resting state, a default condition of brain function that is disrupted in addiction. We are in agreement with the concept that resting state functional connectivity may have valuable clinical relevance to the development of and risk for RDS behaviors. Studies have shown that addicted individuals tended to show decreases in the glutaminergic system compared with healthy controls. Moreover, select corticolimbic brain regions showing glutamatergic and/or GABAergic abnormalities have been similarly implicated in resting-state functional connectivity deficits in drug addiction (186). There are many studies showing impairments of resting state functional connectivity with alcohol, opiates, cannabis, psychostimulants, nicotine, glucose and even some of the behavioral addictions, further suggesting the need to find compounds that will restore normal resting state functional connectivity (6, 187-200).

Along these lines, it has been shown that when NAC was compared to placebo, smokers who maintained abstinence, reported less craving and higher positive affect, and concomitantly exhibited stronger rsFC between ventral striatal nodes, medial prefrontal cortex and precuneus-key DMN nodes, and the cerebellum (154). Most recently, our laboratory proposed the combination of NAC with a well-known enkephalinase inhibitor and other pro-DAergic substances to combat aberrant RDS behaviors (6).

6. CONCLUSION

The role of DA in brain function is being clarified by the advancement of neuroimaging tools indicating its critical involvement in resting state functional connectivity in the brain reward circuitry. It is accepted that alterations of dopaminergic regulation, lead to changes in brain functional connectivity considered by many as a key to all addictions. Given the vast amount of research in this area as an emerging science, it is important to realize that ultimately studies on humans are tantamount to the development of clinically relevant therapeutics. However, continued work on animal models of addiction involving, for example, fMRI coupled with optogenetics seems parsimonious to extract not only required neuro-mechanisms of substance and non-substance-related addictive behaviors (RDS) and provide a mechanistic rationale to evaluate promising anti-RDS agents.

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