Autism Spectrum Disorders and Drug Addiction: Common Pathways, Common Molecules, Distinct Disorders?

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Autism spectrum disorders (ASDs) and drug addiction do not share substantial comorbidity or obvious similarities in etiology or symptomatology. It is thus surprising that a number of recent studies implicate overlapping neural circuits and molecular signaling pathways in both disorders. The purpose of this review is to highlight this emerging intersection and consider implications for understanding the pathophysiology of these seemingly distinct disorders. One area of overlap involves neural circuits and neuromodulatory systems in the striatum and basal ganglia, which play an established role in addiction and reward but are increasingly implicated in clinical and preclinical studies of ASDs. A second area of overlap relates to molecules like Fragile X mental retardation protein (FMRP) and methyl CpG-binding protein-2 (MECP2), which are best known for their contribution to the pathogenesis of syndromic ASDs, but have recently been shown to regulate behavioral and neurobiological responses to addictive drug exposure. These shared pathways and molecules point to common dimensions of behavioral dysfunction, including the repetition of behavioral patterns and aberrant reward processing. The synthesis of knowledge gained through parallel investigations of ASDs and addiction may inspire the design of new therapeutic interventions to correct common elements of striatal dysfunction.

Keywords: autism, addiction, striatum, accumbens, synapse, dopamine, medium spiny neuron

INTRODUCTION

Autism spectrum disorders (ASDs) are prevalent and devastating neuropsychiatric conditions with a pathophysiology that remains poorly understood. The high heritability of ASDs has motivated the widespread application of advanced sequencing technology to identify genetic variants associated with these disorders (McCarroll and Hyman, 2013). The resulting data sets have revealed an extremely complex genetic architecture, including many genes that each contribute to a fraction of cases (Chen et al., 2015). To sift through this complexity, a growing number of studies have taken genetic variants identified in human patients with ASDs, and introduced corresponding mutations into the genome of laboratory mice. Mice carrying genetic variants associated with neuropsychiatric disease provide an opportunity to probe brain function in a highly specific fashion, and explore underlying mechanisms in a manner that can inform the rational design of therapeutics (Fuccillo et al., 2016). In terms of modeling complex disorders like ASDs, a significant strength of this

approach is the construct validity provided by studying genetic variants in mice with known ASD association in humans (Nestler and Hyman, 2010). Mice carrying ASD-associated genetic mutations also exhibit behavioral phenotypes that map onto primary ASD symptom domains, including reduced social interaction and repetitive patterns of behavior (Silverman et al., 2010), providing an additional degree of face validity. Some of these behavioral phenotypes can be corrected by drugs approved for treatment of ASDs in humans (e.g., Peñagarikano et al., 2011), although the limited number of effective medications precludes more rigorous evaluation of predictive validity.

Many of the genes associated with ASDs play a role in regulating synaptic transmission between neurons (Zoghbi and Bear, 2012), including synaptic cell adhesion molecules like neurexins and neuroligins (Südhof, 2008), as well as postsynaptic scaffolding molecules like SHANK (Jiang and Ehlers, 2013). The generation of mouse lines carrying these ASD-associated genetic mutations has provided opportunities to evaluate changes in synaptic transmission across a variety of brain regions. The emerging synaptic architecture of ASDs is nearly as complex as its genetic architecture, with little consistency when phenotypes are compared across different brain regions or different ASD-associated mutations. For instance, the same genetic mutation can produce distinct functional changes at different synapses (Etherton et al., 2011; Földy et al., 2013), and the same synaptic process can be oppositely affected by different mutations (Auerbach et al., 2011). These perplexing results highlight the importance of winnowing down the essential synaptic circuits that contribute to ASD pathogenesis.

One such critical pathway may involve the striatum and interconnected basal ganglia nuclei, which have been implicated by a number of recent mouse studies, and exhibit functional and structural changes in human patients with ASDs that often correlate with symptom severity (e.g., Sears et al., 1999; Hollander et al., 2005; Rojas et al., 2006; Voelbel et al., 2006; Langen et al., 2009, 2014; Delmonte et al., 2012; Abrams et al., 2013). This growing literature on striatal dysfunction in ASDs has, rather surprisingly, implicated pathways and circuit elements known to play a role in drug addiction. The development and progression of addiction have long been tied to a number of striatal neurochemical systems (e.g., Wise, 1987; Koob and Bloom, 1988; Sarnyai and Kovacs, 1994). More recently, chronic drug exposure has been shown to cause changes in the structure and function of striatal synapses (Russo et al., 2010; Grueter et al., 2012), and these forms of drug-evoked synaptic plasticity contribute to a variety of addiction-related behaviors in rodents. Several recent studies suggest genes and molecules canonically associated with ASDs function in the striatum to regulate drug-evoked synaptic and behavioral plasticity in addiction models - another surprising connection between these seemingly distinct disorders.

