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The pathophysiology of restricted repetitive behavior

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Abstract Restricted, repetitive behaviors (RRBs) are heterogeneous ranging from stereotypic body movements to rituals to restricted interests. RRBs are most strongly associated with autism but occur in a number of other clinical disorders as well as in typical development. There does not seem to be a category of RRB that is unique or specific to autism and RRB does not seem to be robustly correlated with specific cognitive, sensory or motor abnormalities in autism. Despite its clinical significance, little is known about the pathophysiology of RRB. Both clinical and animal models studies link repetitive behaviors to genetic mutations and a number of specific genetic syndromes have RRBs as part of the clinical phenotype. Genetic risk factors may interact with experiential factors resulting in the extremes in repetitive behavior phenotypic expression that characterize autism. Few studies of individuals with autism have correlated MRI findings and RRBs and no attempt has been made to associate RRB and post-mortem tissue findings. Available clinical and animal models data indicate functional and structural alterations in cortical-basal ganglia circuitry in the expression of RRB, however. Our own studies point to reduced activity of the indirect basal ganglia pathway being associated with high levels of repetitive behavior in an animal model. These findings, if generalizable, suggest specific therapeutic targets. These, and perhaps other, perturbations to cortical basal ganglia circuitry are mediated by specific molecular mechanisms (e.g., altered gene expression) that result in long-term, experience-dependent neuroadaptations that initiate and maintain repetitive behavior. A great deal more research is needed to uncover such mechanisms. Work in areas such as substance abuse, OCD, Tourette syndrome, Parkinson's disease, and dementias promise to provide findings critical for identifying neurobiological mechanisms relevant to RRB in autism. Moreover, basic research in areas such as birdsong, habit formation, and procedural learning may provide additional, much needed clues. Understanding the pathophysioloy of repetitive behavior will be critical to identifying novel therapeutic targets and strategies for individuals with autism.

Keywords Autism · Neurodevelopmental disorders · Stereotypy · Compulsions · Rituals · Cortical-basal ganglia circuitry

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Phenomenology of repetitive behavior

Repetitive behavior refers to a broad class of responses characterized by their repetition, rigidity or inflexibility, and frequent lack of obvious function. Repetitive behaviors described in individuals with autism spectrum disorders (ASD) include stereotyped motor movements, repetitive manipulation of objects, repetitive self-injurious behavior, specific object attachments, compulsions, rituals and routines, an insistence on sameness, repetitive use of language, and narrow and circumscribed interests [1, 2]. Turner [2] conceptualized these various categories of restricted repetitive behaviors (RRB) as falling into two clusters: "lower-order" motor actions (stereotyped movements, repetitive manipulation of objects) that are characterized by repetition of movement, and more complex or "higher-order" behaviors (compulsions, rituals, insistence on sameness, and circumscribed interests) that have a distinct cognitive component characterized by an adherence to some rule or

mental set (e.g., needing to have things "just so") and reflect rigidity or inflexibility (Fig. 1) [1–3]. Factor analyses [4, 5] using relevant items from the Autism Diagnostic Interview-Revised (ADI-R) have supported this categorization yielding two factors: repetitive sensory motor behavior and resistance to change/insistence on sameness. Indeed, a recent factor analysis of the structure of the autism symptom phenotype yielded three factors or domains, two of which involved repetitive behavior (inflexible language and behavior, and repetitive sensory and motor behavior) whereas the third factor was social-communication [6]. Lam et al. [7] replicated these two repetitive behavior factors but also found evidence for a third factor that they termed circumscribed interests.

RRB in other disorders

RRB is a common feature of a number of other neurodevelopmental disorders with (e.g., Rett, Fragile X, Prader-Willi syndromes) or without an identifiable genetic defect. In some cases, these neurodevelopmental disorders include expression of other autistic traits or autistic-like behavior (e.g., Fragile X). In other cases, such as idiopathic intellectual and developmental disability, there is less phenomenological overlap with autism [8]. Moreover, RRBs are also part of the phenotype of other CNS disorders including obsessive-compulsive disorder, Tourette syndrome, schizophrenia, and fronto-temporal and Alzheimer's dementia [9–12]. Other conditions including congenital blindness [13] and early social impoverishment [14, 15] are also associated with aberrant repetitive behavior. This shared phenomenology over a number of clinical disorders and conditions has important implications and challenges for identifying pathophysiological mechanisms of RRB in autism. The most obvious implication is that repetitive behavior likely arises from multiple etiologies or sources of CNS insult. Another obvious implication is that such behavior, given its complexity and heterogeneity, is mediated by complex circuitry which can be dysregulated via a number of disparate perturbations (e.g., early social deprivation, gene x environment interactions, etc.).

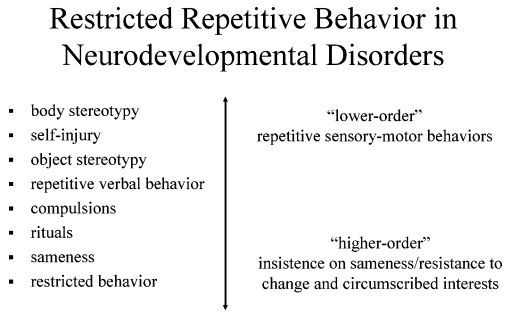

Fig. 1 Specific categories of restricted repetitive behavior ranging from "lower order" or motor behavioral to "higher order" or cognitive behavioral based on Turner [2]

RRB and normative development

Any consideration of the pathophysiology of repetitive behavior in autism must take into account the ubiquity of RRB in normative development (e.g., [16, 17]). Throughout early childhood, children engage in a number of repetitive motor (e.g., swaying, rocking, flapping) and compulsive and ritualistic behaviors (e.g., insistence on certain clothing or foods, bedtime rituals) [18]. Thelen [19] showed, for example, that infants engaged in a wide variety of repetitive, rhythmical behavior that peaked in frequency at 24 months of age and consumed approximately 40% of their time. During the preschool years, children begin to exhibit more complex repetitive behaviors that are characterized by a surprising rigidity or inflexibility. They may show an insistence on sameness, rigidity in terms of likes and dislikes, ritualization of daily activities, and even compulsive ordering and arranging until some subjective criterion of "just right" is met [17]. Attachment to a favorite object and perseverating on certain thoughts and topics are also common in preschoolers. Typically developing children also exhibit intense, restricted interests. These intense interests can appear as early as 2 years of age or younger, be relatively long lasting, be exhibited in multiple contexts, and come to the attention of non-family members [20].

As Symons et al. [21] have pointed out, very little is known about the developmental course of repetitive behaviors in children at risk for autism. The continuities and discontinuities in the normative and pathological expression of these behaviors have not been the subject of systematic study. The developmental timing of the transition from normative to pathological repetitive behavior has not been examined, nor have the biological and environmental mechanisms that mediate this transition and the persistence of repetitive behavior. Developmentally normative repetitive behavior calls for a dimensional rather than a categorical, or "disease state," approach. Consistent with this would be an emphasis on mechanisms of experience-dependent neuroplasticity, reviewed in a later section, that drive the shift from normative to pathological.

Specificity of RRB in autism

An important question to consider is whether individuals with ASD have a unique pattern of RRB and whether this implies differential pathophysiology. It also raises the question of whether different neurobiological mechanisms mediate repetitive sensory motor behavior versus resistance to change versus circumscribed interests.

