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## Review

# The neurobiology of repetitive behavior: ...and men

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### ABSTRACT

In young, typically developing children, repetitive behavior similar to that in certain neuropsychiatric syndromes is common. Whereas this behavior is adaptive in typical development, in many disorders it forms a core component of symptoms and causes prominent impairment in the daily life of affected individuals. Understanding the neurobiological mechanisms involved repetitive behavior will improve our understanding of the pathogenesis of developmental neuropsychiatric disorders, stimulating novel approaches to these conditions. However, studies on the neurobiology of human repetitive behavior have often been limited to distinct conditions and generalization has been hindered by inconsistent terminology. In this paper, we synthesize the ‘disorder-driven’ literature, building on findings from fundamental animal research and translational models. These findings suggest a model for classifying repetitive behavior by its neuroanatomical correlates.

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## 1. Introduction

During early development, children engage in a significant amount of ritualistic, repetitive, and compulsive-like activity that

is part of the normal behavioral repertoire (Evans et al., 1997). This developmental phase is characterized by perfectionism, preoccupation with ordering objects just-so, attachment to a favorite object, concerns about dirt and cleanliness, preferred household routines, actions repeated over and over or a specific number of times, rituals for eating, awareness of minute details in the home, hoarding, and bedtime rituals (Boyer and Liénard, 2006). It is thought that such ritualization and compulsions may serve to ward off anxiety (Evans et al., 1997) and may represent a mechanism for organizing, accommodating to and eventually mastering the environment (Gesell et al., 1974). In other words: childhood

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rituals are hypothesized to be a way to calibrate the system (Boyer and Liénard, 2006). As such, early theories of child development include hypotheses of an adaptive role for repetitive behavior (Gesell, 1928; Piaget, 1952). The wide variety of ritualistic, repetitive, stereotyped and compulsive behavior that can be observed in typically developing young children has striking similarities to the ritualistic and compulsive behavior observed in psychiatric disorders such as obsessive–compulsive disorder (OCD), Gilles de la Tourette syndrome and autism spectrum disorders (ASD) (Evans et al., 1997; Boyer and Liénard, 2006). Clearly, the adaptive element of this behavior is lost in such neuropsychiatric conditions, where they cause prominent impairment to the daily life of affected individuals.

Repetitive behavior was recognized as a common characteristic of mental illness from early on. In a historical overview of repetitive behavior in schizophrenia, Frith and Done (1990) quote from 18th century publications: “We see also mad people, in whom phancy reigns, to run upon some action, as reading, or knitting of straws, without variation” (Grew, 1701) and “When lunatics attempt to write, there is a perpetual recurrence of one or two favorite ideas, [...] patients will run their ideas in the very same track for many weeks together...” (Ferrier, 1795). Later, Kahlbaum (1874) described repetitive behavior in his work on catatonia, as did Kraepelin (1899) in his characterization of dementia praecox and Asperger (1944) and Kanner (1943) in the first reports of autism spectrum disorders. In modern-day neuropsychiatry, the term repetitive behavior is an umbrella term, used to refer to broad and often disparate classes of behavior linked by repetition, rigidity, invariance, and inappropriateness and observed in a wide array of developmental, psychiatric and neurological disorders (Turner, 1999). Across disorders, many varieties of behavior are included in this term, including stereotypies, rituals, compulsive and obsessive behavior, circumscribed interests, echolalia, insisting on sameness, tics, perseveration and self-stimulation or self-injury. Even when only one particular disorder, e.g. autism, is considered, there is little consensus in the terminology used among clinicians (Bodfish et al., 2000). Furthermore, it has been argued that the use of categorization such as the often-used subdivision into lower level (motor) and higher level (cognitive) repetitive behavior may further obscure key differences between different forms of repetitive behavior, as such broad categories may oversimplify by grouping together relatively heterogeneous behaviors (Turner, 1999). In other cases, categorization may falsely suggest differentiation between behaviors, for example, when it arises from a clinical need, whereas the distinction may not be so clear behaviorally or biologically (Garner, 2006). In sum, difficulties in classification and quantification complicate systematic research of repetitive behavior in distinct neuropsychiatric disorder.