The purpose of this article is to review the emerging intersection between ASDs and addiction in the striatum, and consider potential implications for the pathophysiology and treatment of both disorders. Many of the topics covered below relate recent publications in the realm of ASDs to longstanding

or established concepts in addiction research, though recent examples of addiction research are included when appropriate. The topics and references are drawn from personal familiarity with both fields of research, as well as manual review of literature searches including autism and addiction, autism and striatum, or autism and each of the various signaling pathways discussed below. The manuscript is organized on the basis of emerging common themes, and thus represents an integrative review of select literature that highlights areas of overlap and potential shared mechanisms, rather than a comprehensive or systematic review of research on either ASDs or addiction (Whittemore et al., 2014).

STRIATAL PATHWAYS IN ASDs

The striatum serves as a gateway to the basal ganglia, receiving synaptic input from numerous cortical, thalamic, and limbic brain regions, and relaying information to downstream processing stations in the basal ganglia (Sesack and Grace, 2010; Nelson and Kreitzer, 2014). In humans and primates, the striatal complex includes the caudate nucleus, the putamen, and a ventral striatal region known as the nucleus accumbens. In rodents, the nucleus accumbens also occupies the ventral portion of striatum, while the caudate and putamen roughly correspond to medial and lateral subregions of the dorsal striatum, respectively (Graybiel, 2008). Of these striatal subregions, the nucleus accumbens is most closely associated with reward-related behavioral functions (Carlezon and Thomas, 2009; Sesack and Grace, 2010). Many of these functions pertain to learning reward-related associations, either in terms of cues that predict delivery of reward (classical/Pavlovian conditioning), or actions that must be completed to obtain reward (operant/instrumental conditioning). In human brain imaging studies, normal reward-related activation of the nucleus accumbens is disturbed in patients with ASDs (e.g., Scott-Van Zeeland et al., 2010; Delmonte et al., 2012; Dichter et al., 2012; Kohls et al., 2013; Richey et al., 2014).

Dorsal striatal subregions also play a role in processing reward, particularly in terms of the movements and actions that must be learned and executed in order to obtain reward (Balleine et al., 2007). A number of important dissociations have been reported in the behavioral functions of dorsomedial and dorsolateral striatum in rodents (Yin and Knowlton, 2006; Balleine and O'Doherty, 2010). The model emerging from these studies suggests that dorsomedial striatum is important for behaviors that are flexible and sensitive to outcome, which is often the case early in learning. As actions are repeated many times and become streamlined and automatic, they also become less sensitive to outcome, and this late stage of learning involves dorsolateral striatum. These inflexible and ingrained patterns of behavior are considered "habitual," and the process of habit formation could contribute to some of the repetitive and stereotyped routines and rituals observed in patients with ASDs. Indeed, many studies have reported structural and functional alterations in the caudate and putamen of human patients with ASDs (e.g., Sears et al., 1999; Eliez et al., 2001; Levitt et al., 2003; Hollander et al., 2005; Haznedar et al., 2006; Silk et al., 2006; Turner et al., 2006; Voelbel

et al., 2006; Langen et al., 2007, 2012; Takarae et al., 2007; Di Martino et al., 2011).

Many robust behavioral assays for striatum-dependent reward processing have been developed in rodents. One example is the place conditioning assay, which involves the association between a rewarding stimulus and a distinct set of contextual cues (e.g., floor texture, wall pattern, or chamber odor). The choice to spend time in the presence of these cues vs. a neutral set of cues is operationally defined as a conditioned place preference (CPP), and most drugs of abuse produce CPP (Tzschentke, 1998). Rodents will also develop CPP for contextual cues associated with social interaction with conspecifics, relative to cues experienced during social isolation (Panksepp and Lahvis, 2007; Trezza et al., 2009). This preference for cues associated with social interactions (i.e., "social CPP") is likely related to the preference for pair-bonded partners exhibited by monogamous species like prairie voles (Carter et al., 1995) and titi monkeys (Carp et al., 2015). Many of the same striatal pathways contribute to social behavior as well as drug reward, suggesting neurochemical systems that originally evolved to mediate social attachment may be hijacked by drugs of abuse (Insel, 2003; Burkett and Young, 2012). Recent studies of mice carrying ASD-associated genetic mutations point to dysfunction of these same striatal systems, which will be reviewed below in terms of both basic function as well as dysfunction in ASDs.

Oxytocin

The peptide hormone oxytocin contributes to a myriad of social behaviors across many mammalian species (Anacker and Beery, 2013). The pro-social effects of oxytocin have generated substantial interest in its use as a treatment for social deficits associated with ASDs, and there is also some evidence for genetic polymorphisms in the oxytocin receptor associated with ASDs (reviewed by Yamasue et al., 2012). The monogamous behavior of prairie voles is associated with a high density of oxytocin receptors in the nucleus accumbens, and pharmacological blockade of these receptors prevents pair bond formation (reviewed by Insel and Young, 2001), pointing to a key role for oxytocin signaling in the nucleus accumbens in social behavior.