We do know that children with ASD between the age of 18 months and 24 months exhibit more frequent repetitive sensory motor behavior and for a longer duration than both intellectually disabled and typically developing controls [22]. This finding, when added to similar observations of older subjects and matched controls [23–27], does not suggest, however, a qualitatively different set of behaviors. Bodfish et al. [8] assessed the occurrence of specific topographies of repetitive behaviors as well as their severity in individuals with intellectual disability with and without autism. The occurrence of each behavior category, except dyskinesias, was higher in the autism group. In addition, autistic subjects exhibited a significantly greater number of topographies of stereotypy and compulsions and significantly greater severity ratings for compulsions, stereotypy, and self-injury. Again, these differences are largely quantitative, not qualitative. Examination of compulsive behavior in autism suggests little difference in expression from individuals with obsessive compulsive disorder (OCD). McDougle and colleagues reported that individuals with OCD have more cleaning, checking, and counting behavior, and individuals with autism have more hoarding, ordering, touching/tapping/rubbing, and self-injurious behaviors [28]. When controlling for intellectual level, however, adults with high functioning autism exhibited similar frequencies of OC symptoms to adults with a primary diagnosis of OCD, with only somatic obsessions and repeating rituals being more common in the OCD group [29].

Routines and rituals do seem to occur at a much higher rate in children with autism than age and ability matched control subjects [26, 30, 31]. Moreover, Szatmari et al. [27] reported insistence on sameness and circumscribed interests to be significantly more common in high-functioning individuals with autism than in socially odd psychiatric control subjects. Thus, an elevated pattern of occurrence and severity of RRB, particularly rituals and restricted interests, appears to distinguish autism from other disorders [7, 8, 30]. Repetitive behavior is not specific to autism, however, and no single type (or factor) of RRB is pathognomonic to autism.

Cognitive, sensory, and motor abnormalities and RRB

A related question is whether there are specific cognitive, sensory, or motor abnormalities that co-occur with RRB and provide clues to its pathophysiology. In the cognitive domain, the genesis and maintenance of repetitive behavior has been conceptualized as consequent to deficits in executive function [32]. Executive function is a broad category of cognitive processes involved in the planning and execution of flexible, goal-directed behavior [33]. Aspects of impairment in executive function have been widely demonstrated in individuals with autism, irrespective of intellectual capability. Much of the work suggests impairment in cognitive flexibility [33–35] as well as set shifting and inhibition of pre-potent responses. These deficits would seem to be consistent with "higher order" repetitive behaviors, and indeed, repetitive behavior symptoms have been related to performance deficits in executive functioning tasks [32, 36]. Evans et al. [37] have shown that some executive function tasks, such as set-shifting and response inhibition/motor suppression, are related to the frequency and intensity of compulsive behaviors in typically developing children. In the Lopez et al. study [36], the degree of restricted, repetitive behavior in individuals with autism was correlated positively with deficits on tasks that index cognitive flexibility. Importantly, this association was observed after controlling for level of cognitive function. It should be noted, however, that other groups have either provided only partial support [38] or failed to find a significant association between repetitive behaviors and aspects of executive functioning [39]. In a recent review, Geurts et al. [40] have concluded that there is no consistent evidence for cognitive flexibility deficits in autism and that the link between cognitive flexibility and restricted, repetitive behavior has not been clearly established [40].

Weak central coherence or the preferential processing of specific or local features of the environment rather than global features has also been invoked to account for RRB in autism. Specifically, individuals who exhibit weak central coherence would be expected to have high levels of restricted, repetitive behavior. In typically developing young children, Evans et al. [41] observed that higher levels of repetitive behavior were associated with better performance on the Embedded Figures Task. In children with ASD, however, either a weak association [42] or no association was noted between repetitive behavior and central coherence [43].

In general, sensory processing abnormalities are frequently reported in autism and have been linked to restricted, repetitive behavior [2, 44–46]. Indeed, preoccupation with sensory features (e.g., texture) of stimuli is included as a repetitive behavior in the ICD-10. Repetitive behaviors have been theorized to provide a mechanism to modulate sensory problems resulting in reduced or increased levels of stimulation. Nonetheless, as Rogers and Ozonoff [47] have concluded in a recent review, sensory symptoms do not differentiate autism from other developmental disorders. Moreover, abnormal sensory responses and repetitive behaviors are clearly differentiable. Although there is little evidence functionally linking sensory abnormalities to repetitive behavior, Chen et al. [42] found that, in children with autism, more severe sensory processing abnormalities were associated with more restricted, repetitive behavior.

Motor impairments in children with ASD, including clumsiness, motor incoordination, postural instability, and

poor performance on standardized tests of motor functioning, have been reported [48–54]. There are also reports of children with ASD with delayed or abnormal attainment of developmental milestones, such as skipping the crawling stage, asymmetry in arms and/or legs when crawling, or uncoordinated arm and leg swings when walking [55, 56]. It is certainly reasonable to hypothesize that an association exists between motor impairments and, particularly, repetitive sensory motor behaviors. Nonetheless, such a relationship has not been systematically established in autism. Bodfish et al. [57] assessed postural stability in individuals with intellectual and developmental disabilities, with and without stereotyped behavior using a force platform and computerized posturographic techniques. The results showed that the stereotypy group demonstrated markedly different postural movement profiles versus controls and demonstrate that motor control deficits are associated with stereotypy.

In summary, there is little evidence for robust associations between repetitive behavior and specific cognitive, sensory or motor impairments. Thus, abnormalities in these domains identified in individuals with autism would not appear to provide much useful information relevant to the pathophysiology of restricted repetitive behavior.

Genetics of restricted repetitive behavior

Autism spectrum disorder (ASD) has a strong genetic component with complex inheritance. Concordance rates in monozygotic twins have been reported to range from 60–91% as compared to the 0–10% range reported for dizygotic twins [58, 59]. The sibling recurrence rate has been estimated to be 4.5% [60] and estimates of the number of genes involved in ASD range from 3–10 [61, 62] to more than 15 [63]. Several candidate loci for autism have been reported, although there has been little replication across studies. Phenotypic heterogeneity has no doubt confounded the identification of autism susceptibility genes. Therefore, there has been an effort to facilitate genetic research by stratifying sample into more homogeneous groups using "sub-phenotypes," such as age of first words or phrases spoken [7, 64, 65]. RRB may also be used to identify homogenous subgroups within autism [7].

Several lines of evidence indicate that circumscribed interests, rituals, and compulsions have an underlying genetic component. In autism, the repetitive behavior phenotype shows a strong tendency to run within families, indicating a common genetic etiology. Moreover, restricted, repetitive behavior is likely influenced by genes that are largely independent of those that influence the social or communication deficits that make up the remaining diagnostic domains of autism [66–68]. Similar indications come from assessment of behavioral subtypes within OCD, where high levels of particular behaviors, such as symmetry/ordering or obsessions/checking, confer greater genetic risk among relatives [69].

