CHAPTER

38

The Developmental Neurobiology of Repetitive Behavior

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OUTLINE

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38.1 INTRODUCTION

Repetitive behavior can be expressed as a variety of topographies, ranging from very simple motor behaviors to extremely complex rituals. The most succinct terminology for these related behaviors comes from the autism literature, where restricted, repetitive behavior (RRB) refers to a broad class of behaviors linked by repetition, inflexibility, and lack of obvious purpose or function. As detailed later, RRB is characteristic of a number of neurodevelopmental and neuropsychiatric disorders, but various forms of aberrant RRB also occur in a significant percentage of individuals without cognitive or neuropsychiatric impairment (Castellanos et al., 1996; Rafaeli-Mor et al., 1999; Singer, 2009). A number of neurobiology research tools have improved the understanding of the mediation of RRB, including molecular genetics, neuroimaging, and animal models. Data from these different methodological domains are beginning to coalesce, resulting in the identification of key brain regions, circuits, and neurotransmitter systems.

38.2 PHENOMENOLOGY OF REPETITIVE BEHAVIOR

38.2.1 Normative Developmental Pattern of Repetitive Behavior

Repetitive motor behavior, compulsions, and rituals are well documented in normative development, and some attempts have been made to chart the developmental trajectory of such behaviors. For example, Thelen (1980) demonstrated that specific rhythmical, stereotyped movements in infants have a clear onset, peak (at about 2 years of age), and decline coincident with emerging voluntary motor control. Whereas very young children engage in a number of repetitive motor behaviors (e.g., swaying, rocking, and flapping), older children display a variety of behaviors that are compulsive and ritualistic (e.g., insistence on certain clothing or foods and bedtime rituals), reflecting an insistence on sameness (IS), rigidity, and ritualization of daily activities (Thelen, 1980). Attachment to a favorite object, perseverating on certain thoughts and topics, and having intense, restricted interests are also common in preschoolers. Evans et al. (1997) have shown that such behaviors peak at about 2–3 years of age and begin to decline after about age 5.

38.2.2 Phenomenology and Treatment of Repetitive Behavior in Tourette Syndrome

Tourette syndrome (TS) is defined by repetitive behaviors that include both motor and vocal tics (American Psychiatric Association, 2000). Motor tics are stereotyped movements that range from very simple, such as an eye blink, to more complex, such as a full body salute. Vocal tics similarly range from very simple, such as throat clearing, to more complex, including complete phrases. Although patients often describe a premonitory urge or sensory experience preceding a tic, no description of an internal experience is necessary to make the diagnosis. Men are more likely to be affected, and TS follows a developmental time course, with onset typically in middle childhood and slow improvement of behavior in many patients as they enter adulthood (Bloch and Leckman, 2009).

Many people with TS do not require medical care, but treatment is often helpful. Behavioral therapy, which includes monitoring of urges and the use of voluntary replacement behaviors, has been shown to be effective in many patients (Piacentini et al., 2010). A variety of medications have been tested in patients with TS, with most data favoring dopamine receptor D2 antagonist drugs that were developed as antipsychotics (reviewed in Swain et al., 2007). Data also support the use of norepinephrine alpha-2 agonist drugs, such as clonidine, in the treatment of TS (Leckman et al., 1991). Importantly, patients with TS are often more severely impaired by comorbid conditions, such as attention deficit hyperactivity disorder (ADHD) or obsessive–compulsive disorder (OCD), than by the tics themselves.

38.2.3 Phenomenology and Treatment of Repetitive Behavior in OCD

OCD is characterized by repetitive, distressing thoughts and accompanying repetitive behaviors that relieve distress (American Psychiatric Association, 2000). OCD can emerge during childhood or adulthood, with men more likely to have earlier onset and an associated tic disorder or TS. Most people with OCD experience both obsessive thoughts and compulsive behaviors, but some, particularly children, manifest only compulsions. In turn, some, particularly adults, manifest only obsessions, often with compulsive thoughts but no outward compulsive behavior. Unlike the repetitive tics of TS, repetitive behavior in OCD is typically purposeful, such as hand washing to eliminate germs. Obsessions and compulsions can be divided into a variety of semi-independent symptom dimensions, including forbidden thoughts, symmetry, cleaning, and hoarding (Bloch et al., 2008).

Treatment for OCD is often partially effective but rarely relieves symptoms completely. Cognitive behavioral therapy (CBT), which involves exposure to the obsessive stimulus without engaging in the compulsive response, has been shown to be helpful in many patients (Foa et al., 2005). Serotonin reuptake inhibitors (SRIs),

but not other monoamine reuptake inhibitors (Leonard et al., 1989), are also helpful, particularly when combined with CBT (Pediatric OCD Treatment Study Team, 2004). Dopamine receptor D2 antagonist drugs can also be helpful when added to SRIs (Bloch et al., 2006). More recent data suggest that medications acting on the glutamate system may also be helpful for some people with OCD (Pittenger et al., 2006). Severe cases of OCD have also been treated successfully with a variety of neurosurgical approaches, including cingulotomy and deep brain stimulation (DBS) in the ventral internal capsule/ventral striatum region (Greenberg et al., 2008).

38.2.4 Phenomenology and Treatment of Repetitive Behavior in Autism Spectrum Disorder

As a cluster of positive symptoms, RRB rather than general developmental delay is often the first clue that a child has an autism spectrum disorder (ASD) (Pediatric OCD Treatment Study Team, 2004). The category of RRB in ASD is broad and heterogeneous, including (1) encompassing preoccupation; (2) apparently inflexible adherence to specific, nonfunctional routines or rituals; (3) stereotyped and repetitive motor mannerisms; and (4) persistent preoccupation with parts of objects (American Psychiatric Association, 2000). Turner (1999) conceptualized repetitive behaviors as falling into two clusters: 'lower order' motor actions that are characterized by repetition of movement, and more complex or 'higher order' behaviors that have a distinct cognitive component. Since then, several groups (Cuccaro et al., 2003; Lam et al., 2008; Szatmari et al., 2006) have examined the structure of RRB as measured on the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994), the gold standard instrument for autism ascertainment. These studies have identified a three-factor model of RRB: repetitive sensory and motor behavior (RSMB), which corresponds to 'lower order' RRB, IS, and circumscribed interest (CI).

Further support for a developmental pattern of repetitive behavior emergence and resolution can be found in studies of children with developmental disorders. For example, Esbensen et al. (2009) assessed individuals with autism across a wide range of ages (2–62 years) using a modified cross-sectional design. They found that repetitive behaviors decreased across age regardless of subtype of repetitive behavior. Somewhat different results were obtained by Richler et al. (2010), who assessed the development of RRB longitudinally at 2, 3, 5, and 9 years of age in children with autism and developmental delay. They measured two major subtypes of repetitive behaviors (repetitive sensorimotor behavior and IS), and reported decreased sensorimotor repetitive behaviors and increased IS behaviors with increasing age. Further research is needed to understand the transition between normative developmental RRB and pathological RRB that exceeds the expected level of RRB at a particular developmental stage. Such information would allow for identification of environmental and neurobiological mechanisms that mediate this transition and the persistence of repetitive behavior.

The occurrence of RRB in normative development, as well as in TS and OCD, raises the question of whether there is a unique pattern of behavior in ASD. Most data suggest that RRB is quantitatively increased at each developmental stage in ASD, but without a unique topography that distinguishes this behavior from normative development or OCD (Bartak and Rutter, 1976; Bodfish et al., 2000; Freeman et al., 1981; Hermelin and O'Connor, 1963; Lord, 1995; Lord and Pickles, 1996; Russell et al., 2005; Szatmari et al., 1989; Watt et al., 2008; Wing and Gould, 1979). Instead, an elevated pattern of occurrence and severity of RRB, particularly rituals and restricted interests, appears to distinguish autism from other disorders (Bartak and Rutter, 1976; Bodfish et al., 2000; Lam et al., 2008). Most attempts to treat RRB in ASD center on the same systems and approaches used in OCD and TS, with most data favoring the use of dopamine D2 antagonist drugs (McDougle et al., 2005) and not so much supporting SRIs (King et al., 2009).