A recent study by Dölen et al. (2013) found that pharmacological antagonism of oxytocin receptors in the nucleus accumbens also blocks social CPP in mice. This result was somewhat surprising, as mice were previously reported to have a relatively low density of oxytocin receptors in the nucleus accumbens compared to other rodent species (Olazábal and Young, 2006). However, conditional genetic deletion of the oxytocin receptors in the nucleus accumbens itself did not impair social CPP. Instead, the oxytocin receptors that mediate social CPP appeared to be expressed on the axon terminals of serotonergic fibers that originate in the dorsal raphe nucleus, and pharmacological antagonism of serotonin 5HT1B receptors in the nucleus accumbens also blocked social CPP (Dölen et al., 2013).

Synaptic plasticity in the nucleus accumbens may be important for encoding the association between social interaction and contextual cues that leads to social CPP. In acute brain slice preparations, stimulation of either oxytocin or serotonin 5HT1B receptors in the nucleus accumbens produced a long-term depression (LTD) of excitatory synapses onto MSNs (Dölen et al., 2013). This reduction of excitatory synaptic drive was associated with a decrease in the probability of presynaptic glutamate release, and provides a plausible synaptic mechanism that may contribute to social reward. Other forms of nucleus accumbens LTD that involve presynaptic changes in glutamate release are impaired by addictive drug exposure (e.g., Fourgeaud et al., 2004; Grueter et al., 2010). This occlusion could contribute to decrements in social behavior caused by drug exposure, like the impairment of social bonding in prairie voles caused by amphetamine exposure (Liu et al., 2010). This impairment can be reversed by oxytocin administration (Young et al., 2014), and oxytocin can attenuate other behavioral effects of psychostimulant administration (reviewed by Sarnyai and Kovács, 2014), clearly demonstrating an interaction between drug effects and the oxytocin system. However, the neurobiological substrata of social and drug reward are at least partially separable, because pharmacological antagonism of oxytocin receptors does not block cocaine CPP (Dölen et al., 2013).

Dopamine Release

Dopaminergic input to the nucleus accumbens originates from dopamine neurons in the ventral tegmental area of the midbrain, and this "mesolimbic" dopamine pathway is closely tied to motivation, reward, and the development of addiction (for reviews, see Wise, 2004; Berridge, 2007; Salamone and Correa, 2012). Mesolimbic dopamine is also important for social behavior in rodents, including pair bond formation in prairie voles (reviewed by Curtis et al., 2006). In mice, activity of the mesolimbic dopamine pathway corresponds to social behavior in real time, and optogenetic manipulations of this pathway affect social interaction (Gunaydin et al., 2014). Given these critical functions of dopamine in social behavior and reward, it is perhaps not surprising that genetic polymorphisms in dopamine signaling genes are also associated with ASDs (e.g., Comings et al., 1991; Hettinger et al., 2008, 2012; De Krom et al., 2009; Hamilton et al., 2013; Bowton et al., 2014; Staal et al., 2015).

A recent report by Karayannis et al. (2014) examined the function of the mesolimbic dopamine system in mice following genetic deletion of *Cntnap4* (also known as *Caspr4*), the gene encoding contactin-associated protein-like 4 (Cntnap4). Cntnap4 is a transmembrane protein that belongs to the neurexin superfamily of cell adhesion molecules, which interact with presynaptic proteins involved in neurotransmitter release (Spiegel et al., 2002). Genetic mutations in other members of this family of molecules have been previously reported in patients with ASDs, and Karayannis et al. (2014) report several new ASD probands with *CNTNAP4* gene disruptions. In mice, they found that expression of Cntnap4 was enriched in midbrain dopamine neurons, as well as inhibitory interneurons in the cerebral cortex, and therefore examined the release of dopamine and GABA from these populations of brain cells. While the release of GABA from cortical interneurons was substantially reduced in *Cntnap4* mutant mice, the release of dopamine in the nucleus

accumbens was significantly increased. These divergent effects on release of two different neurotransmitters further underscore the heterogeneous effects that a single ASD-associated genetic mutation can have on different types of synapses.

Cntnap4 mutant mice also exhibited a variety of aberrant behavioral phenotypes (Karayannis et al., 2014). Most striking was hair loss on the snout, face, and body, which was caused by over-grooming of offspring by parents carrying the *Cntnap4* mutation. This excessive grooming phenotype was reversed by chronic treatment with haloperidol, a dopamine D2 receptor antagonist, suggesting over-grooming was caused by excessive dopamine signaling. Social behavior was not assessed by Karayannis et al. (2014) in *Cntnap4* mutant mice, though it is disrupted by mutations of *Cntnap2*, another member of this protein family (Peñagarikano et al., 2011; Burkett et al., 2015). It will be fascinating to see whether excessive dopamine signaling in the nucleus accumbens of *Cntnap4* mutant mice alters either social reward or behavioral responses to addictive drug exposure.