Use of the restricted, repetitive behavior phenotype has been shown to reduce heterogeneity and has led to the identification of potential ASD susceptibility genes. For example, Shao et al. [70] have found increased linkage evidence at the *GABRB3* locus in 15q11-q13 region in families sharing the insistence on sameness factor score. Recently, Brune et al. [71] reported an association between 5HTTLPR long/long genotype of the serotonin transporter gene (*SLC6A4*) and repetitive sensory-motor behaviors.

Autism family studies have also suggested the familiality of RRB. Silverman et al. [68] examined 212 siblingships with at least one autistic proband and another sibling with either autism or an ASD ("broadly defined multiplex siblingships") ascertained by the ADI-R for sibling concordance pattern of RRBs. Among these, 136 siblingships were defined as "autism multiplex siblingships," while the rest were "broadly defined multiplex siblingships." In this study, evidence for familiality was defined as significantly reduced variability by analysis of variance and covariance in autistic-related domains within siblingships. The familiality of RRB was examined using the ADI-R subdomain and individual scores. Statistically significant familiality was found for D1 (encompassing preoccupation/circumscribed pattern of interest) and D2 (apparently compulsive adherence to nonfunctional routines/rituals) subdomain scores on the ADI-R, especially for encompassing preoccupation/circumscribed patterns of interest and apparently compulsive adherence to nonfunctional routines/rituals. All of the ADI-R items contributing to these categories were also significant. The autism multiplex siblingships had RRB scores suggestive of higher familiality than the whole group ("broadly defined multiplex siblinghips") probably due to reduced heterogeneity. Interestingly, stereotyped and repetitive motor mannerisms (D3 subdomain) and preoccupation with parts of objects or nonfunctional elements of materials (D4 subdomain) did not appear to have significant familiality in studied siblingships. Similar to this study, Szatmari et al. [5] also found evidence for moderate familial aggregation among affected sibling pairs within the Insistence on Sameness (IS) factor in 339 individuals with ASD.

15q11-q13 and RRB

The chromosome 15q11-q13 region has been implicated in autism and RRB, based on the following observations: 1) maternal duplication of this region is the most common chromosomal abnormality associated with autism [72–81]; 2) genetic markers near *GABRB3* within the 15q11-q13 region have been implicated in autism through both linkage and association studies [70, 82–90]; and 3) clinical and

genetic overlaps between Prader-Willi syndrome (PWS) and ASD. PWS is a rare genetic disorder caused by the structural or functional absence of paternally inherited genes in the 15q11-q13 region. The majority of PWS individuals suffer from high levels of RRB, [91–94] and an increased rate of ASD has been reported among individuals with PWS [95].

As indicated, chromosome 15q11-q13 harbors a set of three GABA receptor subunit genes (*GABRB3*, *GABRA5*, and *GABRG3*). For example, Shao et al. [70] developed a novel statistical method, ordered-subset analysis (OSA), to identify a homogeneous subset of families that contribute to overall linkage at a given chromosomal location, and thus to potentially help in the fine mapping and localization of the susceptibility gene within a chromosomal area. In their analysis, increased linkage at the *GABRB3* locus in 15q11-q13 region was observed in families sharing a high insistence on sameness factor score. Furthermore, four other GABA system genes (*GABRA4*, *GABRB1*, *GABRR2*, and *ABAT*) have been also associated with autism [96–98].

Dopamine genes and RRB

Pharmacological studies have established the importance of the nigrostriatal dopamine pathyway in the mediation of stereotypies [1]. Administration of indirect and direct acting dopamine agonists or repeated administration of a potent and selective dopamine uptake inhibitor has been shown to induce stereotypic behaviors or self-mutilation [99, 100]. The severe repetitive self-injurious behaviors in patients with Lesch-Nyhan syndrome have been associated with markedly fewer dopaminergic nerve terminals and cell bodies [101]. Other dopamine related genes implicated in RRB include catechol-o-methyltransferase (COMT) and dopamine transporter (DAT) genes. *COMT* is a strong candidate gene for schizophrenia, another RRB associated disorder, due to its role in dopamine metabolism and the location of the gene within the deleted region in Velocardiofacial syndrome, a disorder associated with high rates of schizophrenia. *DAT* knockout mice, so called "hyper-dopaminergic mutant mice" showed greater invariance in complex fixed action patterns suggesting an association between abnormal dopamine levels and repetitive behaviors [102]. However, few molecular genetic studies have examined the association between dopamine system related genes and autism and there is no evidence to date for dopamine genes playing a role in RRB in autism.

Glutamate genes and RRB

The excitatory neurotransmitter glutamate has been implicated in RRB, based on its role in cortico-striatal-thalamic-cortical circuitry. Moreover, spontaneous repetitive behavior in mice appears to be mediated, at least in part, through the cortico-striatal glutamatergic system [103, 104]. Furthermore, *SLC1A1*, a glutamate transporter gene, has been identified as a susceptibility gene for obsessive compulsive disorder (OCD) [105, 106] and was one of several genes centered under the highest linkage peak in the recently completed Autism Genome Project scan [80]. In addition, several lines of evidence implicate glutamate system genes as autism risk genes [107] including evidence for a positive association between two glutamate receptor subunit genes (*GRIK2* and *GRIN2A*) and autism [98, 108, 109].

Other candidate genes related to excitatory synapses include two neuroligin genes (*NLGN3* and *NLGN4X*), neurexin 1, neurexin 3 and *SHANK3*. Neuroligins function as ligands for the neurexin family of cell surface receptors. Interestingly, two putative missense variants and hemizygous deletion of coding exons of neurexin 1 (*NRXN1*) have been also reported in ASD [80, 110]. Furthermore, a strong linkage signal to compulsive hoarding was detected near neurexin 3 (*NRXN3*) among multiplex OCD families with two or more hoarding relatives [111]. SHANK3 is related to Prosap1 in rat, a scaffold protein highly enriched in the postsynaptic density of excitatory synapses [112]. *SHANK3* is one of the genes disrupted in patients with the 22q13.3 deletion syndrome but has yet to be implicated in RRB [113]. In mice, overexpression and deletion of genes that code for other glutamate synapse proteins were shown to result in repetitive behavior (see "Animal models of restricted repetitive behavior").

Serotonin genes and RRB

The serotonin transporter (5-HTT) has been considered a strong candidate gene for autism based on reports of hyperserotonemia and the efficacy of selective 5-HT reuptake inhibitors (SSRIs) in treating repetitive behaviors. Although association studies involving the functional insertion/deletion polymorphism in the promoter (5-HTTLPR) and a polymorphism in intron 2 have been inconclusive (possibly due to phenotypic heterogeneity), several groups identified evidence for genetic linkage of autism to the chromosome 17q11.2 region that harbors the 5-HTT locus (*SLC6A4*) [88, 114–116]. In a family based association study, Sutcliffe et al. (2005) found an association between novel variants at the serotonin transporter locus (*SLC6A4*) and rigid compulsive behavior. Additionally, Brune et al. [71] also found an association between 5-HTTLPR long/long genotype of the serotonin transporter gene (*SLC6A4*) and repetitive sensory-motor behaviors.

