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Modeling Restricted Repetitive Behavior in Animals

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Abstract

Restricted, repetitive behavior is one of the three diagnostic domains for autism spectrum disorders, and commonly observed in a number of other neurodevelopmental disorders. Despite its clinical significance, effective treatments for restricted, repetitive behavior are limited including few, if any, pharmacological interventions with demonstrated efficacy. This is in large measure due to the lack of knowledge of the pathophysiological mechanisms that mediate the development and expression of repetitive behaviors in autism spectrum disorders. Therefore, animal models, particularly those that encompass both lower order and higher order repetitive behaviors, could be particularly useful. Such models could identify various potential etiologies, characterize commonalities in pathophysiology, identify novel potential therapeutic targets, and guide the development and validation of novel treatments. We have organized existing models of restricted, repetitive behavior in animals into four different categories: repetitive behavior resulting from a specific CNS insult (e.g. genetic mutation); repetitive behavior induced by specific pharmacological agents (e.g. amphetamine); repetitive behavior consequent to confined or restricted housing (e.g. laboratory caging); and repetitive behavior associated with specific inbred mouse strains. We have reviewed the literature from each of these categories of animal models, and discuss their multiple etiologies in light of a potential shared common pathophysiology: alterations in cortical-basal ganglia circuitry. Our own work with deer mice as a model of restricted, repetitive behavior suggests reduced activity in the indirect pathway of the basal ganglia, and has identified novel potential therapeutic targets. Other promising models are emerging that can take full advantage of modern genetics and molecular neuroscience that can be used to elucidate the pathophysiology of restricted, repetitive behavior. However, much more work must be done in this area to uncover the mechanisms underlying restricted, repetitive behavior, a critical step in finding effective new treatments for individuals with autism spectrum disorders.

Keywords: Repetitive behavior; Stereotypy; Cortical-basal ganglia circuitry; Autism spectrum disorders

Abbreviations: RRB: Restricted Repetitive Behavior; ASD: Autism Spectrum Disorders; CNS: Central Nervous System; OCD: Obsessive Compulsive Disorder; STN: Subthalamic Nucleus; GP: Globus Pallidus; SNpr: Substantia Nigra pars reticulata; CO: Cytochrome Oxidase

Introduction

Restricted, repetitive behavior (RRB), one of three diagnostic domains for Autism Spectrum Disorders (ASD) refers to the broad range of responses that include stereotyped motor movements, self-injurious behavior, repetitive manipulation of objects, compulsions, rituals and routines, insistence on sameness, and narrow and circumscribed interests [1]. These forms of RRB have been categorized as either "lower-order" motor actions (stereotyped movements, self-injury, repetitive manipulation of objects) involving repetition of movement, or "higher-order" behaviors (compulsions, rituals, insistence on sameness, and circumscribed interests) involving more complex behaviors characterized by rigidity or inflexibility [1-3]. This categorization has been empirically supported by factor analyses [4,5], using relevant items from the Autism Diagnostic Interview-Revised (ADI-R). These two factors have been labeled repetitive sensory motor behavior and resistance to change/insistence on sameness. Other analyses have presented evidence for a third factor labeled circumscribed interests [6].

RRB at 2 years of age predicts autism diagnosis at age 9, is a major source of stress for parents, results in considerable accommodation by the family and negatively impacts academic achievement [7]. Despite this, treatment options for RRB are limited and there has been a dearth of adequately controlled studies examining such interventions [8]. Of particular relevance here is that few, if any, pharmacological treatments for these behaviors have clearly demonstrated efficacy [9-11]. The lack of efficacious pharmacological treatments is in large measure, due to the lack of understanding of the pathophysiological mechanisms that mediate the development and expression of repetitive behaviors in ASD. There are no post-mortem studies involving individuals with ASD that relate neuropathological findings to RRB [12]. Moreover, only a small number of MRI studies have related volumetric measurements to RRB, and these results have been inconsistent [13-15].

Given this state of affairs, it would seem that animal models of RRB, given the requisite validity, could be particularly useful. Such models could identify various potential etiologies, characterize commonalities in pathophysiology, identify novel potential therapeutic targets, and guide the development and validation of novel treatments.

Modeling Restricted, Repetitive Behavior in Animals

Repetitive sensory motor behaviors can take a number of forms in animals, depending on the species and context in which they are observed. These can include excessive grooming, stereotyped pacing, backward somersaulting, rhythmic body movements, head twirling, and excessive mouthing to name, but several. These behaviors share

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important features with those observed in ASD in being not only repetitive, but having little variation in response form and no obvious purpose or function.