Dopamine-Sensitive Medium Spiny Neurons

A variety of dopamine receptors are expressed by different cell types in the striatum (Gerfen and Surmeier, 2011). While a small fraction of striatal cells are interneurons that release acetylcholine or GABA, the vast majority of striatal cells are medium spiny projection neurons (MSNs). MSNs are the principal neurons of the striatum and relay information to downstream processing stations in the basal ganglia, including the substantia nigra pars reticulata and the globus pallidus. In the dorsal striatum, striatonigral and striatopallidal MSNs represent two discrete subpopulations that differ in expression of D1 vs. D2 dopamine receptors, as well as a variety of other properties (Gerfen and Surmeier, 2011). The nucleus accumbens also contains discrete populations of D1-MSNs and D2-MSNs, but D1-MSNs in the nucleus accumbens project to both the ventral mesencephalon and ventral pallidum, whereas D2-MSNs project only to the ventral pallidum (Kupchik et al., 2015).

The ability to identify and manipulate specific MSN subtypes was dramatically advanced by the development of bacterial artificial chromosome (BAC) transgenic mice (Heintz, 2001), which allow cell type-specific expression of fluorescent proteins (Gong et al., 2003; Shuen et al., 2008) as well as Cre recombinase (Gong et al., 2007; Durieux et al., 2009). The application of these tools to research on drug addiction has revealed that activation of D1-MSNs promotes addiction-related behaviors, whereas activation of D2-MSNs tends to inhibit the same behaviors (Lobo et al., 2010; Bock et al., 2013; Pascoli et al., 2014; reviewed by Smith et al., 2013). These divergent effects are consistent with classic models of basal ganglia function, in which the direct pathway formed by D1-MSNs and the indirect pathway formed by D2-MSNs exert opposite influences on overall basal ganglia output (Albin et al., 1989; DeLong, 1990).

Striatal MSNs show enriched expression of genes associated with ASDs (Chang et al., 2015), and recent studies have begun to explore how ASD-associated mutations affect specific MSN subtypes. One study focused on ASD-associated mutations in neuroligin-3 (*Nlgn3*), a synaptic cell adhesion molecule that plays important roles in shaping the functional properties of synaptic transmission. Loss-of-function genetic mutations in *Nlgn3* caused a specific impairment of inhibitory synaptic transmission onto nucleus accumbens D1-MSNs (Rothwell et al., 2014). This reduction of inhibitory synaptic transmission is intriguing because human patients with ASDs have been reported to have decreased GABA receptor binding in the nucleus accumbens (Mendez et al., 2013). In mice, nucleus accumbens D1-MSNs appeared to be selectively vulnerable to genetic deletion of *Nlgn3* because it is expressed at a relatively high level compared to neighboring D2-MSNs, or MSNs in the dorsal striatum. Conditional genetic deletion of *Nlgn3* from nucleus accumbens D1-MSNs also caused the development of a more repetitive motor routine on the accelerating rotarod task (Rothwell et al., 2014). This behavioral phenotype has also been reported in several other mouse lines carrying ASD-associated genetic mutations (Kwon et al., 2006; Etherton et al., 2009; Nakatani et al., 2009), and thus might have some relevance to the repetitive and stereotyped movements and routines associated with ASDs in human patients.

Altered striatal structure and function have also been reported in mice lacking the genes normally found on human chromosome 16p11.2 that are deleted in some human patients with ASDs (Weiss et al., 2008). These 16p11 mutant mice have an increased number of striatal cells expressing markers of D2-MSNs, as well as more MSNs co-expressing both D1 and D2 markers, but no change in the number of D1-MSNs (Portmann et al., 2014). These changes in cell number were associated with a relative enlargement in the size of the nucleus accumbens as well as the globus pallidus, which receives synaptic input from D2-MSNs. In 16p11 mutant mice, D2-MSNs also appeared to send ectopic projections to the medial globus pallidus, which is normally only targeted by D1-MSNs. Nucleus accumbens MSNs of 16p11 mutant mice had altered excitatory synaptic properties, including a presynaptic increase in the probability of glutamate release and changes in postsynaptic glutamate receptor complement. Mutant mice also exhibited behavioral phenotypes that included hyperactivity, circling, and a lack of habituation to novelty.

Opioids

Striatal opioid systems play an important role in the rewarding aspects of social interaction (Burkett et al., 2011; Trezza et al., 2011; Resendez et al., 2013), as well as the rewarding properties of opiate narcotics and other abused drugs (Befort, 2015). The mu opioid receptor (MOR) is a particularly critical mediator of the rewarding effects of opiates like morphine (Matthes et al., 1996). Juvenile mice lacking the MOR gene (*Oprm1*) exhibit a diminished behavioral response to separation from their mothers, suggesting that interaction with the mother may be less rewarding (Moles et al., 2004). Adult *Oprm1* knockout mice also exhibit other ASD-related behavioral phenotypes, including decreased sociability and stereotyped behaviors (Becker et al., 2014). These behavioral changes were associated with dramatic gene expression changes in the nucleus accumbens and dorsal striatum, including a number of genes involved in excitatory synaptic signaling. One of these genes (*Grm4*) encodes the

metabotropic glutamate receptor mGluR4, and administration of an mGluR4 positive allosteric modulator effectively relieved many of the behavioral phenotypes exhibited by MOR knockout mice.