Associations of the 5-HT transporter and RRB are consistent with the dense innervation of cortical-basal ganglia circuitry by 5-HT and the expression of many of the 5-HT receptor sub-types in basal ganglia [117]. In

addition, serotonin provides most of the innervation of the pre-frontal cortex including the motor cortex and 5-HT projections from raphe nuclei innervate both dopaminergic and GABAergic cells in substantia nigra and their terminal fields. Functionally, tryptophan depletion was shown to worsen repetitive motor behaviors in adults with autism [118] and 5-HT_{1D} agonist-induced growth hormone response was positively correlated with baseline compulsion scores in subjects with autism [119].

Genetic syndromes associated with RRB

Specific, relatively rare, genetic syndromes are also associated with RRB [120]. PWS (OMIM 176270), caused by an absence of paternal contribution in the 15q11-q13 region, with an estimated incidence rate of ~1 in 15,000 [121], has shown to be associated with substantial RRB [91–94]. Skin-picking is reported in 69–100% of individuals with PWS [91, 122–126]. Prominent obsessive compulsive symptoms (hoarding, ordering/arranging, concerns with symmetry/exactness, rewriting, need to tell/know/ask) were also reported in 37–58% of individuals with PWS [127]. A recent study also confirmed that individuals with PWS have higher hoarding behavior and preference for routines when compared with other genetic syndromes associated with RRB; however, this study revealed lower stereotypic and tidying up behaviors [120]. Absence of maternally inherited genes in the same chromosomal locus produces Angelman syndrome (OMIM 105830, AS). Although more severely affected than PWS patients [128, 129], individuals with AS exhibit a less severe repetitive behavior phenotype which includes stereotypic hand flapping and fascination with water [130].

Fragile X syndrome (OMIM 300624, FXS) is the most common inherited cause of intellectual disability and autism. FXS is caused by an expansion of a single trinucleotide gene sequence (CGG) in the FMR-1 gene, and results in a failure to express the FMR-1 protein that is required for normal neural development. Individuals with FXS show a high frequency of occurrence of hand flapping, tidying up, lining up, restricted conversation, echolalia, preference for routines, just right behavior, repetitive phrases and restricted interests [120, 131, 132].

Rett syndrome (OMIM 312750, RS), a pervasive developmental disorder, is caused by mutations in the gene *MECP2* located on the X chromosome (Xq28) and occurs almost exclusively in females. The affected infants show normal prenatal and postnatal development for the first 5 months, which is followed by a deceleration of head growth rate, loss of acquired skills, impairments in social communication, and characteristic stereotypic repetitive hand movements such as mouthing or wringing [133].

Cri-du-Chat syndrome (OMIM 123450) caused by a missing part of chromosome 5 (5p15) [134] is associated with moderate to severe mental retardation as well as stereotypic body rocking, echolalia, and attachments to objects [120, 135, 136]. Cornelia de Lange syndrome (OMIM 122470, 300592, 610759) is caused by mutations in genes encoding components of cohesion complex, such as the *NIPBL* gene in the 5p13, the *SMC1L1* gene in the Xp11.2, and the *SMC3* gene in the 10q25. Cornelia de Lange syndrome is also associated with mild to profound mental retardation, stereotypic movements (e.g., body rocking, body postures), spinning objects, lining up, tidying up, and ritualistic behavior [120, 137, 138].

Lowe syndrome (OMIM 309000; Oculocerebrorenal syndrome) is an X-linked recessive disorder associated with the gene *OCRL*, and characterized by hydrophthalmia, cataracts, intellectual disabilities, aminoaciduria, reduced renal ammonia production and vitamin D-resistant rickets. The majority of Individuals with Lowe syndrome show repetitive hand movements, and lining up behaviors [120, 139].

Smith-Magenis syndrome (OMIM 182290) is caused in most cases (90%) by a 3.7-Mb interstitial deletion in chromosome 17p11.2. The disorder can also be caused by mutations in the *RAI1* gene, which is within the Smith-Magenis chromosome region. The individuals with Smith-Magenis syndrome show stereotypic body movements (e.g., mouthing objects, hand teeth grinding, body rocking, spinning/twirling, lick and flip), restricted interests, obsession, repetitive speech, ritualistic behavior, and attachment to people (preference for adults) [120, 140–142].

Summary

It is clear that autism has a strong genetic etiology and that genes controlling RRB are likely independent of genes controlling social and communication deficits. Clinical and animal studies have provided only very limited findings with respect to specific genes or genetic loci that may control restricted, repetitive behavior, however. Moreover, repetitive behavior has been linked to mutations at disparate chromosomal loci. This is not surprising given the complexity and heterogeneity of these behaviors. One implication of the genetic findings is that pathological repetitive behavior is mediated by complex circuitry involving a very large number of genes. Mutations of even one or a few such genes could result in significant disruptions to this circuitry and full expression of the behavioral phenotype (e.g., [104]).

Neuropathology of restricted, repetitive behavior in autism

There have been no attempts of which we are aware to link post-mortem neuropathological findings to restricted repeti-

tive behavior in individuals with autism. Indeed, as pointed out by Amaral et al. [143], there is also no evidence from post-mortem studies for basal ganglia or thalamus abnormalities, brain regions often linked to repetitive behavior (see following sections).

There are some neuroimaging findings, however, that link repetitive behavior to regional volumetric differences. For example, Sears et al. [144] reported a significant negative association between caudate volume and three ADI repetitive behavior items: difficulties with minor changes in routine, compulsions/rituals, and complex mannerisms. Hollander et al. [145] found increased right caudate volumes in individuals with autism and reported a positive correlation between right caudate volumes and ADI repetitive behavior domain total scores. This relationship was driven by the association between right caudate volume and the insistence on sameness/resistance to change factor scores. The same pattern was observed when putamen volumes were correlated with repetitive behavior scores. Rojas et al. [146] in a study of regional grey matter volume, found increased right caudate gray matter volume in subjects with ASD after controlling for age and whole brain grey matter volume. In addition, they reported significant positive partial correlations with the ADI-R repetitive and stereotyped behavior domain in the caudate. Similar correlations were also found in the left inferior frontal gyrus and right amygdala. Smaller volumes of the superior temporal gyri, left post-central gyrus and cerebellar regions were associated with worse repetitive behavior domain scores. In a study of exploratory behavior of young children with autism, Pierce and Courchesne [147] found a positive correlation between repetitive behavior exhibited in the experimental setting of an exploration task and frontal lobe volume. This measure of repetitive behavior was negatively correlated with cerebellar vermis volume. These neuroanatomic measures were not associated with ADI-R or ADOS repetitive behavior scores, however.

Restricted repetitive behavior has also been linked to activation of the anterior cingulate cortex (ACC) in a fMRI study of response monitoring [148]. An anti-saccade task, which involves suppression of the pre-potent response of looking toward rather than away from a stimulus, was used. A high functioning ASD group showed significantly higher error rates in the anti-saccade condition and significantly increased ACC activation for correct trials. Moreover, higher ADI-R repetitive behavior scores were associated with greater ACC activation during correct trials with repetitive sensorimotor behavior scores more strongly related to ACC activation than resistance to change/insistence on sameness factor scores. This link between overactive response monitoring and RRB in ASD complements the finding of an exaggerated ACC response to correct trials observed with OCD subjects.