A clear challenge for animal studies is to model "higher order" RRB or resistance to change/insistence on sameness. Although stereotyped motor behaviors have typically been the focus, some animal work has addressed the domain of cognitive rigidity or resistance to change. This domain can be assessed in animals using a variety of tasks including response extinction, reversal learning, and intra- and extra-dimensional set shifting (e.g. [16]). Specific examples of such tasks include extinction and reversal learning in a Morris water or T-maze task [17,18], and perseveration in a variation of a gambling or a two-choice guessing task [19-21]. Other tasks such as marble burying behavior and restricted exploration in a hole-board task [22-25] have been advanced to model perseveration or compulsion and restricted behavior or interest.

Models of restricted, repetitive behavior in animals can be roughly organized into four different categories: repetitive behavior resulting from a specific CNS insult (e.g. gene mutation, lesion); repetitive behavior induced by specific pharmacological agents (e.g. amphetamine, cocaine); repetitive behavior consequent to confined or restricted housing (e.g. laboratory cage); and repetitive behavior associated with specific inbred mouse strains. In the following sections, we will update information from our previous review [26], expand our treatment of animal models to specific inbred mouse strains, and provide a summary of our recent work on the neurobiology of repetitive behavior in mouse models.

Repetitive behavior following CNS insult

Genetic mutations: Mice carrying targeted genetic mutations as models of various clinical disorders have increased dramatically. Thus, it is not surprising to see more repetitive behavior phenotypes associated with genetic alterations as a consequence. For example, Rett syndrome has been linked to mutations in the methylCpG binding protein 2 (MECP2), and mice with mutations in this protein demonstrate stereotypic forelimb behavior mimicking the characteristic hand stereotypies seen in patients [27]. Autism, along with Prader-Willi and Angelman syndromes has been linked to changes in a specific region (q11-13) of chromosome 15 carrying the *GABRB3* gene. The creation of the *Gabrb3* knockout mouse revealed a mouse model that displayed intense stereotyped circling behavior. RRB can also be modeled in mice with perturbations to the *Hoxb8* gene, which display excessive grooming that can lead to wound infliction [28].

More recently, alterations in molecular regulators of excitatory synaptic structure and function have emerged as mediators of aberrant repetitive behavior. For example, a targeted deletion of a postsynaptic scaffolding protein at excitatory synapses, SAPAP3, which is highly expressed in the striatum, produced a mouse model of reduced cortico-striatal synaptic transmission and glutamate receptor function, and excessive self-grooming behavior [29]. SHANK genes encode another postsynaptic scaffolding protein family enriched at excitatory synapses, and mutations in ProSAPs/SHANK genes have been associated with autism. SHANK1 deletion has been identified in a small number of males with higher-functioning autism [30]. SHANK2 and 3 mutations have been found in some, but not all cases of autism and intellectual disability [31,32]. Disruption of the *Shank3* gene in mice results in functional deficits to glutamatergic synapses and autistic-like behaviors, which includes repetitive behavior in the form of increased grooming, sniffing and object manipulation (e.g. [33]). Follow-up work found phenotypic specificity, as a result of the precise location of the mutation within the SHANK3 gene [34]. Comparison of *Shank2* and *Shank3* mutant mouse data similarly demonstrates that phenotypic differences can result from the different synaptic glutamate receptor expression abnormalities [35]. *Shank2* knockout mice display a range of autistic-like behaviors, including hyperactivity and repetitive jumping, although, decreased digging behavior [35,36]. Some [35], but not all investigators have reported increased grooming behavior in *Shank2* knockout mice [36]. Other candidate genes for autism that are related to excitatory synapses include the neuroligin and neurexin genes. Neuroligins are a family of postsynaptic cell-adhesion molecules that associate with presynaptic neurexins to influence synaptic maturation. Blundell et al. [37] characterized neuroligin 1 (NL1) deficient mice in tests relevant to autism. Compared to controls, NL1 KO mice groomed for twice the amount of time, and the behavior was associated with a ~30% reduction of the NMDA/AMPA ratio in the dorsal striatum. Systemic administration of a NMDA receptor partial co-agonist (D-cycloserine) rescued the abnormal grooming phenotype, suggesting a mechanism for increased grooming in NL1 KO mice is decreased NMDA receptor-mediated synaptic transmission [37]. Deficits in spatial learning and memory that correlated with impaired hippocampal long-term potentiation and minimal social impairments were also noted. Although NL1 is ubiquitously expressed, KO mice were normal in a different task of repetitive behavior (marble burying), learning and memory (fear conditioning), and several other tests (e.g. tests of anxiety, activity, motor function, sensory) [37]. Generation of neurexin1α deficient mice revealed behavioral changes, including increased grooming and impaired nest-building behavior, although no obvious deficits in social behavior or learning [38].