Endogenous opioids may interact with other neuromodulatory systems in the nucleus accumbens. MOR knockout mice exhibit a dramatic decrease in mRNA levels for oxytocin in the NAc (Becker et al., 2014). Conversely, oxytocin receptor levels in the NAc are increased (Gigliucci et al., 2014), which could represent a homeostatic response to compensate for loss of endogenous ligand. Intranasal administration of oxytocin to adult male MOR-KO mice led to an increase in the number of ultrasonic vocalizations emitted during interaction with a female mouse (Gigliucci et al., 2014). This interaction between opioid and oxytocin signaling in the NAc suggests a convergence of multiple signaling pathways that may contribute to ASD pathophysiology.

Endocannabinoids

Brain cannabinoid receptors are activated by both exogenous and endogenous cannabinoids, and play an important role in drug reward (Befort, 2015). Endogenous cannabinoid systems in the nucleus accumbens also regulate social behavior, as local blockade of endocannabinoid degradation enhances social play (Trezza et al., 2012). Social interaction increases levels of anandamide (an endogenous cannabinoid) in the nucleus accumbens, an effect that is stimulated by oxytocin and may contribute to social reward (Wei et al., 2015). Endocannabinoids are important for regulating synaptic function in a variety of ways, including a key role in many forms of synaptic plasticity. Mice lacking FMRP have an impairment of endocannabinoid-dependent LTD of excitatory synapses in the NAc (Jung et al., 2012). This impairment is due to a mislocalization of diacylglycerol lipase-α (DGL-α), a key enzyme in the biosynthetic pathway for the endocannabinoid 2-arachidonoyl-sn-glycerol (2-AG). In the absence of FMRP, DGL-α is localized farther away from the postsynaptic density and is not robustly activated by stimulation of mGluR5. However, this signaling deficit could be rescued by inhibiting the degradation of 2-AG, leading to a normalization of LTD in the NAc as well as some behavioral phenotypes of FMRP knockout mice. ASD-associated genetic mutations in *Nlgn3* did not appear to affect endocannabinoid-dependent LTD in the nucleus accumbens (Rothwell et al., 2014), though these mutations do alter endocannabinoid signaling in other parts of the brain (Földy et al., 2013). In the dorsal striatum, exaggerated LTD has been reported in mice overexpressing eukaryotic translation initiation factor 4E (Santini et al., 2013), which is encoded by the ASD candidate gene *Eif3e* (Neves-Pereira et al., 2009).

Pathways to Dorsal Striatum

The progression of drug abuse is thought to involve a transition in the control of behavior from ventral to dorsal striatum (for a recent review, see Everitt and Robbins, 2016). This transition corresponds with a shift in the motivation to take drugs, which becomes less goal-directed and more compulsive or habitual (i.e., insensitive to outcome), leading to continued use despite

adverse consequences. This transition in behavioral control may involve polysynaptic pathways that link ventral striatum with dorsal striatum, as neurons in the nucleus accumbens project to dopaminergic centers in the midbrain that subsequently project to more dorsal striatal subregions (Haber et al., 2000; Ikemoto, 2007). This ascending spiral of connectivity may be engaged over the course of chronic drug use and contribute to habitual patterns of addiction (Belin and Everitt, 2008).

Changes in the nucleus accumbens caused by ASD-associated genetic variants could accelerate the transition of behavioral control to more dorsal striatal subregions, leading to more repetitive, stereotyped, or habitual patterns of behavior. However, changes that directly affect the dorsal striatum may also produce similar behavioral consequences: for example, the exaggeration of dorsal striatal LTD in *Eif3e* mutant mice could potentially affect the process of habit formation (Santini et al., 2013). Dysfunction in the dorsal striatum has also been reported in mice carrying gene deletions of *Shank3* (Peca et al., 2011), which encodes a synaptic scaffolding protein and is disrupted in Phelan-McDermid syndrome (an autism spectrum disorder) as well as idiopathic ASDs (reviewed by Jiang and Ehlers, 2013). These *Shank3* mutant mice exhibit reduced social interaction and excessive self-grooming to the point of skin lesions (Peca et al., 2011). MSNs in the dorsal striatum exhibited abnormal morphology and impaired excitatory synaptic transmission, although it is presently unclear if D1- or D2-MSNs were preferentially affected.

ASD MOLECULES IN ADDICTION

Genes and molecules that have been extensively studied in the realm of ASDs have recently emerged as potential mediators of addiction-related behavior. These include the genes known to cause Rett syndrome (MECP2—Amir et al., 1999) and fragile X syndrome (FMR1—Pieretti et al., 1991), which have been topics of sustained research since their initial identification. MeCP2 and FMRP play important roles in the regulation of gene transcription and translation, respectively. In mice, genetic mutations in *Mecp2* and *Fmr1* cause a variety of deficits in synaptic transmission and plasticity throughout the brain, which are thought to contribute to the ASD-related symptoms frequently observed in patients with these syndromes (Zoghbi and Bear, 2012).