Shafritz et al. [149] examined the neural correlates of both a response shifting and a set shifting cognitive task in individuals with high-functioning autism using fMRI. Compared to controls, individuals with autism showed deficits in response shifting but, surprisingly, not cognitive set shifting. These subjects also showed reduced activation in frontal, striatal, and parietal regions during these trials. The severity of restricted, repetitive behaviors was negatively correlated with activation in anterior cingulate and posterior parietal regions. These data support a relationship between deficits in executive function, restricted repetitive behavior, and fronto-striatal circuitry.

Animal models of restricted repetitive behavior

Animal models relevant to restricted, repetitive behavior in humans generally fall into three classes: repetitive behavior associated with 1) targeted insults to the CNS; 2) administration of specific pharmacological agents; and 3) exposure to restricted environments and experience [150].

Repetitive behavior and targeted CNS insult

A repetitive behavior phenotype has been observed in several mutant mouse models. For example, mice expressing truncated MeCP2 protein exhibit repetitive forelimb movements resembling the distinctive hand stereotypies (e.g., hand-wringing, waving, and clapping) observed in Rett syndrome patients [151, 152]. The *gabrb3* homozygous knockout mouse also shows stereotyped behavior such as intense circling or "tail-chasing" which may continue for hours [153, 154]. As described in a previous section, this gene, which codes for the beta3 subunit of the $GABA_A$ receptor, lies within the q11-13 region of chromosome 15. Deletions of this region are associated with Prader-Willi syndrome, of which compulsive behaviors are a particularly salient feature of the behavioral phenotype [155]. Compulsive grooming leading to hair removal and self-inflicted wounds has been identified as a major behavioral phenotype of the *Hoxb8* homozygous mutant mouse [156] and the *Sapap3* KO mouse [104]. In the latter model, the SAPAP3 protein is expressed selectively in glutamate synapses in striatum, whereas high levels of expression of *Hoxb8* were observed in brain regions known to comprise circuitry mediating OCD symptoms in patients. These models are particularly relevant to trichotillomania (compulsive hair pulling) and self-injurious behavior. Interestingly, an amyloid precursor protein (APP) transgenic mouse model of Alzheimer's disease (TgCRND8) has been reported to exhibit marked stereotypies (e.g., jumping, cage top circling) with the former topography being exhibited exclusively by transgenic animals [157]. This finding is consistent with the

repetitive behavior reported in fronto-temporal dementia and Alzheimer's disease. Of interest given the relationship between Alzheimer's disease and Down syndrome, is the observation that *Ts65Dn* mice, a model for Down syndrome, exhibit repetitive jumping and cage-top twirling [158]. Transgenic animals overexpressing neuroligin2 (*TgNL2*) were shown to have altered synapse development and neuronal excitability. Behaviorally, these animals exhibited limb clasping similar to *MECP2* KO mice and Rett syndrome patients. Moreover, TNL2 but not WT mice exhibited stereotyped vertical jumping in both an open field and the home cage [159].

Other animal models have pointed to the role of non-genomic factors in RRB. For example, exposure to valproic acid on embryonic day 12.5 in rats results in increased time spent engaged in stereotypic activity [160–162]. The stereotypies expressed by the valproate treated rats were attenuated by housing in an enriched environment [163]. Repetitive behavior has also been linked to viral infection and lesion-induced damage during early development. For example, intracerebral inoculation of newborn rats with Borna disease virus results in spontaneous stereotypies [164] and, in non-human primates, early damage to amygdala, hippocampal formation and adjacent temporal cortex resulted in a number of behavioral abnormalities including stereotypies [165]. A delayed (after year 1 of life) emergence of repetitive motor behavior following amygdala or hippocampal lesions in macaque infants has been reported by Bauman et al. [166]. This developmental effect is consistent with rodent work showing a delayed effect of similar lesions on frontal lobes and sub-cortical dopamine function [167]. Interestingly, in the Bauman study, a distinct pattern of repetitive behavior was associated with each type of lesion with amygdala damage inducing self-directed behaviors and hippocampal lesions inducing repetitive head twisting. A very provocative non-human primate study from this same research group [168] provides evidence for a potential autoimmune etiology of repetitive behavior in at least some individuals. Pregnant rhesus monkeys were exposed to IgG purified from serum collected from mothers who had at least two children with ASD. Offspring of monkeys treated in this way exhibited spontaneous whole body stereotypies that persisted in the 6 months following weaning and that were observed in multiple test conditions. Prenatal exposure to IgG purified from mothers of typically developing children had no such effect. Exposure to maternally derived IgGs that cross the placenta has been implicated in other disorders involving tics and compulsive disorder.

It is important to point out that for many of these studies, repetitive behavior was not the focus or rationale for the work. Thus, the repetitive behavior observed following the CNS insult has generally not been well characterized. The Amaral lab studies [166, 168] provide an important exception to this generalization. Further, little systematic effort has gone into investigating the pathophysiology associated with the expression of repetitive behavior in many of the models cited.

Restricted, repetitive behavior in inbred mouse strains

In the course of behavioral testing a variety of inbred mouse strains for autistic-like traits, Moy et al. [169, 170] observed serendipitously that C58/J mice displayed non-drug related stereotyped jumping and backward flipping behaviors. In addition, compared to control strains, these mice exhibit reduced exploratory behavior. A similar behavioral phenotype has been reported in the C57BL/10 strain [171] with mice of this strain exhibiting spontaneous repetitive vertical jumping with no such behavior observed in the closely related C57BL/6 strain. We have confirmed both sets of observations (unpublished findings). These two inbred mouse strains provide an opportunity to model aspects of the abnormal repetitive behavior symptom domain of autism in a model amenable to genetic dissection.

Drug-induced repetitive behavior

By far, most of what has been learned about the neurobiological basis of repetitive motor behavior comes from studies of drug induced stereotyped behavior in animals. Early experiments established the importance of the basal ganglia in the mediation of repetitive behaviors by showing that dopamine or a dopamine agonist (e.g., apomorphine) injected into the striatum induced stereotyped behavior in rats (e.g. [172]). Similarly, intrastriatal administration of the glutamate receptor ligand, NMDA, also induced stereotyped behavior [173]. Intracortical manipulations enhancing the activity of excitatory cortico-striatal projections exacerbate the expression of stereotypy. For instance, administration of either the D_2 antagonist sulpiride or the GABA antagonist bicuculline into the frontal cortex enhances the motor stimulatory effects of amphetamine [174, 175]. Conversely, amphetamine-induced stereotypy can be attenuated via intracortical infusion of DA or GABAergic agonists [175]. Experiments in which the expression of drug-induced stereotypy was shown to be sensitive to manipulations in the substantia nigra pars reticulata (SNpr) and the sub-thalamic nucleus (STN) also support the hypothesized role of cortical-basal ganglia circuitry in repetitive behaviors [176, 177]. These, and many other relevant findings, provide clear evidence of the pre-eminent role played by cortical-basal ganglia circuitry in the expression of repetitive motor behaviors.

Repetitive behavior and environmental restriction

Abnormal repetitive behaviors are commonly displayed in animals housed in restricted (e.g., zoo, farm, laboratory) environments, as well as animals subjected to early social deprivation [178]. Indeed, repetitive behaviors are the most common category of abnormal behavior observed in confined animals [179]. Some examples of aberrant repetitive behaviors observed in animals maintained in confinement include crib-biting and head-shaking in horses [180–182] and head-twirling in mink [183]. Our work has employed deer mice (*Peromyscus maniculatus*) which exhibit repetitive hindlimb jumping and backward somersaulting as a consequence of being reared in standard laboratory caging. These behaviors occur at a high rate, persist across much of the life of the animal and appear relatively early in development, sometimes as early as weaning.