Sala et al. [39] have demonstrated deficits in reversal learning in oxytocin receptor knockout mice. Daily intracerebroventricular (ICV) injections of vehicle or oxytocin showed that oxytocin normalized reversal learning deficits in these mice. These mice also demonstrated deficits in social and communicative behavior [40]. A study by Hollander et al. [41] evaluated the effect of oxytocin on repetitive behavior in adults. ASD subjects received both oxytocin and placebo challenges, each serving as their own control and then, were observed for repetitive behavior (repetitive behavior categories: need to know, repeating, ordering, need to tell/ask, self injury and touching). Repetitive behavior decreased following oxytocin infusion [41].

Non-genomic factors: Other animal models take advantage of the strong influence that the prenatal environment has on risk for offspring development of autistic-like behaviors. For example, *in utero* injections of Valproic Acid (VPA) during sensitive periods of embryonic development produce rodent offspring that show developmental delays, impairments in social behavior and increased lifetime stereotypic behavior [42,43]. Environmental enrichment has been shown to attenuate the repetitive behavior associated with *in utero* exposure to VPA [44].

Repetitive behavior and other autistic-like behaviors have also been linked to perturbations during early development, such as lesion-induced damage. For example, lesioning the amygdala and hippocampus in early postnatal development of rhesus monkeys caused delayed development of stereotypies, first apparent in post-weaning juveniles [45]. Further, lesion-specific topographies of repetitive behavior were documented, such that amygdala lesioned infants were more likely to develop self-directed stereotypies (body rocking, self-biting and self-clasping), compared to hippocampal lesioned infants that were more likely to develop repetitive head-twisting behavior [45]. However, similar lesions in adult animals failed to produce the same

severity of repetitive behavior [45]. These recent findings complement previous studies in rats that found specific lesions of the hippocampus in early development (postnatal day 3) increased repetitive behavior, while the same lesion in later development (postnatal day 14) and adults attenuated repetitive behavior [46]. These studies support a behavioral outcome that is dependent on the timing of lesions and a potential sensitive period for the development of stereotypic behavior.

Immune factors: A potential role for altered immune function in the genesis of autism is an area of considerable interest. Several recent reports have highlighted altered immune processes associated with the development of repetitive behavior in animals. The first of these was an intriguing study by Martin et al. [47] examining the effect of maternal antibodies on non-human primate fetal brain. Here, pregnant rhesus macaques were exposed to purified IgG from sera of human mothers who had at least two children with ASD, and whose sera was shown to be reactive to fetal brain protein. Offspring of the exposed macaques exhibited motor stereotypies, not observed in control monkeys. Additional evidence for a link between anti-neuronal antibodies and repetitive behavior comes from exposing Balb/c mice to IgM antibodies to streptococcus group A bacteria [48]. Mice so treated exhibited repetitive stereotyped movements, including head bobbing, intense grooming, sniffing, and showed increased Fos-like immunoreactivity in regions included within cortico-striato-thalamic circuitry. These findings are consistent with previous reports that infusion of serum or purified IgG from Tourette syndrome patients into rat striatum induced motor stereotypies [49]. Immune responses are mediated in part by various cytokines (e.g. interleukins, interferons) and their receptors. Soluble interleukin-6 receptor administration has been shown by Patel et al. [50] to induce motor stereotypies in Balb/c mice. These behavioral effects were accompanied by evidence for localization of these IL-6 receptors in brain regions included in cortical basal ganglia circuitry. Finally, maternal infection, a risk factor for autism, was modeled in mice by administration of poly(I:C), to induce a proinflammatory antiviral response, starting at embryonic day 10.5 [51]. As adults, offspring of these maternally infected mice exhibited increased marble burying and elevated self-grooming. Interestingly, marble burying levels were normalized to control levels, following irradiation and bone-marrow transplantation of poly(I:C) exposed offspring [52].