These ASD-associated molecules have been shown to regulate multiple aspects of striatal function. For example, dopamine signaling in the striatum is regulated by both MeCP2 (Su et al., 2015) and FMRP (Wang et al., 2008). Genetic deletion of *Fmr1* also affects synaptic structure, function, and plasticity in the nucleus accumbens (Jung et al., 2012; Smith et al., 2014; Neuhofer et al., 2015) as well as the dorsal striatum (Centonze et al., 2008; Maccarrone et al., 2010). The development of drug addiction is strongly tied to dopamine signaling and synaptic remodeling in the striatum, motivating several recent investigations of how genetic mutations in *Mecp2* and *Fmr1* affect behavioral responses to addictive drugs. These studies focused on common behavioral outcomes in addiction research, including CPP as a measure of drug reward, as well as performance an instrumental

response to receive contingent delivery of the drug (i.e., drug self-administration). These studies also examined psychomotor activation following acute drug administration, as well as the psychomotor sensitization that occurs following repeated drug exposure, as these behavioral processes are closely tied to striatal dopamine release and remodeling of striatal circuitry (for reviews, see Vanderschuren and Kalivas, 2000; Grueter et al., 2012).

Methyl CpG-Binding Protein-2 (MeCP2)

Psychostimulant administration induces MeCP2 phosphorylation in the nucleus accumbens (Deng et al., 2010, 2014). This effect is not seen in MSNs, but is instead selective for fast-spiking GABAergic interneurons that express parvalbumin and GAD67. Behavioral responses to amphetamine administration are altered by a constitutive hypomorphic mutation in *Mecp2* (Deng et al., 2010), as well as a Ser421Ala mutation in Mecp2 that prevents psychostimulant-induced phosphorylation (Deng et al., 2014). Enhanced behavioral sensitivity to psychostimulants is also observed following restricted knockdown of *Mecp2* expression in the nucleus accumbens. These findings suggest phosphorylation of MeCP2 in the nucleus accumbens plays a role in constraining behavioral responses to psychostimulants. However, the role of MeCP2 may be different in the dorsal striatum, as a separate study found cocaine self-administration was reduced following restricted knockdown of *Mecp2* expression in the dorsal striatum (Im et al., 2010).

Fragile X Mental Retardation Protein (FMRP)

Constitutive genetic deletion of *Fmr1* did not alter the acute locomotor response to cocaine, but decreased locomotor sensitization over course of repeated cocaine exposure, and also attenuated cocaine CPP (Smith et al., 2014). Conditional genetic deletion of *Fmr1* in the nucleus accumbens also decreased locomotor sensitization, though it did not affect cocaine CPP. Cocaine-evoked changes in the structure and function of excitatory synapses onto nucleus accumbens MSNs were also enhanced in *Fmr1* constitutive knockout mice. These data suggest that FMRP serves as a negative regulator of the structural and functional changes at nucleus accumbens synapses caused by chronic drug exposure, similar to MeCP2 (Deng et al., 2014).

OUTLOOK AND OPEN QUESTIONS

How do these emerging parallels between ASDs and addiction (**Table 1**) inform our understanding of the pathophysiology of each disorder in relationship to the striatum? Despite these parallels, these are clearly two distinct disorders, as evidenced not only by distinct symptomatology but also the lack of comorbidity. Nevertheless, ongoing research may benefit from more careful consideration of neurobiological and psychological process that may be commonly affected in both disorders. This approach is reminiscent the Research Domain Criterion (RDoC) initiative by the U.S. National Institute of Mental Health

(Insel et al., 2010; Insel and Cuthbert, 2015), which aims to establish a new framework for psychiatric research that moves away from specific clinical diagnoses and toward dimensions or constructs with well-defined neurobiological substrata that may be impaired across multiple mental disorders. Below, I consider two behavioral dimensions that may be commonly affected in both ASDs and addiction, as well as potential neural mechanisms and therapeutic implications raised by the shared and distinct elements of these disorders.

Repetitive Behavioral Patterns as a Common Dimension of Dysfunction

One hallmark of both ASDs and addiction is the repetition of specific patterns of behavior, sometimes in the absence of an obvious goal or even in the face of adverse consequences. Indeed, the transition from casual to compulsive or habitual drug use is one of the defining features of addiction. Conversely, ASDs are associated with behavioral patterns that are performed in a stereotyped fashion and are resistant the change. This can include simple movements like hand flapping, as well as more complex routines and rituals. While somewhat different terminology is used to describe these behavioral patterns (e.g., "compulsive" or "habitual" for addiction, "repetitive" or "stereotyped" for ASDs), all may be characterized by a failure to inhibit the repetition of behavioral patterns. This lack of inhibitory control over repetitive behavior may also contribute to other mental disorders, such as obsessive-compulsive disorder, which is also linked to striatal dysfunction (Burguière et al., 2015).