38.2.5 Cognitive, Sensory, and Motor Correlates of RRB in Typical and Atypical Development

Deficits in executive function are often reported in individuals with RRB (Turner, 1997). Executive function is defined as a broad category of cognitive processes involved in the planning and execution of flexible, goal-directed behavior (O'Hearn et al., 2008). Evans et al. (2004) demonstrated that some executive function tasks, such as set shifting and response inhibition/motor suppression, were related to the frequency and intensity of compulsive behaviors in typically developing children. In individuals with ASD, positive correlations are seen between executive function deficits and RRB symptoms (Lopez et al., 2005; Turner, 1997). Furthermore, Lopez et al. (2005) reported that the degree of RRB in individuals with autism was positively correlated with deficits in cognitive flexibility, even after controlling for level of cognitive function. However, other groups have had mixed results in ASD (Joseph and Tager-Flusberg, 2004; South et al., 2005). Consistent with results in typical development and in ASD, individuals with OCD also show deficits in executive function, including response inhibition, set shifting, and reversal learning (Menzies et al., 2008). Some executive function deficits are also reported in TS, particularly in response inhibition, although these studies may be complicated by the common comorbidity with ADHD (Eddy et al., 2009).

38.2.6 Medication-Induced Repetitive Behavior

A number of medications have been observed to cause or exacerbate repetitive behavior in clinical populations. This is most commonly seen in the context of an existing neuropsychiatric disorder that has led to medication treatment in the first place. One obvious appeal to these observations is the opportunity to translate these induced repetitive behavior symptoms into animal models that could probe the underlying mechanisms of action, as well as potential treatments.

The most common scenario is the child with ADHD who develops a motor tic after starting a dopamine reuptake-inhibiting stimulant medication, such as methylphenidate, or a dopamine-releasing medication, such as amphetamine or dextroamphetamine. Given the frequency of comorbid tic disorder or TS in ADHD, many instances of tics emerging during stimulant treatment may not be due to the medication. Overall, the data suggest that it is no more common for tics to worsen than to improve on methylphenidate, and that high doses of dextroamphetamine appear to worsen tic severity (Bloch et al., 2009).

In addition, chronic dopaminergic replacements, such as L-DOPA (L-3,4-dihydroxyphenylalanine) treatment for Parkinson's disease (PD) or high-dose psychostimulants (e.g., cocaine and amphetamine), have been shown to cause dyskinesias, compulsions, and punding (i.e., abnormal repetitive nongoal-oriented behavior) (Fasano and Petrovic, 2010; O'Sullivan et al., 2007; Voon et al., 2009). Treatment strategies include a gradual reduction in dopamine dosage and N-methyl-D-aspartate (NMDA) blockers (e.g., amantadine) in PD patients.

Two other medications have been reported to either trigger or increase OCD symptoms in some, but not all, studies. At high doses, clozapine and, to a much lesser extent, other atypical antipsychotics can lead to repetitive behaviors or OCD symptoms (Sa et al., 2009). The complex pharmacology of clozapine, with actions on multiple receptors in the serotonin, dopamine, and histamine systems, makes it difficult to assess what particular receptors are responsible for this effect. Susceptibility to clozapine treatment-emergent OCD symptoms was associated in one study with polymorphisms in the neuronal glutamate transporter SLC1A1 gene (Kwon et al., 2009), which is also associated with idiopathic OCD, as reviewed later. Finally, serotonin receptor 5-HT_{1B} agonists, including sumatriptan, have been reported to cause worsened OCD symptoms in some patients with existing OCD (Gross-Isseroff et al., 2004), but reports are mixed across studies.

38.2.7 Autoimmune-Mediated Repetitive Behavior

Interest in the relationship between repetitive behavior and immune system response to infection first emerged from the observation of tics and compulsions in some children with Sydenham's chorea (SC), a movement disorder that emerges during poststreptococcal infection rheumatic fever (RF). Swedo and colleagues assessed whether some children may have OCD or tic symptoms without manifesting the full symptoms of SC or RF, identifying a subset of children who follow a pattern that they termed postinfections autoimmune neuropsychiatric disorders associated with group A streptococcal (PANDAS) infection (Swedo et al., 1998). In addition to tic or compulsive symptom onset soon after a strep infection, individuals who fit the PANDAS pattern are typically prepubertal, often show additional comorbidities such as hyperactivity, and are more likely to show a variable, intermittent pattern of symptoms (Murphy et al., 2010). Plasma exchange and intravenous immunoglobulin showed promise in an initial randomized, controlled trial in the PANDAS population (Perlmutter et al., 1999). Similarly, one study shows successful prevention of symptom exacerbations with antibiotic treatment (Snider et al., 2005). While these preliminary treatment studies are encouraging, it has been more difficult to connect symptom exacerbations to strep infections or to connect PANDAS pattern to a specific autoimmune mechanism. While some studies show increased antistreptolysin O titers in children with tics (Cardona and Orefici, 2001), prospective data are limited and do not yet show a clear relationship between strep infections and symptom exacerbations (Leckman et al., 2011). Considerable effort has gone into pursuing the specific antibody or immune cell response that may mediate PANDAS (reviewed in Murphy et al., 2010), with some promising, but not yet consistent, findings.

38.3 GENETICS OF REPETITIVE BEHAVIOR

A variety of approaches has been brought to bear on understanding the genetic susceptibility to repetitive behavior across neurodevelopmental and neuropsychiatric disorders. Twin studies are the gold standard for evaluating the genetic contribution to susceptibility. Family studies can offer further support for genetic susceptibility and allow for modeling of inheritance patterns, but environmental effects within families can confound results. A variety of molecular approaches is applied to try to locate genes that may contribute to susceptibility. Chromosomal rearrangements, deletions, or duplications that are detected by karyotyping can point to regions of interest or even implicate single genes that are disrupted. Linkage mapping within extended families or sibling pairs can identify chromosomal regions that are shared more often than chance among affected family members. Association studies can identify particular alleles that are more common among people with a disorder than in the general population. Each of these

approaches has strengths and weaknesses, and multiple approaches are often required to identify a gene of interest. Technology is moving rapidly in this arena, with the promise of whole-genome sequencing in the near future. The limiting factor in gene identification may be collecting samples of sufficient size to apply the latest technologies while correcting for the huge number of statistical tests performed across the genome. Given the rapid movement in this area, only those studies with the highest impact or replication across multiple samples are reviewed below.

38.3.1 Genetic Susceptibility to TS

TS affects approximately 1% of the population (Robertson, 2008), with isolated motor and vocal tic disorders affecting a larger number. The largest twin study suggests that TS is strongly heritable, with 53% of monozygotic twins (MZ) sharing the diagnosis compared to only 8% of dizygotic twins (DZ) (Price et al., 1985). These numbers rise when chronic tics are included, suggesting that isolated motor tics or, less commonly, vocal tics share a genetic susceptibility with TS. Family studies also support a significant role for heritability in TS (reviewed in O'Rourke et al., 2009). In addition to chronic tic disorders, OCD is also more common in the relatives of probands with TS (Pauls et al., 1986). While early segregation analysis suggested dominant inheritance of TS (Pauls and Leckman, 1986), genetic linkage studies have not yet revealed a major susceptibility gene.