Although experientially-induced stereotypies share some similarities with drug-induced stereotypies, they can be dissociated. For example, in our own studies, neither systemic nor intrastriatal administration of the dopamine agonist apomorphine increased cage related stereotypies in deer mice, although other repetitive behaviors (e.g., stereotyped sniffing) were observed [184, 185]. These results were consistent with work done showing that neither apomorphine nor the NDMA antagonist MK-801 affected environmentally induced stereotypies in bank voles [186, 187].

Finally, animal models focused on repetitive behavior induced by experiential restriction may not, at first glance, seem relevant to autism. We would argue, however, that the early occurrence of social, communicative and adaptive behavior deficits in young children with autism likely markedly attenuate experience-dependent behavioral and brain development. Moreover, there is evidence that environmental restriction (e.g., orphanages) can induce repetitive behavior in children.

Resistance to change/insistence on sameness

Most animal models of repetitive behavior have generally focused on stereotyped motor behaviors which, in animals, are easier to model than, for example, rituals or insistence on sameness. Nevertheless, some animal work has addressed the domain of cognitive rigidity or resistance to change characteristic of RRB. Cognitive flexibility, or resistance to change, can be assessed in animals using a variety of tasks that range in complexity from response extinction to reversal learning to intra- and extradimensional set shifting (e.g., [188]). Recent work conducted with several different species has demonstrated that motor stereotypies are inversely correlated with measures of cognitive flexibility. For example, in bank voles and bears extinction learning was significantly inversely correlated with the amount of environmental restriction-induced stereotypy exhibited [189, 190]. Similarly, Orange wing Amazon parrots were assessed for stereotypy and performance on a variation of a gambling task which indexed the tendency to repeat responses or perseverate. Animals with higher stereotypy scores exhibited greater sequential dependency in their responses on this task [191]. In our own work, we have examined the performance of deer mice in a procedural learning task that involved learning to turn down the right or left arm of 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 [192]. In this study, we showed that environmental enrichment was associated with better reversal learning as well as attenuating stereotyped motor behavior. The relationship between cognitive rigidity (deficits in set shifting, extinction, and reversal learning) and motor stereotypy is perhaps not surprising given the common mediation by cortical-basal ganglia pathways. Much greater emphasis needs to be placed on modeling "higher order" repetitive behaviors in animals in future studies, however.

Neurocircuitry of repetitive behavior

Basal ganglia pathways

The circuitry hypothesized to mediate the expression of repetitive behavior includes pathways that link select areas of cortex and basal ganglia (Fig. 2). The striatum, a key

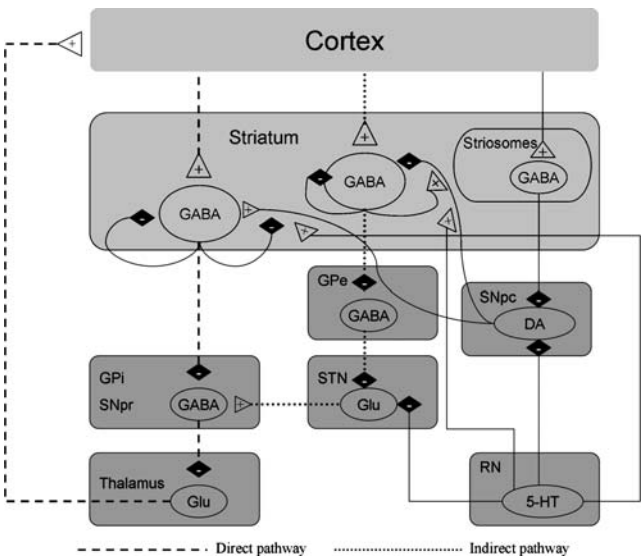

Fig. 2 Schematic of cortical basal ganglia circuitry illustrating direct and indirect basal ganglia pathways as well as the striosomal pathway

component of this circuitry, has a compartmental organization with patchy areas or striosomes distributed throughout an extra-striosomal matrix. Striosomal projection neurons receive input preferentially from limbic cortical areas (e.g., orbitofrontal cortex, anterior cingulate/posterior medial PFC) and, in turn, project to substantia nigra pars compacta [193, 194]. Thus, striosomal projections can directly mediate nigrostriatal dopamine pathway activity and, in turn, influence reinforced behavior. Support for this hypothesis is supported by the work of White and Hiroi [195] who showed that high rates of intracranial self-stimulation (ICSS) were associated with electrode placement either in or next to striosomes. In contrast to reinforced behavior, there is some evidence in rats that the extra-striosomal matrix mediates "normal" sensory-motor function (e.g., grooming, locomotion)[196]. Recent evidence from non-human primates has suggested that striosomal output, at least in these animals, innervates SNpr and GP as well as SNpc [197]. Thus, these pathways also may not be as segregated as once believed.

The matrix compartment of the striatum contains a majority of the medium spiny GABA projection neurons as well as many of its interneurons. These neurons receive projections from sensory-motor and associative areas of cortex, and, in turn, give rise to the direct and indirect pathways. In the direct pathway, D_1 dopamine receptors are co-expressed with glutamate receptors on GABAergic medium spiny neurons of the striatum neurons [198–200]. These neurons also express the neuropeptides dynorphin and substance P as well as A_1 adenosine receptors. These neurons send projections from the striatum to the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). In the indirect pathway, D_2 receptors are co-expressed with the glutamate receptors on striatal medium spiny neurons neurons [198–200]. These neurons also express the neuropeptide enkephalin and A_{2A} adenosine receptors. These 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.

In primates, striatal efferents appear to be highly collateralized and do not innervate GPe, GPi, or SN exclusively [197]. In rats, the large majority of striatal neurons were shown to project to more than one striatal site [201]. In addition, a significant number of neurons express both D_1 and D_2 dopamine receptors as well as enkephalin and Substance P, although direct pathway projection neurons contain high levels of D_1 receptors and low levels of D_2 receptors, with the converse being true for the indirect pathway [202]. Thus, the two pathways are not as segregated as once thought. Nonetheless, this model of basal ganglia function remains a useful framework for examining mechanisms of disordered motor, cognitive, and affective behavior.

Repetitive behavior and cortical-basal ganglia circuitry

The very few studies (reviewed in a previous section) of individuals with autism that have linked MRI findings to restricted repetitive behavior have implicated nuclei (e.g., caudate) that make up cortico-striato-thalamo-cortical circuitry. Additional evidence for altered cortical-basal ganglia circuitry comes from Turner et al. [203] who assessed functional connectivity between caudate and cortical areas in autism spectrum subjects by fMRI during a simple visuomotor coordination task. Compared to matched controls, subjects with autism exhibited atypical connectivity patterns between caudate and cortical areas. Atypical fronto-striatal connectivity was also reported by Horwitz et al. [204] who assessed regional cerebral metabolic rates for glucose using positron emission tomography. The autistic group showed significantly lower correlations of the thalamus and caudate with frontal and parietal region. Indeed, many of these correlations were negative in the autism group and positive in controls. It should be noted, however, that these last two studies did not attempt to assess repetitive behavior or relate such behavior to neuroimaging results. Nonetheless, atypical cortical-basal ganglia connectivity would be consistent with the development and expression of RRB.