Drug-induced repetitive behavior

For more than four decades, we have known that specific pharmacological agents (e.g. amphetamine, apomorphine) can induce repetitive motor behavior in humans and animals. Early experiments highlighted the importance of basal ganglia in mediating the induction of repetitive behavior by such drugs. For example, injection of dopamine or a dopamine agonist (e.g. apomorphine) into the striatum of rats induced repetitive behavior [53]. Bi-directional models of selective pharmacological agents further affirm the role of the cortical-basal ganglia circuitry in repetitive behavior. For example, modulation of dorsal striatal glutamate receptors by intrastriatal injection of NMDA, a glutamate receptor ligand, induced stereotypic behavior, whereas intrastriatal injection of CPP, an NMDA receptor antagonist, reduced stereotypic behavior [54]. Amphetamine induced stereotypy can be enhanced by intracortical administration of D_2 or GABA antagonists, and attenuated by DA or GABAergic agonists (reviewed in [26]). Evidence of the important role of the cortical-basal ganglia circuitry in repetitive behaviors is further demonstrated in studies that alter levels of drug-induced stereotypy by manipulations to the Substantia Nigra pars reticulata (SNpr) and Subthalamic Nucleus (STN). The SNpr sends GABAergic projections to the thalamus as part of the direct pathway of the basal ganglia (see following sections), whereas the STN sends glutamatergic projections to the SNpr as part of the indirect pathway. Increased stereotypy as a result of intranigral GABA agonist administration and reduced stereotypy by injection of serotonergic antagonists into the STN, manipulations that alter inhibitory tone in the thalamus either directly or indirectly, thus support the hypothesized role of these structures and respective pathways in repetitive behavior (reviewed in [26]). Finally, Grabli et al. [55] have reported induction of stereotyped behavior (e.g. licking and biting of fingers) in monkeys by the GABA antagonist bicuculline microinjected into the limbic aspect of the GPe (part of the indirect pathway). In a follow-up study, this group showed that Deep Brain Stimulation (DBS) applied to the STN dramatically reduced these drug-induced repetitive behaviors [56].

Repetitive behavior following environmental restriction

Abnormal repetitive behaviors are commonly seen across species maintained in confined or restricted environments (e.g. zoos, farms, laboratories) [57], or reared under conditions of early social deprivation (e.g. [58,59]). Estimated numbers of stereotypic captive animals exceed 85 million [60], supporting repetitive behavior as the most common category of abnormal behavior observed in environmentally restricted animals [61]. Some examples of confinement-induced repetitive behavior include bar-biting in sows and laboratory mice; pacing in bears, monkeys, and birds; and head-twirling in mink [57]. Our own work shows that deer mice reared in standard laboratory caging display high levels of vertical jumping and backward somersaulting; behaviors that appear early in development and persist through adulthood (e.g. [62,63]).

Environmental restriction has also been shown to be associated with cognitive inflexibility, as well as motor stereotypies. This has been demonstrated using an extinction task with bears as well as bank voles [64,65]. Orange wing Amazon parrots with higher motor stereotypy scores exhibited greater sequential dependency in a variation of a gambling task, which indexed the tendency to repeat responses or perseverate [19]. In our own work, we tested deer mice in a procedural reversal learning task that involved learning to turn right or left in a T-maze for reinforcement. Following acquisition, the reinforced arm was reversed. Our results indicate that high levels of stereotypy in deer mice were associated with deficits in reversal learning in the T-maze [18].

Environmental enrichment: Compelling evidence for the causative role of environmental restriction on the induction of repetitive behavior comes from studies of environmental enrichment. Enrichment has been shown to induce rapid, profound and persistent effects on brain and behavioral development [66]. Moreover, studies of rodent models of various brain disorders have highlighted the impact of environmental enrichment on attenuating disease onset, progression and severity [67]. Not surprisingly then, enrichment studies using multiple species have consistently shown that animals reared in complex environments show less stereotypic behavior than their environmentally restricted counterparts [26,68]. Moreover, we have shown that enrichment not only improved motor stereotypies, but also increased cognitive flexibility in a reversal learning task [18].

Enrichment has been shown to impact a large number of measures of brain structure and function. For example, exposure to an enriched environment increased cortical thickness, dendritic length and spine density, and synaptic plasticity [67,69]). Despite decades of research on the neurobiological effects of enrichment, however, neurobiological mechanisms by which such experience alters repetitive behavior are

still largely unidentified. Our own work using a deer mouse model demonstrated that environmental enrichment induced changes in cortical-basal ganglia circuitry (e.g. increased striatal dendritic spine density and Brain-derived neurotrophic factor (BDNF) that were selectively associated with reduced stereotypic behavior [63,70,71]. Moreover, we have shown that enrichment related changes in repetitive behavior were associated with increased indirect basal ganglia pathway activation [18].