The initial molecular genetic studies in TS used candidate gene association approaches with little success. Several small- to medium-sized genetic linkage studies have been conducted, with only one achieving genome-wide statistical significance on chromosome 2p23 (Tourette Syndrome Association International Consortium for Genetics, 2007). Linkage mapping in a single family followed by full exon sequencing of 51 genes on chromosome 15q led to the identification of a nonsense mutation in the L-histidine decarboxylase gene (*HDC*) in all affected family members (Ercan-Sencicek et al., 2010). Expression of this HDC nonsense variant interfered with the activity of the wild-type allele, suggesting that it acts in a dominant negative fashion to decrease synthesis of histamine (Ercan-Sencicek et al., 2010). Recurrent chromosomal rearrangements have been reported at a number of sites, and copy number variants may also play a role in TS susceptibility (Sundaram et al., 2010). A chromosome 13q inversion in one patient with TS pointed toward the slit- and trk-like 1 neuronal trophic factor (*SLITRK1*) as a positional candidate gene (Abelson et al., 2005). One frameshift mutation and a recurrent rare variant at a microRNA-binding site were identified in a group of TS patients, although subsequent studies have provided only mixed support (O'Roak et al., 2010). Despite their rarity, the promising findings at *HDC* and *SLITRK1* may point toward molecular mechanisms involved in the larger group of patients with TS.

38.3.2 Genetic Susceptibility to OCD

OCD affects approximately 2% of the population, with similar numbers of females and males, but with an earlier onset in males. Twin studies with modern diagnostic criteria are lacking, but more recent twin studies based upon OCD symptoms rather than diagnosis suggest a strong heritability (Hudziak et al., 2004). Family studies strongly favor genetic susceptibility, with most evidence coming from families of probands with childhood-onset OCD (Nestadt et al., 2000). TS and chronic tic disorders are also more common in first-degree relatives of probands with OCD (Grados et al., 2001), paralleling what is seen in probands with TS.

Most molecular genetics studies in OCD have focused on candidate genes, with mixed success. Based on response to the SRIs, the most studied candidate gene is the serotonin transporter (SERT, *SLC6A4*). Studies of common *SLC6A4* polymorphisms also favor a role for the serotonin transporter gene (SERT, *SLC6A4*) in OCD, but different polymorphisms have been associated across studies, with some suggestion of sex differences (Voyiaziakis et al., 2011; Wendland et al., 2008). Ozaki et al. (2003) identified a rare, hyperfunctioning Ile425Val variant of *SLC6A4* in two families with OCD and other psychiatric disorders, although subsequent studies have provided mixed support (Voyiaziakis et al., 2011). Only three small- to medium-sized genome-wide linkage studies have been carried out, with no statistically significant findings in any study (Hanna et al., 2002, 2007; Shugart et al., 2006). A follow-up linkage study for hoarding symptoms in OCD families yielded a significant linkage finding on chromosome 14q (Samuels et al., 2007). Additionally, one suggestive linkage finding on chromosome 9p24 (Hanna et al., 2002) was replicated in an independent linkage sample (Willour et al., 2004). Follow-up studies of the neuronal glutamate transporter EAAC1 gene (*SLC1A1*) have revealed a significant association in multiple samples, although different polymorphisms in the 3′ region of the gene have been associated across studies (reviewed in Wendland et al., 2009). Single candidate gene association studies have pointed to other genes in the glutamate system, converging on the finding that cerebrospinal fluid glutamate levels are elevated in OCD patients (Chakrabarty et al., 2005).

38.3.3 Genetic Susceptibility to Repetitive Behavior in ASD

ASD is a highly heritable complex genetic disorder with much higher concordance rates in monozygotic twins (64–91%) than in dizygotic twins and siblings

(0–9%) (Bailey et al., 1995; Bolton et al., 1994; Steffe nburg et al., 1989). The ADI-R and Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999, 2000), the gold standard instruments for ASD ascertainment, have been used extensively to reduce phenotypic heterogeneity in ASD research (Hus et al., 2007; Veenstra-VanderWeele and Cook, 2004). In addition, researchers have applied a stratification strategy by using 'subphenotypes' to enhance the ability to dissect the genetic etiology of ASD (Buxbaum et al., 2001; Cuccaro et al., 2003; Lam et al., 2008; Shao et al., 2002). Since RRB is one of the core domain features of ASD, specific forms of RRB can be used as a 'subphenotype' to identify a common genetic etiology in ASD. For example, Shao et al. (2003) have found increased linkage evidence at the *GABRB3* locus in the15q11-q13 region in families sharing high IS factor scores. Brune et al. also reported an association between the 5-HTTLPR long/long genotype of the serotonin transporter gene (*SLC6A4*) and RSMB (Brune et al., 2006).

Several groups have reported that RRB has a strong tendency to run within ASD families, indicating separate genetic factors for RRB. For instance, Silverman and colleagues examined the variance of the RRB subdomain scores on the ADI-R in 212 ASD sibling pairs (Silverman et al., 2002). They found statistically significant familiality in two ADI-R subdomains that captures the RRB similar to the CI and IS factors. In line with the Silverman study, Tadevosyan-Leyfer and colleagues also reported the familiality of the 'compulsion' factor derived from the ADI-R that captures both CI and IS factors (Tadevosyan-Leyfer et al., 2003). However, the RSMB factor did not appear to be familial in these studies. Instead, the RSMB factor was associated with individual characteristics, such as IQ, age, social/communication impairments, and the presence of regression (Lam et al., 2008). In summary, 'higher order' RRBs, such as IS and CI, appear to be under genetic control, whereas the 'lower order' RSMB factor reflects variation in developmental levels. Moreover, genetic factors for RRB are likely independent of those that influence the social or communication deficits in ASD (Mandy and Skuse, 2008; Ronald et al., 2006; Silverman et al., 2002).

38.3.4 Simple Genetic Disorders with Repetitive Behavior Phenotypes

RRB is also common in specific, relatively rare, genetic syndromes including but not limited to the genetic syndromes detailed below. A few example syndromes are reviewed briefly here, but further details can be found on the Online Mendelian Inheritance in Man (OMIM), which provides a comprehensive review of individual genetic syndromes. These individual syndromes may provide insight into the molecular pathways and brain systems involved in RRB in the larger group of patients with developmental or neuropsychiatric disorders. Syndromes other than those highlighted below, including Angelman syndrome, Cornelia de Lange syndrome, Down syndrome (DS), and Cri-du-Chat syndrome, also include RRB as a significant part of their clinical profile. Each of these syndromes includes some degree of intellectual impairment, which raises the issue of interpretation of RRB in the developmental context. Importantly, individuals with each of these syndromes appear to have more RRB than IQ-matched peers.

Prader–Willi syndrome (PWS, OMIM #176270) is a rare genomic imprinting disorder with an estimated incidence rate of ~1 in 15000 (Butler, 1990). PWS occurs when the *paternal* contribution is absent in the 15q11-q13 region. Interestingly, studies have reported a higher rate of ASD among individuals with PWS (Veltman et al., 2005). In addition, PWS has been associated with clinically significant RRB (Bittel and Butler, 2005; Dykens and Shah, 2003; Dykens et al., 1999; State and Dykens, 2000). For example, skin picking is reported in most individuals with PWS (Dykens et al., 1999; Thompson and Gray, 1994; Torrado et al., 2006; Veltman et al., 2004; Webb et al., 2002; Whitman and Accardo, 1987). A sizable group of individuals with PWS has prominent OCD symptoms, such as hoarding, ordering/arranging, concerns with symmetry/exactness, rewriting, and need to tell/know/ask (Dykens et al., 1996).

Rett syndrome (RS, OMIM #312750) is classified as one of the pervasive developmental disorders in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 2000). RS is caused by mutations in *MECP2*, located on the X chromosome (Xq28), and occurs almost exclusively in females with an estimated prevalence of ~1 in 20000 females (Kozinetz et al., 1993; Leonard et al., 1997). The affected infants show normal prenatal and postnatal development for the first 5 months, 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 hand-wringing (Ben Zeev Ghidoni, 2007). Interestingly, an increase in *MECP2* gene dosage also appears to be pathological. Ramocki and colleagues described clinical characteristics of nine boys with duplication of the chromosomal interval including *MECP2* (Ramocki et al., 2009). This *MECP2* duplication syndrome is associated with severe to profound mental retardation, as well as repetitive behaviors including hand stereotypies and resistance to changes (Ramocki et al., 2010).