Perturbations in cortical-basal ganglia circuitry appear to be associated with repetitive behavior in non-autism populations, as well. For example, Kates et al. [205] compared boys with stereotypies who had no other known developmental or neurological disorder with matched controls. In this study, decreases in frontal white matter were found even after total white matter volume was taken into account. Caudate volumes did not differ between groups when expressed relative to total brain volume. MRI findings have revealed alterations in putamen volume of individuals suffering from trichotillomania or repetitive hair-pulling [206]. Similarly, magnetic stimulation and fMRI studies demonstrate increased cortical excitability and abnormal cortico-basal ganglia activation, respectively, in individuals with Tourette syndrome [207]. Caudate volumes in children with Tourette syndrome predicted the severity of tic and obsessive–compulsive symptoms in early adulthood [208], and, in adults with TS, Peterson et al. [209] showed that during tic suppression, prefrontal cortical, thalamic and basal ganglia areas were activated and that these activations were inversely correlated with tic severity. Finally, considerable evidence from functional imaging studies of OCD patients supports a generalization of altered neuronal activity in key cortical (e.g., orbito-frontal cortex, anterior cingulate) and sub-cortical (caudate

nucleus, thalamus) areas making up cortical basal ganglia circuitry. These studies indicate that symptomatology was significantly correlated with alterations in activation of the orbito-frontal cortex [210] and head of the caudate, particularly. OCD patients have also been reported to have fewer striatal D2 dopamine receptors, suggesting a potential loss of activity of the indirect pathway [211] or reduced number of autoreceptors leading to decreased autoinhibition.

Our studies of early socially deprived non-human primates also support the association of repetitive behavior and alterations in cortical-basal ganglia function. Stereotyped behavior, a predictable consequence of early social deprivation in this species, was associated with dopamine receptor supersensitivity [212], loss of dopamine innervation in striatum and dopamine cells in substantia nigra, and decreases in medium spiny striatal projection neurons as indexed by neuropeptide staining [213].

Further evidence for the importance of cortico-basal ganglia circuitry in repetitive behavior comes from phenotypic studies of the *SAPAP3* knock out mouse [104]. *SAPAP3* is post-synaptic scaffolding protein, highly expressed in striatum, and important in regulating glutamatergic cortico-striatal synapses. Mice homozygous for the gene deletion express a behavioral phenotype involving excessive grooming to the point of inducing lesions to the head, neck, and snout. In addition, these animals exhibited increased anxiety-like behavior in several standard behavioral paradigms and alterations in AMPA and NMDA receptor dependent transmission at cortico-striatal synapses. Interestingly, administration of the serotonin uptake inhibitor fluoxetine given systemically for 6 days reversed the compulsive grooming as well as the anxiety-like behavior. Finally, the behavioral phenotype was rescued by transduction of the *SAPAP3* gene into preweaning mice. This elegant study demonstrates that deletion of even a single protein that functions to maintain the activity of cortical-basal ganglia circuitry can result in a robust repetitive behavior phenotype. Moreover, a SSRI can reverse the effects of loss of a glutamate synapse protein. This suggest that circuitry of this complexity can be effectively modulated in multiple ways and underscores the danger of making inferences about pathophysiology based on treatment. Finally, it provides some evidence for an association of RRB and anxiety.

Grabli et al. [214] have reported that stereotyped behavior (e.g., licking and biting of fingers) was induced in monkeys when the GABA antagonist bicuculline was microinjected into the limbic aspect of the GPe (part of the indirect pathway). In a follow-up study [215], this group showed that deep brain stimulation (DBS) applied to the subthalamic nucleus (STN) dramatically reduced these drug-induced repetitive behaviors without affecting a control motor task. The importance of the STN was also highlighted by Winter et al. [216] who have shown that rats that sustained ibotenic acid lesions to this nucleus exhibited an increase in compulsive lever pressing in the signal attenuation model of OCD. This same research group has also shown that bilateral high frequency stimulation of the STN as well as pharmacological inactivation of the STN reduced compulsive checking in rats induced by the dopamine agonist quinpirole [216]. This latter finding is consistent with clinical observations that DBS applied to the STN reduced the severity of symptoms in previously treatment refractory OCD patients [217].

Our studies with deer mice have shown that early environmental enrichment markedly attenuated the development of stereotypy. Moreover, brain changes associated with this behavioral outcome pointed to selective effects in cortical basal ganglia circuitry (see [218]). In more direct tests of the role of cortical-basal ganglia circuitry in mediating stereotypy in deer mice we blocked cortico-striatal glutamatergic projections or nigrostriatal dopaminergic projections with selective pharmacological agents [219]. Stereotypy was attenuated selectively (i.e., non-stereotypic motor behavior was not affected) via intra-striatal administration of either the NMDA receptor antagonist MK-801 or the D_1 dopamine receptor antagonist SCH23390. Importantly, no such attenuation was observed following intrastriatal administration of the D_2 dopamine receptor antagonist raclopride [185].

Dysregulation of cortico-striato-thalamo-cortical circuitry associated with motor disorders is thought to be due to an imbalance between the direct and indirect pathways comprising this circuit. As dynorphin and enkephalin serve as markers for direct and indirect pathway neurons, respectively, concentrations of these striatal neuropeptides were measured to index the relative activation of these basal ganglia pathways in stereotypic deer mice [220]. Measurements were made in dorsolateral striatum using deer mice exhibiting different levels of spontaneous stereotypy. Results indicated significantly increased dynorphin/enkephalin content ratios in high-stereotypy mice relative to low-stereotypy mice. This ratio difference was due to significantly lower leu-enkephalin content in high stereotypy mice. Moreover, a significant positive correlation was found between the dynorphin/enkephalin content ratio and frequency of stereotypy in these mice whereas a significant negative correlation was found for enkephalin content and stereotypy. These data are consistent with the hypothesis that spontaneous stereotypic behavior is expressed as a consequence of relative hyperactivity along cortico-basal ganglia-cortical feedback circuits involving the direct pathway, but suggest that perturbations to the indirect pathway may give rise to such imbalanced activity.

To extend these findings, we assessed indirect pathway activation relative to stereotypy by measuring neuronal metabolic activation of the STN, a key brain region in the

indirect pathway [221]. Using cytochrome oxidase (CO) histochemistry to index long-term neuronal activation, we found that CO staining in the subthalamic nucleus (STN) was significantly reduced in high-stereotypy mice. Further, CO staining was significantly negatively correlated with the frequency of stereotypy. Thus, higher rates of spontaneous stereotypy were associated with reduced neuronal activation of the indirect pathway. Finally, in ongoing work in our lab, we have pilot findings that suggest that pharmacological activation of the indirect pathway reduces repetitive behavior in deer mice in a selective fashion. Conversely, pharmacological blockade of the indirect pathway induces repetitive behavior in deer mice (unpublished observations).