### 1.1. Scope of this review

The occurrence of similar repetitive behaviors in diverse neuropsychiatric disorders, as well as in certain phases of typical development, raises a key question: to what extent are these phenomenologically related behaviors mediated by overlapping versus distinct neural substrates? Understanding the neural networks involved in repetitive behavior and related problems will improve insight into the pathogenesis of neuropsychiatric and developmental disorders. This in turn will stimulate novel approaches in thinking about this behavior, encouraging new therapeutic initiatives. In this paper we aim to investigate the neurobiological systems associated with various clinical manifestations of repetitive behavior. The phenomenology and neurobiology of human repetitive behavior has been studied from many different perspectives, but has often been limited to distinct

conditions in which these phenomena occur. In this review, we aim to synthesize findings across disparate syndromes, while building on findings from fundamental animal research and translational models that are discussed in a separate review (Langen et al., 2010). We have separated the discussion of animal and human work, as translating findings from animal work to the human field is not easy, complicating comparisons of the neurobiological mechanisms of animal and human repetitive behavior.

In this paper, we do not include cognitive findings or (neuro)psychological models of repetitive behavior. Cognitive models have provided valuable guiding hypotheses for how neurobiological circuitry might be disturbed in repetitive behavior, as well as insights into how different facets of repetitive behavior relate to each other. However, we chose not to include the ‘in-between step’ of cognitive models to avoid losing focus in this paper, but rather have restricted ourselves to the neurobiological data available.

The structure of this paper is as follows: first we briefly discuss the anatomy of the corticostriatal circuits that are central to repetitive behavior. Next, we discuss neurobiological findings in neurodevelopmental disorders that involve repetitive behavior. Rather than to discuss all clinical conditions where repetitive behavior is seen (e.g. addiction, schizophrenia, trichotillomania, anorexia, hypochondria, body dysmorphic disorder), we have chosen to focus on three neurodevelopmental disorders that include repetitive behavior in their core symptoms and have an extensive literature on this topic available: Gilles de la Tourette syndrome (Section 3), obsessive–compulsive disorder (Section 4) and autism spectrum disorders (Section 5). In Section 6, we discuss research on Parkinson’s disease (PD) and Huntington’s disease (HD). Finally, in Section 7, we synthesize the findings and present a functional and neuroanatomical classification of human repetitive behavior, as well as a suggestion for how these behaviors may group together in symptom clusters as seen in various psychiatric disorders.

## 2. Anatomy of the corticostriatal circuits

The corticostriatal circuits are multiple parallel, segregated feedback circuits with outputs from striatum targeting primary motor areas, and specific pre-motor and prefrontal cortical areas. They are typically grouped in (1) the sensorimotor circuit, (2) the associative or cognitive circuit and (3) the limbic circuit. These circuits innervate the motor and pre-motor cortex; the dorsolateral prefrontal cortex; and the lateral orbitofrontal and anterior cingulate cortex, respectively. The primary function of the corticostriatal circuits is to control and select goal-directed motor, cognitive and motivational behavior. Disruption of co-ordinated function within the basal ganglia or between striatal and forebrain structures results in changes in behavior, often including repetitive or stereotyped behavior: feedback to frontocortical areas becomes dysfunctional, resulting in inadequate repetition of a behavioral set, inability to switch to other behavior, or facilitation of inappropriate behavioral sets. More detailed information on corticostriatal anatomy and a discussion on how this circuitry is thought to be involved in repetitive behavior in animals is presented in a separate paper (Langen et al., 2010).

## 3. Gilles de la Tourette syndrome

Gilles de la Tourette syndrome (TS) is a genetically based, childhood-onset neurodevelopmental disorder that is defined by the presence of phonic and motor tics (Makki et al., 2008) (see Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) for diagnostic criteria). These tics characteristically

wax and wane and often respond fairly well to treatment with dopamine antagonists (Albin and Mink, 2006). TS is defined as part of a spectrum of tic disorders, which includes transient and chronic tics. Tics usually appear around the age of 5–7 years, peak at the age of twelve and steadily decline after puberty (Swain et al., 2007). TS is associated with several comorbid conditions including OCD and ADHD. Although the neural basis of TS is not fully understood, anatomical and functional disturbances in corticostriatal circuits are thought to be centrally involved in the pathogenesis of tics (Sowell et al., 2008).