Repetitive behavior in inbred mouse strains

Inbred strains of mice have become the most frequently employed model for studying human brain disorders. Thus, identifying an inbred strain that exhibits repetitive behavior not requiring a specific perturbation (lesion, drug or genetic mutation) would be of significant importance to the field. Indeed, at least two inbred strains appear to be good candidate models. The BTBR mouse has been advanced as exhibiting a number of autistic-like traits [72], including repetitive behavior in the form of elevated levels of self-grooming [24,72]. Interestingly, the mGluR5 antagonist, MPEP, was found to decrease repetitive self-grooming in these animals selectively [73]. To address the resistance to change/insistence on sameness behavioral domain, Amodeo et al. [22] employed a spatial reversal learning task with BTBR mice. Compared to C57BL/6 mice, BTBR mice performed similarly to controls in acquiring the spatial discrimination, but were impaired on reversal learning. Interestingly, this impairment was only observed when feedback for a correct choice was decreased to an 80% probability (i.e. occasional lack of reinforcement for a correct choice, with occasional reinforcement for an incorrect choice). BTBR mice also display inflexibility in the exploration of a hole-board and more patterned sequences in sequential investigations of a novel object, suggesting this strain demonstrates both cognitive inflexibility and stereotypic motor behaviors [24,74].

The second inbred mouse strain that would seem to hold considerable promise for furthering our understanding of the neurobiology of repetitive behavior is the C58 strain. The UNC group reported repetitive hindlimb jumping and persistent backflipping in these mice [74,75]. Of note, the former topography was observed in some mice prior to weaning. Subsequently, we [23] have confirmed these observations showing that compared to C57BL/6 mice, C58 mice exhibited high rates of spontaneous hindlimb jumping and backward somersaulting reaching asymptotic levels by 5 weeks post-weaning. We also showed that six weeks of environmental enrichment following weaning substantially reduced repetitive behavior. In our hands, C58 mice did not exhibit increased marble burying, nor did they display reduced exploratory behavior in the hole-board task. Further investigation of cognitive inflexibility in this strain will be important in determining the utility of this model for modeling resistance to change/insistence on sameness.

Cortical Basal Ganglia Circuitry and Repetitive Behavior

The models reviewed in the previous sections highlight the fact that repetitive behavior in animals, consistent with what we know in humans, can have multiple etiologies or inducing conditions. These include, but are not limited to gene alterations, lesions, toxicants, anti-neuronal antibodies and restricted environments. There is some, but limited evidence that these etiologies share a common pathophysiology: alterations in cortical-basal ganglia circuitry. For example, some of the genetic mutations reviewed impact cortico-striatal glutamatergic synapses, whereas some anti-neuronal antibodies associated with repetitive behavior are directed at basal ganglia. Selective pharmacological agents that induce repetitive behavior have molecular targets expressed in basal ganglia, and environmental restriction associated with repetitive behavior alters basal ganglia functioning.

Cortical basal ganglia circuitry involves pathways that project from select areas of cortex to striatum, then to other basal ganglia nuclei (globus pallidus, substantia nigra), then to thalamus and finally back to cortex [76]).This cortico-striato-thalamo-cortical circuitry is thought to be comprised of multiple, parallel loops that while interacting are functionally and anatomically distinct [77,78]. Five loops have been proposed based on their cortical targets: the motor, occulomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate loops. From a functional perspective, three loops are generally considered: the sensorimotor (motor and oculomotor), associative (dorsolateral prefrontal), and limbic (lateral orbitofrontal and anterior cingulate) loops. These loops mediate motor, cognitive and affective functions, respectively. Of these, the motor circuit has been the most studied and emerges as the best candidate for mediation of repetitive motor movements. The limbic loop may be the best candidate for mediation of some "higher order" repetitive behaviors, particularly compulsions. This hypothesis is based largely on neuroimaging studies of individuals with obsessive compulsive disorder or OCD [79,80].