Smith–Magenis syndrome (SMS, OMIM #182290) is most commonly caused by a 3.7-Mb interstitial deletion in chromosome 17p11.2. SMS can also be caused by

mutations in *RAI1* within the chromosome 17p11.2 region. The individuals with SMS show brachycephaly, midface hypoplasia, prognathism, hoarse voice, and speech delay with or without hearing loss, psychomotor and growth retardation, as well as RRB, such as stereotypic body movements (e.g., mouthing objects, hand biting, teeth grinding, body rocking, spinning/twirling, and lick and flip), restricted interests, obsessions, repetitive speech, ritualistic behavior, and attachment to people (preference for adults) (Clarke and Boer, 1998; Dykens and Smith, 1998; Dykens et al., 1997; Moss et al., 2008).

Smith–Lemli–Opitz syndrome (SLOS, OMIM #270400) is an autosomal recessive genetic disorder caused by a defect in cholesterol biosynthesis due to mutations of *DHCR7*. The estimated incidence of SLOS varies, ranging from 1 in 20 000 to 1 in 80 000 births (Kelley and Hennekam, 2000; Lowry and Yong, 1980; Ryan et al., 1998). The SLOS phenotypes vary but include microcephaly, mental retardation, hypotonia, facial dysmorphism, digital anomalies, and ambiguous genitalia. In addition, various forms of RRBs are common in SLOS. For instance, Tierney and colleagues reported repetitive forceful and rapid backward head/trunk arching and backward thrusting (opisthokinesis) in 50% of their study subjects, stereotypic stretching with brief and rapid hand movements, as well as self-injurious behavior, such as biting themselves or banging their heads on objects (Tierney et al., 1999, 2000).

38.4 NEUROPATHOLOGY AND NEUROIMAGING OF REPETITIVE BEHAVIOR

Neuropathology studies of RRB in human samples have been limited by sample availability. Even in TS, where a number of studies have been published, there are not sufficient samples to allow for replication of key findings. Neuroimaging techniques are a promising avenue and are yielding some consistent findings across studies. A variety of structural and functional neuroimaging techniques have been applied to the study of repetitive behavior in defined neurodevelopmental or neuropsychiatric syndromes. The structural techniques include variations on magnetic resonance imaging (MRI), including structural MRI, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging. A variety of techniques is also used to evaluate functional activity of particular brain regions, including positron emission tomography (PET), which is typically used as a measure of brain metabolism, as well as single-photon emission computed tomography (SPECT) and functional MRI, which are used as measures of regional blood flow. Additionally, each of these functional measures can be applied in the resting state or during the performance of particular cognitive tasks, making the resulting findings quite difficult to evaluate for consistency. Finally, various PET ligands can be used to evaluate the availability or binding of specific receptor or transporter proteins. The summaries that follow reflect findings that have emerged in large sample sizes or across multiple studies. Except where noted, most of these studies have been conducted in older children, adolescents, and adults because of the difficulties in imaging younger children. Importantly, data across these disorders point to common brain regions, including the basal ganglia, but findings are sometimes in opposite directions in different disorders, making it difficult to draw clear lines between RRB and specific regional alterations.

38.4.1 Neuropathology and Neuroimaging in TS

A limited number of postmortem cases are available in TS. In small sample studies, two findings have emerged with evidence across at least two studies or different brain regions. First, dopamine transporter binding density is decreased in both the basal ganglia and the frontal cortex (Singer et al., 1991; Yoon et al., 2007). Although this finding provides further support for the involvement of the dopaminergic system in TS and RRB, it is difficult to evaluate whether it is a primary or secondary change due to exposure to medications acting on the dopamine system as well as chronic TS. Second, two studies have found a decrease in parvalbumin-positive interneurons in the caudate (Kalanithi et al., 2005; Kataoka et al., 2010). As detailed below, this may point to a more specific population of neurons than can be identified in structural neuroimaging studies.

The presence of frequent motor tics may limit the ability of patients with TS to remain in the scanner. Perhaps as a result, relatively few structural neuroimaging studies have been performed in TS, with little consistency among studies to date (Plessen et al., 2009). The largest structural MRI study pointed to decreases in caudate volume in children and adults with TS (Peterson et al., 2003). A follow-up study provided further support for the importance of caudate volume, observing that lower caudate volume during childhood predicted higher tic severity in young adulthood (Bloch et al., 2005). The same large study found increased volumes in the orbitofrontal and parietal cortex of children with TS but decreased volumes in adults (Peterson et al., 2001). Furthermore, cortical volumes correlated inversely with symptom severity, suggesting that these alterations may serve to compensate for the primary deficit in TS (Peterson et al., 2001). Abnormalities have also been reported in other brain regions, including the corpus callosum, the limbic system, and the thalamus, but

consistent findings have yet to emerge (Plessen et al., 2009). A variety of PET ligands has been used to examine monoamine receptors and transporters in TS, with a particular focus on the basal ganglia. The most consistent finding to emerge from these studies is an increase in amphetamine-induced release of dopamine, as assessed by a change in receptor binding after drug administration (Singer et al., 2002; Steeves et al., 2010; Wong et al., 2008).

Functional neuroimaging studies in TS have shown little consistency, likely because of variation in methodologies and subject populations (Rickards, 2009). If subjects are able to remain still in the scanner to allow adequate image acquisition, they will, as a result, be scanned in the act of tic suppression, regardless of what other cognitive task may be assigned. Perhaps as a result, PET, SPECT, and fMRI studies show considerable variability, with some support for decreased metabolism or blood flow in the basal ganglia (Braun et al., 1993; Eidelberg et al., 1997; Klieger et al., 1997; Peterson et al., 1998; Riddle et al., 1992). When considering the neuroimaging results as a whole, then, there is reasonable evidence favoring the involvement of the basal ganglia and the dopamine system, but much less consistency regarding the importance of other brain regions.

38.4.2 Neuroimaging of OCD

Postmortem studies have not been published to date in OCD. Individual structural MRI studies vary, but the aggregate data provide significant support for cortical–striatal pathology in OCD. Radua and Mataix-Cols (2009) performed a voxel-wise meta-analysis to identify individual regions with consistent findings across 12 MRI studies, including 3 studies of children and adolescents, and 9 of adults. Increased gray matter volume was found in the basal ganglia, including a large portion of the putamen and extending into the caudate. The severity of OCD in the patients included in each study correlated with the severity of this increased basal ganglia volume. Additionally, decreased gray matter volume was found in a continuous region encompassing the dorsal mediofrontal cortex and anterior cingulate cortex. No consistent evidence was obtained for changes in the orbitofrontal cortex (OFC), although individual structural neuroimaging studies do report changes in this region (Pujol et al., 2004; Szeszko et al., 2008), as do the functional neuroimaging studies reviewed later.

MRS has also been applied in OCD to understand the chemical composition of brain regions implicated in functional studies. A couple of studies have reported decreased *N*-acetylasparate, a putative marker of neuronal integrity, in the anterior cingulate cortex (Jang et al., 2006; Yucel et al., 2007). The Rosenberg group has also reported increased glutamatergic signal, comprising both glutamate and GABA, in the caudate that normalizes with treatment with SRIs in pediatric OCD patients (Rosenberg et al., 2000). This may match one study that found increased glutamate levels in cerebrospinal fluid from patients with OCD (Chakrabarty et al., 2005). PET and SPECT studies have also been used to evaluate ligand binding to particular receptor and transporter proteins in OCD. Despite some inconsistency, a few studies report decreased binding to the serotonin transporter in a number of regions, including the thalamus (Matsumoto et al., 2010; Reimold et al., 2007; Zitterl et al., 2007). Other studies implicate the dopamine system, including decreased ligand binding to the dopamine D2 receptor, suggesting increased dopamine in the synapse (Moresco et al., 2007; Perani et al., 2008).