Structural MRI studies have often focused on the basal ganglia in TS. These have typically reported reductions in volume (Bloch et al., 2005; Hyde et al., 1995; Peterson et al., 1993, 2003), although both increases (Fredericksen et al., 2002) and similar volumes (Singer et al., 1993; Zimmerman et al., 2000) have also been reported (for a review: see Albin and Mink, 2006). Some studies have also investigated related cortical areas: in a study of cortical thickness, Sowell et al. (2008) showed cortical thinning in the motor and sensorimotor cortex in groups of children with TS relative to controls. Furthermore, cortical thickness in these areas was correlated with tic symptom severity. Other studies have directly related the volume of striatal structures to symptoms of TS. Interestingly, these studies have typically shown an inverse relationship between caudate volume and severity of TS symptoms (Bloch et al., 2005; Hyde et al., 1995). Furthermore, Plessen et al. (2004) demonstrated an association between larger prefrontal cortical volumes and lower tic severity in children with TS, suggesting that increased prefrontal volumes may represent a compensatory mechanism, facilitating control of tics. A functional MRI study showed that conscious tic suppression in TS involved activation of regions of the prefrontal cortex and caudate nucleus and deactivation of putamen and globus pallidus (Albin and Mink, 2006; Leckman, 2002; Peterson and Leckman, 1998). Other functional neuroimaging studies using fMRI, positron emission tomography (PET) or single photon emission computed tomography (SPECT) have associated several cortical regions with both TS and tic expression in TS, including prefrontal, frontal, pre-motor, motor and cingulate areas and of basal ganglia and thalamus (Berardelli et al., 2003; Biswal et al., 1998; Braun et al., 1993, 1995; Chase et al., 1986; Eidelberg et al., 1997; George et al., 1992; Peterson and Leckman, 1998; Sawle et al., 1993; Stern et al., 2000; Stoetter et al., 1992; Turjanski et al., 1994). A recent study using diffusion tensor imaging (DTI) to investigate the microstructural integrity of the subcortical regions in TS showed increased mean diffusivity bilaterally in the putamen and relatively decreased fractional anisotropy in the right thalamus. These results suggest disruption to the structural organization or integrity of corticostriatal white matter tracts (Makki et al., 2008).

Clinical symptoms of TS are often effectively treated with dopamine antagonists and selective serotonin re-uptake inhibitors implicating dopamine and serotonin systems in this disorder. This suggests that brain regions where dopamine and serotonin interact may be candidates for changes in TS, e.g. the striatum, the substantia nigra and the prefrontal cortices (Albin and Mink, 2006). In addition to previously discussed neuroimaging work, neurochemical studies have also shown involvement of corticostriatal circuitry in TS. Pre-synaptic dopamine activity has been suggested to be abnormally high in TS, as is indicated by PET and SPECT studies showing increased densities of dopamine transporter (DAT) (Cheon et al., 2004; Serra-Mestres et al., 2004), increased levels of dopamine-synthesising enzyme (Ernst et al., 1999), increased amphetamine-evoked dopamine release in putamen (Singer et al., 2002), or increased number of dopamine terminals in ventral striatum (Albin et al., 2003) in patients with TS (reviewed by Srouf et al., 2008). Especially the study by Cheon et al. (2004) is of interest here, since this study included only medication-naïve

children with TS, diminishing potential contributing factors such as medication use or disease progress. Taken together, these findings have been taken to tentatively suggest that dopamine neurons may release greater amounts of transmitter than normal when they are activated, possibly resulting in loss of control over motor functions, and the emergence of tics (Hoekstra et al., 2004). Furthermore, in a study with twins discordant for TS, differences in dopamine D2 receptor binding in the head of caudate nucleus predicted differences in phenotypic severity (Wolf et al., 1996). This fits with scientific and anecdotal reports of efficacy of dopamine D2 receptor antagonists (such as haloperidol) in treating tics. The localization of the finding to the head of caudate nucleus, known to be the striatal node of the dorsolateral prefrontal corticostriatal circuit, links TS symptoms to cognitive, non-motor circuits and distinguishes them from traditional hyperkinetic movement disorders that are linked more to motor corticostriatal circuitry (Wolf et al., 1996). Only limited additional data are available to suggest the involvement of other neurotransmitter systems than the dopamine system (Hoekstra et al., 2004), although there have been some suggestions of changes in serotonin (Anderson et al., 1992; Müller-Vahl et al., 2005), noradrenaline (Leckman et al., 1995) glutamate (Anderson et al., 1992) and endogenous opioid systems (van Watum et al., 2000).