Long term neuroadaptations and RRB

The development and persistence of repetitive behavior in autism presumably involves long-term, experience-dependent striatal plasticity. Evidence for such dynamic neuroadaptation comes from studies of habit learning or habit formation. As Graybiel [222] has suggested, repetitive behaviors can be seen as "extreme" habits. Like RRB, habits can have cognitive and motor components and represent sequential, repetitive behaviors that when triggered by relevant stimuli proceed to completion without conscious cognitive control or clear contingency. Habit formation, typically examined in the context of procedural learning, involves adaptations of cortical-basal ganglia loops and chronic electrophysiological monitoring of ensembles of neurons in rodents and non-human primates have revealed discrete shifts in patterns of neural activity that overlay the transition from goal directed to habit driven behavior (reviewed in [222]). The relevance of this work to RRB in autism is highlighted by the finding that amphetamine sensitization, another model of dopamine-dependent striatal plasticity, accelerates the development of habit learning or formation [223]. Amphetamine sensitization which involves long-term neuronal changes following repeated, intermittent drug exposure also results in significantly increased levels of repetitive motor behavior [224].

Additional evidence for the role of experience-dependent basal ganglia pathway adaptations in the transition from variable to stereotyped responding comes from work on birdsong. For example, oscine songbirds imitate older members of their species and progress through stages where song production starts out highly variable but becomes increasingly stereotyped. Recent studies have determined that lesions of the anterior forebrain pathway (AFP; homologous to basal ganglia thalamo-cortical loops) in juvenile zebra finches markedly disrupt song development but have few effects in adult birds. Specifically, inactivation of an AFP nucleus (lateral magnocellular nucleus of the nidopallium or LMAN) results in a dramatic loss of variability in song typical of juveniles [225]. Instead song production is highly stereotyped, similar to that observed in adults.

Molecular mechanisms involved in experience-dependent neuroadaptation that give rise to repetitive behavior appear to involve transcription factors which can effect changes in gene expression. Nestler et al. [226, 227] have suggested that the transcription factor ΔFosB may be a good candidate for mediating long term striatal plasticity. Following chronic stimulation ΔFosB undergoes post-translational modifications and generates highly stable isoforms which heterodimerize with Jun proteins and bind to AP-1 sites expressed in the promoter regions of genes encoding key striatal proteins (e.g., AMPA glutamate receptor subunit, GluR2, and dynorphin; [228–230]). ΔFosB is induced after chronic exposure to stimuli relevant to repetitive behavior (e.g., stress, drugs of abuse, chronic wheel running) and persists in brain for long periods of time [231]. Thus, ΔFosB might have a more general role in the development of repetitive behavior induced by a wide range of stimuli.

Chronic L-DOPA treatment in Parkinson's disease (PD) patients is associated with the development of repetitive behavior including compulsions and dyskinesias. In relevant animal models, L-DOPA-induced dyskinesias in rats are correlated with increased ratio of FosB in striosomes, relative to matrix [232, 233]. In a primate model of PD, striatal ΔFosB was markedly elevated following pulsatile administration of a D_1 dopamine agonist but only in animals which developed dyskinesias [234]. These FosB-related proteins appear to be expressed preferentially in direct pathway neurons [233]. In addition, activation of ERK, the extracellular-regulated kinases that mediates down-stream transcription, is restricted to the direct pathway neurons in mouse models of L-DOPA-induced dyskinesias [235]. Compulsive wheel running also induces ΔFosB in striatal direct pathway neurons. Interestingly, transgenic animals that selectively overexpress ΔFosB in these projection neurons exhibit excessive or compulsive wheel running, whereas wheel running is significantly inhibited in animals that overexpress the gene in enkephalin containing or indirect pathway projection neurons [236].

Fos related proteins are also associated with the development of stereotypies following repeated intermittent exposure to drugs such as cocaine and amphetamine (i.e., sensitization). In this model, increased Fos protein expression is preferentially exhibited in striatal striosomes (e.g., [237]). Indeed, this increased striosomal expression of Fos and FosB following drug exposure reliably predicts motor stereotypies [224]. Such plasticity related changes also appear to be progressively more evident in the dorsal aspect of the striatum with increased drug exposure. In addition, the shift in metabolic activity to striosomes appears to be due largely to a decline in matrix activity. This shift from

matrix to striosomes could reflect a shift toward more motivationally driven behavior with a consequent narrowing of focus and escalation of repetition [238]. As yet, there is no evidence for either a matrix to striosome shift or a ventral to dorsal striatum shift in neuronal activation in non-drug induced repetitive behavior.

Summary

Restricted, repetitive behaviors are a heterogeneous group of behaviors, ranging from stereotypic body movements to more cognitively mediated symptoms such as restricted (circumscribed) interests or preoccupations [1, 239]. RRB is most strongly associated with autism but occurs in a number of other clinical disorders as well as in typical development. There does not seem to be a pattern or category of RRB that is unique or specific to autism and RRB does not seem to be robustly correlated with specific cognitive, sensory or motor abnormalities or deficits in autism. Despite its clinical significance, little is known about the pathophysiology of RRB. As we have indicated, specific genetic alterations appear to be important risk factors to isolate as there are findings from both clinical and animal models studies linking repetitive behavior to genetic mutations. Moreover, a number of specific genetic syndromes have RRB as part of the clinical phenotype. As the pathophysiological sequelae of these genetic mutations are mapped out, we will have additional clues as to the biological substrate of aberrant repetitive behavior. Gene by environment relationships seems crucial as discrete genetic risk factors may interact with broad experiential factors resulting in the extremes in repetitive behavior phenotypic expression that characterize autism. For example, restricted or impoverished environments have often been associated with repetitive behavior in animals and humans and there is overwhelming evidence supporting the positive effects of environmental complexity on brain structure and function, including the amelioration of abnormal repetitive behavior. Few studies of individuals with autism have attempted to correlate MRI findings and RRB and no attempt has been made to associate RRB and post-mortem tissue findings. The one replicable finding is the association of RRB and caudate volume. This is consistent with studies of other clinical disorders and animal models, reviewed here, which suggest that functional and structural alterations in circuitry that link specific areas of cortex and basal ganglia appear to be crucial for the expression of RRB. Animal models have provided critical information about the neurobiology of repetitive behavior. These models, however useful, have focused on repetitive sensory motor behavior and have inadequately modeled RRB reflecting resistance to change or insistence on sameness. The neurobiological model emphasized in this review posits that repetitive behaviors are associated with neuroadaptations in cortical-basal ganglia pathways arising from the dynamic interplay of genetic and experiential factors. Our own studies point to reduced activity of the indirect basal ganglia pathway being associated with high levels of repetitive behavior in deer mice. These findings, if generalizable, suggest specific therapeutic targets. These, and perhaps other, perturbations to cortical basal ganglia circuitry are mediated by specific molecular mechanisms (e.g., altered gene expression) that result in long-term, experience-dependent neuroadaptations that initiate and maintain repetitive behavior. A great deal more research is needed to uncover such mechanisms. Work in areas such as substance abuse, OCD, Tourette syndrome, Parkinson's disease, and dementias promise to provide findings critical for identifying neurobiological mechanisms relevant to RRB in autism. Moreover, basic research in areas such as birdsong, habit formation, and procedural learning may provide additional, much needed clues. Understanding the pathophysioloy of repetitive behavior will be critical to identifying novel therapeutic targets and strategies for individuals with autism.

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