Functional neuroimaging studies provide further evidence of the involvement of the basal ganglia in OCD and also point to the OFC. Different methodologies have been used to examine functional activation of brain regions in OCD, including PET, SPECT, and fMRI, which are detailed elsewhere in this volume. PET studies emerged first, typically using ^{18}fluorodeoxyglucose to assess regional brain metabolism. SPECT and fMRI use different measures of regional blood flow, which may correspond to regional activation. Measures of metabolism and blood flow may provide different results, although a few consistent findings have emerged across different modalities. These methods can also be applied in different settings, either to measure baseline activity at rest or to measure changes in activity during particular cognitive tasks. Resting PET studies favor increased brain metabolism in the caudate and the OFC, with some evidence also favoring the thalamus (Baxter et al., 1987, 1988; Whiteside et al., 2004), although findings are not always consistent (Whiteside et al., 2004). fMRI, SPECT, and PET studies have also used symptom provocation or executive function tasks to evaluate differences in brain region activation in particular contexts, with the data again highlighting the importance of the basal ganglia and OFC (Chamberlain et al., 2008; Menzies et al., 2008).

The coupling of functional neuroimaging methodology with successful treatment provides the best evidence for involvement of the corticostriatal pathway in OCD. The first reports of increases of caudate and OFC glucose metabolism by PET were followed quickly by reports of decreased caudate and OFC metabolic activity by PET after successful treatment with SRIs (Baxter et al., 1992; Benkelfat et al., 1990). OCD is not the only disorder to be treated with SRIs; they can also be helpful for depression and anxiety disorders, raising the possibility that changes in regional glucose metabolism could be nonspecific. Saxena et al. (2002) tested this possibility by comparing changes in regional glucose metabolism with an SRI in patients with OCD compared to patients with major depression, finding that the decreased metabolic activity

in the caudate and OFC was specific to OCD. Adding further support to the specificity of this change to OCD treatment response, a decreased caudate glucose metabolism was also seen after successful CBT for OCD (Baxter et al., 1992; Schwartz et al., 1996). Taken as a whole, the structural and functional neuroimaging data support the concept of an OCD circuit including the OFC, the anterior cingulate cortex, the basal ganglia, and the thalamus.

38.4.3 Neuroimaging of Repetitive Behavior in ASD

Little, if any, information is available associating postmortem findings with RRB in individuals with neurodevelopmental disorders (Amaral et al., 2008). There are some associations, however, between structural neuroimaging findings (i.e., regional volumetric measurements) and repetitive behavior. For example, Sears et al. (1999) reported a significant negative association between caudate volume and three ADI-R repetitive behavior items: difficulties with minor changes in routine, compulsions/rituals, and complex mannerisms. A directionally different result was obtained by Hollander et al. (2005), who found increased right caudate volumes in individuals with autism and a positive correlation between right caudate volumes and ADI-R repetitive behavior domain total scores. Interestingly, no relationship was found between right caudate volume and RSMB. Instead, the association was due to the correlation between right caudate volume and IS/resistance to change factor scores. The same pattern was observed when putamen volumes were correlated with repetitive behavior scores. These findings were largely replicated by Rojas et al. (2006). In addition, significant positive partial correlations with the ADI-R repetitive and stereotyped behavior domain were also found in the left inferior frontal gyrus and right amygdala. Smaller volumes of the superior temporal gyri, left postcentral gyrus, and cerebellar regions were associated with worse repetitive behavior domain scores. Pierce and Courchesne (2001) found a positive correlation between repetitive behavior exhibited in the experimental setting of an exploration task and frontal lobe volume in a study of young children with autism. 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, Kates et al. (2005) 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.

There has been little utilization of functional MRI to determine the neurobiological basis of repetitive behavior in neurodevelopmental disorders. One notable exception has been the work of Thakkar et al. (2008) who made use of an antisaccade task, which involves suppression of the prepotent response of looking toward rather than away from a stimulus. High-functioning individuals with ASD exhibited significantly higher error rates in the antisaccade condition and significantly increased anterior cingulate cortex (ACC) activation during 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/IS factor scores. An exaggerated ACC response to correct trials has also been observed with OCD subjects. An association between repetitive behavior and ACC activation has also been shown by Shafritz et al. (2008). These investigators used both a response-shifting and a set-shifting cognitive task in individuals with high-functioning autism. Individuals with autism showed deficits in response shifting but, surprisingly, not cognitive set shifting when compared to controls. Reduced activation in frontal, striatal, and parietal regions was observed during these trials in the ASD group. The severity of repetitive behavior was negatively correlated with activation in anterior cingulate and posterior parietal regions.

Despite the paucity of imaging studies related to repetitive behavior, the extant studies, taken together, highlight the importance of corticostriatal-thalamocortical circuitry in the mediation of repetitive behavior, as in TS and OCD. As will be seen in later sections, findings from animal models of repetitive behavior strongly support the involvement of this circuitry. Of particular value for the future would be studies such as the work of Langen et al. (2009), examining trajectories of development of key brain structures such as the caudate. Such work would need, however, to track coincident changes in the expression of RRB (Table 38.1).

38.5 MODELING REPETITIVE BEHAVIOR IN ANIMALS

As reviewed by the authors recently (Lewis et al., 2007), animal models of repetitive behavior that are relevant to clinical disorders can be categorized as follows: repetitive behavior associated with targeted insults to the CNS, repetitive behavior induced by pharmacological agents, and repetitive behavior associated with restricted environments and experience. Since that review, there have been reports confirmed by the authors' own observations of spontaneous repetitive behavior in two inbred mouse strains. As reviewed above, repetitive behavior occurs in multiple clinical populations, and animal models of repetitive behavior are therefore unlikely to be specific to a particular disorder. Even without achieving specificity,

TABLE 38.1 Summary of Clinical Research Areas and Major Findings

Research area	Twin study	Molecular genetic study	Neuropathology and neuroimaging study
TS	53% monozygotic (MZ) versus 8% dizygotic (DZ)	*HDC*	↓ DAT binding density in basal ganglia and frontal cortex
		SLITRK1	↓ Parvalbumin-positive neuron in caudate
		2p23	↓ Caudate volume
			↓ Caudate volume during childhood ↑tic severity in adulthood
			↑ Orbitofrontal and parietal cortex volume in children versus ↓ in adults
			↓ Cortical volume ↑tic severity
			↓ Metabolism in basal ganglia
OCD	None using DSM criteria	*SLC6A4*	↑ Glutamate in CSF
		SLC1A1	↓ Binding to 5-HT transporter
		14q	↓ Ligand binding to D2 receptor
		9p24	↑ Gray matter volume in basal ganglia
			↓ Gray matter volume in dorsal mediofrontal cortex and anterior cingulate cortex
			↑ Metabolism in caudate, thalamus, OFC
			↓ Metabolism in caudate and OFC after successful treatment with SRIs
ASD	~91% MZ versus ~10% DZ	*GABRB3* – IS	↑ ADI-R RRB item score ↓ caudate volume
		SLC6A4 – RSMB	↑ ADI-R IS score ↑ right caudate and putamen volume
			↑ ADI-R RSMB score ↑ left inferior frontal gyrus and right amygdala volume
			↑ RRB ↑ frontal lobe and ↓ cerebellar vermis volume

however, these models can be very useful in deciphering the circuit or the pharmacological contributions to repetitive behavior across clinical and nonclinical populations.