In sum, neuroimaging studies have shown both structural and functional brain changes in TS, particularly in frontostriatal circuits. Neuropharmacological studies have shown involvement of dopamine systems in TS, although it seems that serotonin may also play a role. In all, results have not always been consistent (Albin and Mink, 2006). One factor this may relate to, is that samples have differed in terms of the age range included. This may complicate results, as individuals with tics persisting into adulthood may represent an atypical group, for example, Albin and Mink (2006). Other potential factors contributing to the inconsistencies in results are described in more detail in Section 7 of this paper.

#### 4. Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is clinically characterized by two dimensions of symptoms: obsessions, which are unwanted, intrusive, recurrent thoughts; and compulsions, which consist of repetitively and ritualistically displayed behavior (Graybiel and Rauch, 2000). Patients need to exhibit at least one of both symptoms to have the disorder (see DSM-IV-TR (American Psychiatric Association, 2000) for diagnostic criteria). Repetitive thoughts and behavior thus are core symptoms of OCD. Individuals with OCD are aware of the irrationality of their thoughts and behavior (i.e. ego dystonic), although insight might be lessened during actual execution of the symptoms.

Early studies showed obsessive–compulsive symptoms in patients suffering from focal lesions in the striatum or globus pallidus, implicating the basal ganglia and frontostriatal circuitry in OCD (Chayette and Cummings, 1995; Graybiel and Rauch, 2000; Laplane et al., 1989). Modern techniques including PET and structural and functional MR imaging have confirmed frontostriatal involvement in OCD. A majority of PET-studies has shown increased glucose metabolism in caudate nucleus, orbital prefrontal cortex, anterior cingulate cortex and thalamus in OCD during rest (Baxter, 1990; Baxter et al., 1987, 1992; Evans, 2004; Rauch et al., 1994; Rosenberg et al., 1997; Saxena et al., 1999; Schwartz et al., 1996; Swedo et al., 1989), although a meta-analysis of these data showed that increased metabolism was only consistently found for orbitofrontal cortex and the head of the caudate nucleus (Whiteside et al., 2004). Eliciting OCD symptoms by exposing patients to symptom-provoking stimuli increases cerebral blood flow to the head of the caudate nucleus and orbitofrontal cortex

(McGuire et al., 1994; Mitterschiffthaler et al., 2006; Rauch et al., 1994; Saxena and Rauch, 2000). Successful pharmacological interventions alleviate these OCD-related activation patterns (Baxter et al., 1992; Evans, 2004) whereas these metabolic changes do not occur in non-responders (Benkelfat et al., 1990; Calabresi et al., 1997; Swedo et al., 1992). Taken together, PET-studies suggest that overactivity of striatal-orbitofrontal circuitry is involved in the OCD symptoms (Insel, 1992; Remijnse et al., 2006).