Rodent models of ASDs and addiction obviously lack the nuance and specificity of the clinical condition, but some interesting similarities in repetitive behavioral patterns seem to suggest common striatal circuitry may be affected in both disorders. For example, stereotyped patterns of rotational behavior caused by ASD-associated genetic mutations (Portmann et al., 2014; Rothwell et al., 2014) are also observed following exposure to psychostimulants (Fowler et al., 2001). Similarly, the orofacial stereotypy caused by repeated exposure to a high dose of cocaine is exacerbated in *Fmr1* knockout mice (Smith et al., 2014). While it is obviously difficult to extrapolate these simple rodent behaviors to the symptoms of complex human disorders likes ASDs and addiction, these examples at least illustrate that some elementary forms of repetitive behavior can be similarly affected by addictive drugs and ASD-associated genetic mutations.

Aberrant Reward Processing as a Common Dimension of Dysfunction

The processing of reward-related information represents another behavioral dimension that may be affected in both ASDs and addiction. The concept of reward figures prominently in addiction, where decades of research have led to the identification and dissection of distinct components of reward (reviewed by Berridge et al., 2009). One important distinction is between the hedonic impact or "liking" of reward, and the incentive salience or "wanting" associated with rewards and related environmental stimuli. Repeated drug exposure is thought to

TABLE 1 | Striatal signaling pathways and molecules commonly implicated in both addiction and autism spectrum disorders (ASDs); see text for details.

Pathway/Molecule	Relevance to addiction	Relevance to ASDs
Oxytocin	Attenuates behavioral effects of psychostimulant administration (Sarnyai and Kovács, 2014)	Social reward involves actions of oxytocin in the nucleus accumbens (Dölen et al., 2013)
Dopamine	Important for reward and attribution of incentive salience (Wise, 2004; Berridge, 2007)	Increased release in *Cntnap4* mutant mice (Karayannis et al., 2014)
Opioids	Contribute to rewarding effects of exogenous opiates and other drugs (Befort, 2015)	Autism-related behavioral phenotypes in *Oprm1* mutant mice (Moles et al., 2004; Becker et al., 2014)
Endocannabinoids	Contribute to drug reward and synaptic plasticity (Befort, 2015)	Altered striatal synaptic plasticity in *Fmr1* and *Eif3e* mutant mice (Jung et al., 2012; Santini et al., 2013)
Methyl CpG-Binding Protein-2 (MECP2)	Altered behavioral responses to psychostimulant administration (Deng et al., 2010, 2014; Im et al., 2010)	Deletions cause Rett syndrome (Amir et al., 1999)
Fragile X Mental Retardation Protein (FMRP)	Altered behavioral and synaptic responses to cocaine exposure (Smith et al., 2014)	Deletions cause fragile X syndrome (Pieretti et al., 1991)

selectively exaggerate or sensitize the incentive salience attributed to drugs and drug-related cues, a process that is closely linked to dopamine transmission (for a recent review, see Robinson and Berridge, 2008).

In ASD research, aberrant "reward processing" often refers to altered patterns of brain activity in response to social stimuli or monetary reward (e.g., Scott-Van Zeeland et al., 2010; Delmonte et al., 2012; Dichter et al., 2012; Kohls et al., 2013; Richey et al., 2014). Reduced sensitivity to social stimuli may contribute to the deficits in social behavior associated with ASDs, but the precise nature of this aberrant reward processing remains unclear. For instance, are social deficits in ASDs due to decreased hedonic impact or "liking" of social interaction, or rather to a decrease in the incentive salience or "wanting" associated with social stimuli? An alternative possibility (discussed in more detail below) is that ASDs are associated with indiscriminate attribution of incentive salience to inappropriate stimuli in the environment, which could lead to fixation on these stimuli at the expense of social interaction. Rodents carrying ASD-associated genetic mutations may provide a tractable model to begin disentangling these possibilities, through behavioral assays and direct manipulations of brain function needed to fractionate the different components of reward (Berridge et al., 2009).

Neural Mechanisms for Common and Distinct Dimensions of Dysfunction

In light of the putative behavioral dimensions that are commonly impaired in ASDs and addiction, an obvious question arises regarding the elements of striatal circuitry that could commonly contribute to both disorders. One intriguing possibility involves D1-MSNs in the nucleus accumbens, as these cells appear to be a key locus for structural and functional synaptic changes caused by chronic drug exposure (Grueter et al., 2012; Smith et al., 2013). Drug-evoked plasticity at excitatory synapses on D1-MSNs in the nucleus accumbens appears to drive multiple forms of addiction-related behavior (Pascoli et al., 2012, 2014). Furthermore, direct activation of D1-MSNs in the nucleus accumbens enhances both drug reward and the development of psychomotor sensitization (Lobo et al., 2010; Koo et al., 2014), whereas inhibition of these cells reduces the same behavioral effects (Hikida et al., 2010; Ferguson et al., 2011).