38.5.1 Repetitive Behavior in Animal Models of Targeted CNS Insult

There are a small number of mouse models that involve mutations of specific genes or chromosomal regions that have been reported to result in specific forms of repetitive behavior as part of the phenotype. For example, compulsive grooming resulting in hair removal and self-inflicted wounds has been observed in the *Hoxb8* homozygous mutant mouse (Greer and Capecchi, 2002) and the *Sapap3* KO mouse (Welch et al., 2007). 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 may have specific relevance to OC spectrum disorders such as trichotillomania or self-injurious behaviors common in individuals with severe neurodevelopmental disorders. Mice expressing truncated MeCP2 protein, which serve to model RS, exhibit repetitive forelimb movements resembling the distinctive hand stereotypies (e.g., hand wringing, waving, and clapping) observed in patients with this syndrome (Moretti et al., 2005; Shahbazian et al., 2002). PWS patients exhibit a variety of compulsive behaviors including skin picking associated with deletions of the q11–13 region of chromosome 15 (Dykens, 2004). Among the genes that lie within this region is the *GABRB3* gene, which codes for the β3 subunit of the GABAA receptor. The *Gabrb3* homozygous knockout mouse exhibits stereotyped behavior including intense circling or 'tail-chasing' (DeLorey et al., 1998; Homanics et al., 1997). Ts65Dn mice have segmental trisomy for orthologs of a number of genes on human chromosome 21 and thus serve as a model of DS. The authors have shown that such mice exhibit repetitive hindlimb jumping and cage-top twirling (Turner et al., 2001). Similar stereotypies (jumping and cage top circling) have been reported in the amyloid precursor protein transgenic mouse model of Alzheimer disease (TgCRND8) (Ambree et al., 2006). Alterations in the neurexins, neuroligins, and associated proteins including SHANK3 have been implicated in the etiology of

autism. Transgenic animals overexpressing neuroligin 2 (TgNL2) have altered synapse development and neuronal excitability and behaviorally exhibit limb clasping similar to *MECP2* KO mice and stereotyped vertical jumping (Hines et al., 2008). Neurexin 1α (*Nrxn1*), neuroligin 1 (*Nl1*), and *Shank3* KO mice each show increased grooming behavior, potentially pointing to a common repetitive behavior outcome for disruption of this autism-associated synaptic protein system.

CNS insult leading to repetitive behaviors in animals has also included nongenomic factors. Perhaps the most striking demonstration of such factors comes from Martin et al. (2008). These investigators purified antibodies from women who had at least two children with ASD and injected them into pregnant rhesus macaques. The offspring of these macaques were observed to engage in spontaneous whole-body stereotypies that persisted in the 6 months following weaning and were observed in multiple test conditions. Exposure to maternally derived IgGs that cross the placenta has been implicated in other disorders involving tics and compulsive disorders. Prenatal exposure to valproic acid has been linked to autism susceptibility. In rats, exposure to valproic acid on embryonic day 12.5 induces stereotypic activity (Ingram et al., 2000; Rodier et al., 1997; Schneider and Przewlocki, 2005). Repetitive behavior can also be induced by exposure of newborn rats to Borna disease virus (Hornig et al., 1999). In nonhuman primates, early lesions encompassing the amygdala, hippocampal formation, and adjacent temporal cortex result in repetitive behavior (Bachevalier and Loveland, 2006). A delayed (after year 1 of life) emergence of repetitive motor behavior following amygdala or hippocampal lesions in macaque infants has also been reported by Bauman et al. (2008), who also showed that amygdala damage induced self-directed behaviors, whereas hippocampal lesions induced repetitive head twisting.

Although these studies provide potentially valuable models, repetitive behavior has generally not been the focus or rationale for the work. Thus, the repetitive behavior observed has often not been well characterized and little additional work has investigated the specific neurobiological mechanisms associated with the expression of the repetitive behavior.

38.5.2 Animal Models of Drug-Induced Repetitive Behavior

As early as the 1960s, it was known that specific pharmacological agents such as amphetamine and apomorphine can induce repetitive behavior in animals. As these drugs act on dopamine receptors or uptake sites that are enriched in striatum, these findings pointed to the importance of the basal ganglia in the mediation of repetitive behaviors. Confirmation came from experiments showing that dopamine or a dopamine agonist injected directly into the corpus striatum induced stereotyped behavior in rats (e.g., Ernst and Smelik, 1966). Similarly, intrastriatal administration of the glutamate receptor ligand, NMDA, also induced stereotyped behavior (Karler et al., 1997). Intracortical manipulations enhancing the activity of excitatory corticostriatal 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 (Karler et al., 1998; Kiyatkin and Rebec, 1999). Conversely, amphetamine-induced stereotypy can be attenuated via intracortical infusion of DA or GABAergic agonists (Karler et al., 1998). 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 subthalamic nucleus (STN) also support the hypothesized role of cortical–basal ganglia circuitry in repetitive behaviors (Barwick et al., 2000; Scheel-Kruger et al., 1978). These, and many other relevant findings, provide clear evidence of the preeminent role played by the cortical–basal ganglia circuitry in the expression of drug-induced repetitive motor behaviors.

38.5.3 Repetitive Behavior and Environmental Restriction

Abnormal repetitive behaviors are considered sentinel behaviors by applied ethologists signaling poor animal welfare. This is not surprising as a wide variety of species of animals housed in restricted or impoverished environments (e.g., zoo, farm, and laboratory) exhibit abnormal repetitive behavior (Mason and Rushen, 2006). In fact, as Wurbel (2001) has pointed out, repetitive behaviors are the most common category of abnormal behavior observed in confined animals. Demonstrations of the attenuation or prevention of repetitive behavior by rearing animals in larger, more complex environments (environmental enrichment) provide strong evidence for the role of environmental restriction in the induction of repetitive behavior. Early social deprivation as a special case of environmental restriction has been shown to have powerful deleterious effects on humans and nonhuman primates including the induction of abnormal repetitive behavior (Carlson and Earls, 1997; Mason and Rushen, 2006).

The authors' own work has involved an animal model that falls under the category of repetitive behavior associated with environmental restriction. In this model, deer mice (*Peromyscus maniculatus*) 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. The authors have shown in several studies that environmental

enrichment markedly attenuates the development and expression of the repetitive behavior. This outcome was associated with biochemical and morphological changes in basal ganglia circuitry (Lewis, 2004).

38.5.4 Repetitive Behavior in Inbred Mouse Strains

Examination of inbred mouse strains for autistic-like behavioral traits led to the observation that C58/J mice displayed stereotyped jumping and backward flipping behaviors not observed in other strains (Moy et al., 2008a,b). A similar behavioral phenotype has been reported in the C57BL/10 strain (Deacon et al., 2007), with mice of this strain exhibiting spontaneous repetitive vertical jumping with no such behavior observed in the closely related C57BL/6 strain. The authors have confirmed both sets of observations (unpublished findings). In addition, Crawley and her colleagues have described an excessive grooming phenotype in BTBR (BTBRT+tf/J) mice (Silverman et al., 2010). Thus, several inbred mouse strains display a repetitive behavior phenotype, which should be highly advantageous for addressing the issue of the genetics of repetitive behavior.

38.5.5 Resistance to Change/IS in Animal Models

As the findings in the previous sections make clear, it is the repetitive sensory–motor factor of RRB that is most frequently modeled in animals. This cluster of behaviors is easier to model than behaviors related to the IS or resistance to change factor. Nevertheless, some animal work has addressed cognitive flexibility or resistance to change. This work has entailed a range of behavioral tests from response extinction to reversal learning to intra- and extradimensional set shifting (e.g., Colacicco et al., 2002). In some cases, there has been an attempt to correlate repetitive motor behaviors or stereotypies with measures of cognitive flexibility. For example, the amount of environmental restriction-induced stereotypy observed in bank voles and bears was significantly inversely correlated with extinction learning (Garner and Mason, 2002; Vickery and Mason, 2005). Similar findings were obtained with Orange-wing Amazon parrots using performance on a variation of a gambling task that indexed the tendency to repeat responses or perseverate. Birds with higher stereotypy scores exhibited greater sequential dependency in their responses on this task (Garner et al., 2003). In their own work, the authors have examined the performance of deer mice in a procedural T-maze learning task. Their results indicate that high levels of stereotypy in deer mice were associated with deficits in reversal learning in the T-maze (Tanimura et al., 2008b). 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.