Each of these cortical basal ganglia loops makes use of two distinct basal ganglia pathways that originate from the striatum or caudate-putamen. The striatum is made up of medium spiny GABAergic projection neurons that receive input from sensory-motor and associative areas of cortex, and in turn, give rise to the direct and indirect pathways. Approximately, half of striatal neurons express the neuropeptide dynorphin as well as D_1 dopamine receptors and A_1 adenosine receptors, and constitute striatonigral or direct pathway neurons. These neurons send projections from the striatum to the internal segment of the globus pallidus (GPi) and Substantia Nigra pars reticulata (SNpr). Striatal medium spiny neurons that express the neuropeptide enkephalin, as well as D_2 dopamine receptors and A_{2A} adenosine receptors constitute striatopallidal or indirect pathway neurons. Indirect pathway neurons project to the external segment of globus pallidus (GPe), and then to subthalamic nucleus before projecting to GPi and SNpr. Output from the GPi/SNpr goes to thalamus, and then on to cortex to complete the circuitry [81]. The classic view has been that the direct pathway facilitates movement via disinhibition of glutamatergic thalamo-cortical firing, whereas the indirect pathway inhibits ongoing movement via inhibition of thalamo-cortical afferents [82].

Indirect basal ganglia pathway and repetitive behavior

Work from our lab using the deer mouse model of spontaneous repetitive behavior (e.g., [62,83-87]) has indicated that reduced indirect basal ganglia pathway activation mediates the expression of high levels of repetitive behavior. For example, as dynorphin and enkephalin serve as markers for direct and indirect pathway neurons, respectively, we measured the concentrations of these striatal neuropeptides in animals exhibiting high or low levels of repetitive behavior [84]. Results indicated significantly decreased enkephalin content in high-stereotypy mice, relative to low-stereotypy mice. Moreover, a significant negative correlation was found for enkephalin content and frequency of stereotypy. To extend these findings, we assessed indirect pathway activation relative to stereotypy by measuring neuronal metabolic activation of the Subthalamic Nucleus (STN), a key brain region in the indirect pathway [87]. Using Cytochrome Oxidase (CO) histochemistry to index long-term neuronal activation, we found that CO staining in the STN was significantly reduced in high-stereotypy mice. Further,

CO staining was significantly negatively correlated with the frequency of stereotypy. Consistent with reduced glutamatergic innervation from STN, high stereotypy was also strongly associated with decreased CO staining in SNpr [87]. Thus, higher rates of spontaneous stereotypy were associated with reduced neuronal activation of the indirect pathway.

In order to confirm the role of the indirect pathway in our model, we have used selective pharmacological agents to alter the activity of this pathway. Results from these experiments show that drug combinations designed to increase the activity of the indirect pathway markedly, and selectively reduce repetitive behavior in deer mice [87]. Moreover, unpublished results indicate that drug combinations designed to suppress the activity of the indirect pathway significantly increased repetitive behavior. Beyond providing compelling evidence for the role of the indirect pathway in repetitive behavior, these findings point to specific potential therapeutic targets for drug development.

Summary

There are a number of animal models that have a robust repetitive behavior phenotype. Moreover, these models represent a variety of etiologies or inducing conditions, consistent with the clinical literature. A critical question to be pursued is to what extent these various etiologies share a common or overlapping pathophysiology. A number of models have not yet been systematically pursued to determine how a particular insult (genetic mutation, lesion, toxicant), rearing condition, or genetic background alters neuronal signaling and neural circuitry to induce a complex behavior. The inbred mouse strains reviewed exhibit a robust repetitive behavior phenotype, and provide a particularly promising vehicle for identifying important neurobiological mechanisms (e.g. differential gene expression) and altered neural circuitry mediating repetitive behavior. The link between altered immune function and repetitive behavior is an intriguing one and should be pursued using animal models. Identifying the role of maternal infection or maternal antibodies in the genesis of RRB using animal models would have substantial translational value.

A great deal of effort needs to be directed towards using animal models to understand the pathophysiology of repetitive behavior, as this is key to developing new effective treatments. To date, work directed at identifying specific potential therapeutic targets for drug development to treat RRB using animal models has been very limited. This is a critical need in the field as there are few, if any, pharmacological interventions for the treatment of restricted, repetitive behavior in ASD with established efficacy [11]. In that regard, very little of the work we have reviewed generally has been treatment focused, including testing novel behavioral or biological treatments. Environmental enrichment has been examined by us and others as an experiential intervention [57,68,87]. Novel psychopharmacological treatments have been largely limited to testing a mGluR5 antagonist [88,89], and our work examining drug combinations targeting receptor complexes expressed on indirect pathway neurons [87,90]. Greater use of animal models of RRB to test potential treatments would increase the translational value of such models, substantially.

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