Given this established link between addiction and D1-MSNs in the nucleus accumbens, it was both surprising and fascinating that recent reports linked these same cells to social behavior in wild-type mice (Gunaydin et al., 2014), as well as repetitive behavior in mice carrying ASD-associated mutations in *Nlgn3* (Rothwell et al., 2014). The former study suggests dopamine release and activation of D1-MSNs are both important for the expression of social behavior in mice (Gunaydin et al., 2014), whereas the latter study suggests synaptic disinhibition of D1-MSNs leads to repetitive behavior (Rothwell et al., 2014). These two patterns of results may appear contradictory in relation to ASDs, which are associated with less social behavior and more repetitive behavior. One potential explanation for this apparent contradiction (considered below) also provides insight into how the altered activity of one cell type could lead to both common and distinct dimensions of dysfunction.

Continuous synaptic disinhibition of D1-MSNs may lead to chronic elevation of baseline activity in these cells, thereby occluding phasic increases in activity that encode normal social behavior. Chronic elevation of baseline activity in D1-MSNs may also influence dopamine levels in the striatum, as axonal projections from these cells to the ventral tegmental area appear to synapse preferentially onto interneurons, which in turn inhibit dopamine neurons (Xia et al., 2011; Bocklisch et al., 2013). Disinhibition of D1-MSNs may therefore translate into disinhibition of dopamine neurons and increase dopamine release in the back into the striatum. This continuous increase in dopamine release would resemble the effects of ASD-associated genetic mutations in *Cntnap4* (Karayannis et al., 2014), and could lead to indiscriminate attribution of incentive salience to inappropriate stimuli in the environment. This "non-specific" attribution of incentive salience would be fundamentally different from the attribution of incentive salience in addiction, which is excessively large in magnitude but still specifically attributed to drugs and drug-related cues. Thus, increased activation of D1-MSNs and excessive dopamine release may be a common feature of ASDs and addiction, but there may be differences in how this cellular change is manifested in the clinical features of each disorder.

It is also becoming increasingly apparent that D1-MSNs in the nucleus accumbens exhibit heterogeneity in terms of function,

structure, and neurochemistry. D1-MSNs specifically co-express the neuropeptide dynorphin, and activation of dynorphinergic cells in different subregions of the nucleus accumbens can lead to opposite behavioral effects (Al-Hasani et al., 2015). D1-MSNs in the nucleus accumbens also send axonal projections to both the ventral mesencephalon and ventral pallidum, and therefore contribute to both the direct and indirect pathways through the basal ganglia (Kupchik et al., 2015). Furthermore, a small population of MSNs in the nucleus accumbens appears to express both D1 and D2 dopamine receptor subtypes (Perreault et al., 2011). Subtle differences in how ASDs and addiction impact different subpopulations of D1-MSNs could also contribute to distinct clinical manifestations of these disorders.

Therapeutic Implications

Parallel dissection of striatal circuitry in ASDs and addiction may enable therapeutic advances in one field to inform progress in the other. For example, in the realm of addiction, the key role for D1-MSNs in promoting the behavioral effects of cocaine recently inspired an intersectional approach to reversing cocaine-evoked synaptic plasticity in mice, through the combination of deep brain stimulation of the nucleus accumbens and a pharmacological manipulation that selectively targets D1-MSNs (Creed et al., 2015). This type of intersectional strategy may prove beneficial as deep brain stimulation and other forms of neuromodulation are developed for clinical treatment of patients with ASDs (Sturm et al., 2012; Enticott et al., 2014; Sinha et al., 2015). Other types of intersectional therapeutic strategies could involve simultaneous manipulation of multiple neuromodulatory systems that intersect in the nucleus accumbens, such as oxytocin and serotonin (Dölen et al., 2013), or opioids and cannabinoids

(Befort, 2015). The opioid and cannabinoid systems may be particularly tractable therapeutic targets, given their rich and diverse pharmacology as well as active drug development efforts for treatment of pain.

ASDs and drug addiction are complicated disorders that likely involve many parts of the brain, but the literature reviewed here highlights a central role for the striatum and basal ganglia in both disorders. In the striatum, these disorders impact a variety of neuromodulatory systems converging on multiple postsynaptic cells types. This intrinsic complexity makes it challenging to study striatal circuits in the context of disease, but also increases the number of potential therapeutic targets as well as the possibility of developing interventions that specifically affect individual circuit elements. It is quite likely that some common elements of this circuitry (like D1-MSNs in the nucleus accumbens) contribute to the pathophysiology of both ASDs and addiction, while other elements within or beyond the striatum are uniquely involved in only one disorder. A growing knowledge of both common and distinct dimensions of dysfunction will help guide the development of interventions that could be broadly useful for normalizing neural circuit dysfunction that contributes to behavioral deficits in both ASDs and addiction.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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