38.6 NEUROCIRCUITRY OF REPETITIVE BEHAVIOR

38.6.1 Basal Ganglia Circuitry and Repetitive Behavior

As reviewed recently by the authors (Lewis and Kim, 2009), neural mediation of the expression of repetitive behavior rests on pathways that project from select areas of the cortex to the striatum and then onto other basal ganglia, then the thalamus, and finally back to the cortex. Medium spiny GABAergic striatal projection neurons receive input from sensory–motor and associative areas of cortex, and, in turn, give rise to the so-called direct and indirect pathways that constitute corticostriatothalamocortical loops. GABAergic medium spiny neurons in the striatum that express the neuropeptides dynorphin and substance P as well as D_1 dopamine receptors and A_1 adenosine receptors constitute striatonigral or direct-pathway neurons. These neurons send projections from the striatum to the internal segment of the globus pallidus (GPi) and SNpr. Striatal medium spiny neurons that express the neuropeptide enkephalin as well as D_2 dopamine receptors and A_2 adenosine receptors constitute striatopallidal or indirect-pathway neurons. Indirect-pathway neurons project to the external segment of the globus pallidus (GPe) and then to STN before projecting to GPi and SNpr. Output from the GPi/SNpr goes to the thalamus and then on to the cortex to complete the circuitry (Gerfen, 2000; Olanow et al., 2000; Steiner and Gerfen, 1998). The classic view has been that the direct pathway facilitates movement via disinhibition of glutamatergic thalamocortical firing, whereas the indirect pathway inhibits ongoing movement via inhibition of thalamocortical afferents (Gerfen et al., 1990).

The medium spiny cells that give rise to either the direct or the indirect pathways constitute about 85% of projection neurons and the matrix compartment of the striatum. The remaining projection neurons form patchy areas or striosomes that are distributed throughout the extrastriosomal matrix. Striosomal projection neurons

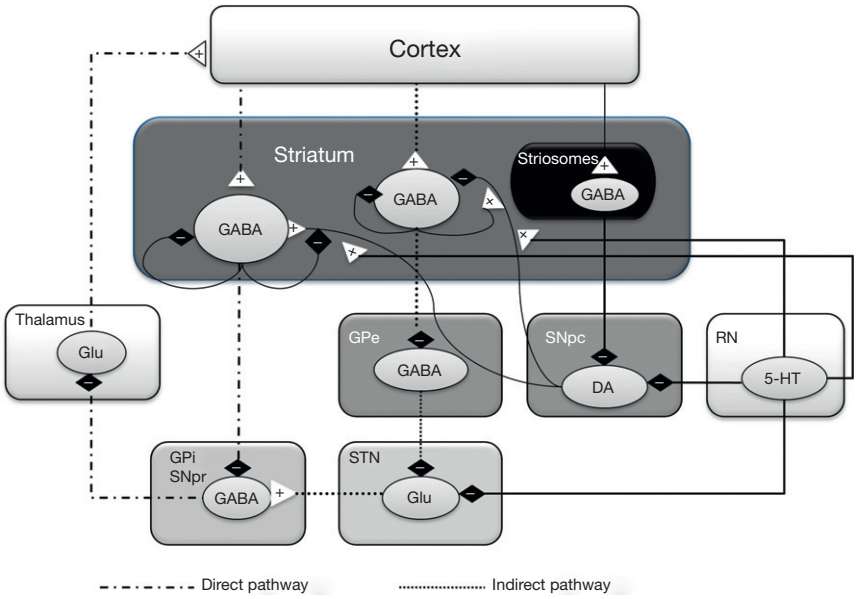

FIGURE 38.1 Cortical–basal ganglia circuitry. The direct and indirect pathways through the basal ganglia are shown, along with other neurotransmitter systems that impact basal ganglia circuitry. +, excitatory input; −, inhibitory input; Glu, glutamate; 5-HT, serotonin; DA, dopamine; GPe, globus pallidus externa; GPi, globus pallidus interna; RN, raphe nucleus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars riticulata; STN, subthalamic nucleus.

receive input preferentially from limbic cortical areas (e.g., OFC, anterior cingulate/posterior medial prefrontal cortex [PFC]) and, in turn, project to the substantia nigra pars compacta (SNpc) (Canales and Graybiel, 2000a,b). Striosomal projections can, therefore, directly mediate nigrostriatal dopamine pathway activity, which, in turn, will strongly influence the activity of direct- and indirect-pathway neurons in the striatum. Moreover, the activity of striosomal projections should strongly impact reward through regulation of ascending DA projections. White and Hiroi (White and Hiroi, 1998) provided some support for this idea by showing that high rates of intracranial self-stimulation were associated with electrode placement either in or next to striosomes. Conversely, 'normal' sensory–motor function (e.g., grooming and locomotion) in rats appears to be mediated by the extrastriosomal matrix (Brown et al., 2002). Findings from nonhuman primates have suggested that striosomal output innervates SNpr and GP as well as SNpc (Levesque and Parent, 2005), so these pathways also may not be as segregated as once believed (Figure 38.1).

38.6.2 Cortical–Basal Ganglia Circuitry and Repetitive Behavior

As many as five parallel information-processing circuits have been identified that make up the cortical–basal ganglia circuitry. These five circuits have been labeled as the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuits (Alexander et al., 1986). These circuits, though anatomically distinct, are nevertheless not segregated. Of these, the motor circuit has been the most studied and emerges as the best candidate for mediation of repetitive behavior.

Direct evidence for the role of such circuitry in repetitive behavior is limited. The authors have shown that stereotyped behavior in early socially deprived rhesus macaques was associated with dopamine receptor supersensitivity (Lewis et al., 1990), 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 (Martin et al., 1991).

The importance of the corticobasal ganglia circuitry in repetitive behavior is further highlighted by the behavioral phenotype of the *Sapap3* knockout mouse (Welch et al., 2007). *Sapap3* encodes a postsynaptic scaffolding protein, highly expressed in the striatum and important in regulating glutamatergic corticostriatal synapses. Mice homozygous for the gene deletion exhibited excessive grooming leading to lesions of the head, neck, and snout. In addition, these animals exhibited alterations in α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and NMDA-receptor-dependent transmission at corticostriatal synapses. Interestingly, administration of the serotonin uptake inhibitor fluoxetine given systemically for 6 days reversed the compulsive grooming. Finally, the behavioral phenotype was rescued by transduction of the *Sapap3* gene into preweaning mice. This work shows that deletion of even a single protein that functions to maintain the activity of the cortical–basal ganglia circuitry can result in a robust repetitive behavior phenotype. Moreover, an SRI can reverse the effects of loss of a glutamate synapse protein. Further support for the involvement of corticostriatal signaling is evidenced by mice lacking the *Slitrk5* gene, which encodes another

member of the protein family that includes *Slitrk1*, implicated in TS. Like the Sapap3 knockout mouse, the *Slitrk5* knockout mouse also shows increased grooming and anxiety-like behavior that improves with fluoxetine (Shmelkov et al., 2010). It also shows abnormalities in corticostriatal neurotransmission, perhaps due to altered striatal cellular composition, and increased OFC activity. These emerging genetic models, while not yet mapping onto known RRB susceptibility genes, suggest that the complex circuitry underlying RRB can be effectively modulated in multiple ways.

Grabli et al. (2004) 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 (Baup et al., 2008), this group showed that DBS applied to the STN dramatically reduced these drug-induced repetitive behaviors. The importance of the STN, and thus the indirect pathway, was also highlighted by Winter et al. (2008). In this study, rats that sustained ibotenic acid lesions to the STN 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 its pharmacological inactivation reduced compulsive checking in rats induced by the dopamine agonist quinpirole (Winter et al., 2008). 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 (Mallet et al., 2008).

The authors have shown, in multiple studies, that early environmental enrichment markedly attenuated the development of repetitive behavior in deer mice. In addition, brain changes associated with this attenuation occurred in brain areas associated with the cortical–basal ganglia circuitry but not in other brain regions (e.g., hippocampus; see Lewis, 2004). In other experiments with deer mice, antagonism of corticostriatal glutamatergic projections or nigrostriatal dopaminergic projections by intrastriatal administration of selective pharmacological agents selectively reduced stereotyped behavior (Presti et al., 2003). Interestingly, the D_1 dopamine receptor antagonist SCH23390 exhibited such effects, whereas no such attenuation was observed following intrastriatal administration of the D_2 dopamine receptor antagonist raclopride (Presti et al., 2004).

Dysregulation of corticostriato-thalamocortical circuitry associated with motor disorders is thought to be due to an imbalance between the direct and indirect pathways comprising this circuit. Because 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 (Presti and Lewis, 2005). 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.

To extend these findings, the authors assessed indirect-pathway activation relative to stereotypy by measuring neuronal metabolic activation of the STN, a key brain region in the indirect pathway (Tanimura et al., 2008a). Using cytochrome oxidase (CO) histochemistry to index long-term neuronal activation, they 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. Thus, higher rates of spontaneous stereotypy were associated with reduced neuronal activation of the indirect pathway.

The authors hypothesized that if high rates of spontaneous stereotypy were associated with decreases in indirect-pathway activation, then stimulation of this pathway by a selective pharmacological agent should attenuate repetitive behavior. As A2A receptors are enriched in striatum, expressed on striatopallidal neurons and activate Gs/olf proteins upon stimulation, activation of these receptors should attenuate stereotypy. When administered alone, however, the selective A2A receptor agonist CGS21680 failed to reduce stereotypy. The addition of the selective A1 agonist N6-cyclopentyladine (CPA) to CGS21680 did selectively attenuate stereotypy in a dose-dependent manner without adverse suppression of general motor activity. The relative efficacy of the combined stimulation of A2A and A1 receptors compared to A2A alone may be explained by the results reported by Karcz-Kubicha et al. (2006). In this work, administration of an A1 or A2A receptor agonist alone did not induce striatal c-Fos expression. Stimulation of both receptor subtypes, however, did induce striatal c-Fos expression and in a selective fashion with activation seen in striatopallidal, but not striatonigral, neurons. This combined treatment of A1 and A2A receptor agonists also increased striatal enkephalin expression. The attenuation by repetitive behavior of this drug combination provides additional evidence for the importance of the indirect pathway and also highlights potential novel therapeutic targets.

38.6.3 Long-Term Neuroadaptations and Repetitive Behavior

The development and persistence of repetitive behavior in neurodevelopmental disorders presumably involve long-term, experience-dependent plasticity in the

cortical–basal ganglia pathways. As yet, there is little information available as to the nature of these neuroadaptations or the mechanisms that mediate such plasticity. There are other models of such long-term basal ganglia neuroadaptations, however, that may be highly informative for the understanding of pathway changes that may mediate the development and expression of repetitive behavior associated with clinical disorders.

One model for such neuroadaptation would be habit learning or habit formation. Habits and repetitive behaviors share a number of important similarities; indeed, as Graybiel (2008) has suggested, repetitive behaviors can be thought of as 'extreme' habits. Habit formation, typically examined in the context of procedural learning, involves adaptations of cortical–basal ganglia loops. Discrete shifts in neural activity patterns associated with the transition from a goal-directed to a habit-driven behavior have been identified using chronic electrophysiological monitoring of ensembles of neurons in rodents and nonhuman primates (reviewed in Graybiel, 2008). Amphetamine sensitization, another model of dopamine-dependent striatal plasticity, involves long-term neuronal changes following repeated, intermittent drug exposure. Amphetamine sensitization accelerates the development of habit learning or formation (Nelson and Killcross, 2006), and also results in significantly increased levels of repetitive motor behavior (Canales and Graybiel, 2000b).

Experience-dependent neuroadaptations are generally thought to be driven by differential gene expression mediated by transcription factors. A leading candidate for mediating long-term striatal plasticity is the transcription factor ΔFosB (Nestler et al., 1999, 2001). ΔFosB undergoes posttranslational modifications that result in 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; Bibb et al., 2001; Chen et al., 1997; Kelz et al., 1999). ΔFosB is induced after chronic exposure to stimuli relevant to repetitive behavior (e.g., stress, drugs of abuse, and chronic wheel running) and persists in the brain for long periods of time (McClung et al., 2004). Thus, ΔFosB might have a more general role in the development of repetitive behavior induced by a wide range of stimuli.

Repetitive behavior including compulsions and dyskinesias can be induced by chronic L-DOPA administration to individuals with PD. In rats, L-DOPA-induced dyskinesias have been shown to be associated with increased striosomal FosB relative to matrix FosB (Andersson et al., 1999; Cenci et al., 1999). Pulsatile administration of a D_1 dopamine agonist to parkinsonian nonhuman primates markedly elevated striatal ΔFosB but only in those animals that developed dyskinesias (Doucet et al., 1996). These FosB-related proteins appear to be expressed preferentially in direct-pathway neurons (Andersson et al., 1999). Similarly, in mouse models of L-DOPA-induced dyskinesias, activation of extracellular-signal-regulated kinase (ERK), the extracellular-regulated kinases that mediate downstream transcription, was restricted to direct-pathway neurons (Santini et al., 2009). Selective induction of ΔFosB in striatal direct-pathway neurons is associated with compulsive wheel running in rodents. Transgenic mice that selectively overexpress ΔFosB in these projection neurons display compulsive wheel running, whereas this behavior is significantly inhibited in animals that overexpress the gene in enkephalin-containing or indirect-pathway neurons (Werme et al., 2002).

The various models described in the previous sections provide important candidate mechanisms that may explain the transition from normative behavior to aberrant repetitive behavior. Identification of such mechanisms would provide novel potential therapeutic targets for drug development.

38.7 SUMMARY

Repetitive behavior has been studied using a variety of tools, from molecular genetics to neuroimaging to model organisms, but the wide variety of repetitive behaviors observed across normative development and human disorders presents a substantial challenge. The phenomenology of repetitive behavior reveals a continuum beginning with very simple repetitive motor sequences, such as hand flapping or grunting, that are typically seen in early childhood and also in ASD and TS. At the other end of the continuum are IS and compulsive rituals, which typically emerge in the preschool years and decline thereafter except when seen in ASD and OCD.

Within the human repetitive behavior disorders, some consistent findings have emerged across cognitive, treatment, genetic, and neuroimaging studies. Neuropsychological testing reveals deficits in executive functioning across disorders. Treatment studies point to behavioral therapies that stress response inhibition in each study, although approaches vary quite widely depending upon the RRB target. Pharmacology studies point to dopamine D2 receptor antagonists across disorders, but there is less consistency in response to SRIs, which are useful in OCD but show mixed data in ASD. Genetic studies support substantial heritability for repetitive behavior, both within and across disorders. Initial genetic findings do not show clear consistency across studies, with the exception of the serotonin transporter gene, which has been implicated in OCD and in RRB within ASD. Neuroimaging studies have coalesced to some degree around the corticostriatal circuit, although the strongest structural findings in TS and

OCD are in opposite directions in the caudate. Other inconsistencies have also emerged across disorders. Multiple studies, from genetics to MRS to CSF, point to the glutamate system in OCD. In contrast, postmortem findings in TS point to decreased GABAergic neurons in the caudate.

Ideally, animal models should be used to dissect the ways that genetic and environmental influences impact brain circuits to feed RRB. Initial work using genetic models points to the same corticostriatal circuits that are implicated by neuroimaging studies. Some of the best current models are combinations of environmental deprivation in species or inbred strains that show some baseline repetitive behavior. These naturalistic models have significant potential to translate back to human disorders. For example, the social disconnectedness that is diagnostic in autism may actually parallel the environmental deprivation that triggers RRB in animals. Research in naturalistic and pharmacological animal models of RRB favors imbalance in the direct and indirect pathway of the basal ganglia. As molecular genetic studies yield more RRB susceptibility genes, the different ways in which this imbalance may be triggered could be better understood. With the rapid progress possible using multiple different research approaches, the emerging understanding of the circuits underlying RRB may translate to potential treatments for TS, OCD, or RRB within neurodevelopmental disorders.

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