Overall, structural MRI findings suggest changes in basal ganglia and frontal cortex in OCD, although results have not been fully consistent: hand-traced measures of the caudate nucleus have suggested both decreases (van den Heuvel et al., 2008; Luxenberg et al., 1988; Robinson et al., 1995), similar (Aylward et al., 1996; Bartha et al., 1998; Kellner et al., 1991; Rosenberg et al., 1997; Stein et al., 1993, 1997), and increases (Scarone et al., 1992) in volume from controls (Huyser et al., 2009; Saxena et al., 2001; van den Heuvel et al., 2008). Fully automated, whole-brain, voxel-based morphometry (VBM) methods have yielded similarly variable results, although changes are often found in these circuits (van den Heuvel et al., 2008). Functional MRI studies have linked OCD symptoms to increased activity in regions in the orbitofrontal and anterior cingulate striatal loops (Fitzgerald et al., 2005; Maltby et al., 2005; Mitterschiffthaler et al., 2006; Remijnse et al., 2006; Thakkar et al., 2008; Ursu et al., 2003; van den Heuvel et al., 2005; van der Wee et al., 2003) whereas decreased activation of the orbitofrontal cortex has been demonstrated during reversal learning, a cognitive function subserving behavioral flexibility (Chamberlain et al., 2008). Findings that activation in anterior cingulate cortex (ACC) increases during symptom provocation in OCD (Breiter et al., 1996), whereas cingulotomy relieves obsessions and compulsions (Dougherty et al., 2002) lends further credibility to a link between ACC function and rigid, repetitive behavior in OCD (Thakkar et al., 2008). Recent studies have investigated neural correlates of discrete symptom dimensions of OCD. Although these studies are preliminary, they suggest that different symptoms may be mediated by distinct neural systems, and that previous discrepant findings may have resulted from phenotypic variations in the studied samples (for an overview: see (Mitterschiffthaler et al., 2006; van den Heuvel et al., 2008).

OCD was originally classified as an anxiety disorder, as the behavior exhibited by sufferers was thought to be aimed at relieving stress and anxiety. Nevertheless, it was the effectiveness of the tricyclic antidepressants that first gave impetus to investigating the neurobiology of OCD (Stein, 2000). Serotonergic antidepressants were shown to be particularly effective for reducing obsessional behavior (Zohar and Insel, 1987), stimulating research on the serotonin system in OCD. As such, a major focus of OCD research has been exploring the role of the serotonin system in this disorder (Micallef and Blin, 2001): recently, Soomro et al. (2008) reviewed 17 studies including over 3000 patients and confirmed the therapeutic effect of SSRIs in OCD, at least in the short-term. The longer term efficacy and tolerability of different SSRI drugs for OCD has yet to be established. However, the mechanism by which serotonin is involved in OCD is not yet fully understood. One hypothesis poses that serotonin transporter availability is reduced in OCD, thereby contributing to the observed overactivity of corticostriatal circuits in OCD (Reimold et al., 2007). A recent PET study showed reduced serotonin transporter availability in thalamus and midbrain of patients with OCD compared to well-matched control subjects (Reimold et al., 2007). These findings are in accordance with some (Hesse et al., 2005; Zitterl et al., 2007), but not all (Pogarell et al., 2003; Simpson et al., 2003; van der Wee et al., 2004) earlier studies on serotonin transporter availability in OCD. Other studies have related pre- and post-SSRI-treatment levels of serotonin transporter (in thalamus and hypothalamus) with pre- and post-treatment severity of OCD

symptoms and showed that (1) less availability of serotonin transporter at baseline was associated with more severe OCD; and (2) higher baseline levels of serotonin transporter were associated with higher efficacy of SSRI-therapy (Zitterl et al., 2008). Taken together, these results suggest that the level of availability of serotonin transporters may be implicated in OCD.

Furthermore, serotonin depletion studies do not result in reversal of anti-obsessive drug action or exacerbation of OCD symptoms as would be predicted by the hypothesis (Delgado and Moreno, 1998). Thus, it would appear that serotonin plays some part in the disorder, but that perhaps its role is secondary or modulatory (Soomro et al., 2008).

Low doses of atypical antipsychotics such as olanzapine, quetiapine, ziprasidone and risperidone are often prescribed in severe cases of OCD and are considered a useful augmentation if SSRI treatment is not successful, putatively suggesting that in OCD dopamine-serotonin interactions may also be relevant (Bloch et al., 2006). In addition, recently, dopamine itself has been implicated in the etiology of repetitive behaviors in OCD (see reviews such as (Denys et al., 2004; Westenberg et al., 2007; Goddard et al., 2008)). Underlying mechanisms could include an imbalance of the direct and indirect pathway of the corticostriatal feedback loops (Westenberg et al., 2007; see also Langen et al., 2010) and hyper-activation of dopamine regulated reward-related systems (Denys et al., 2004).

In sum, several neurobiological focus points have been proposed in OCD. Corticostriatal circuitry is pivotal to this disorder and a number of models have proposed how imbalances in the corticostriatal loops could induce OCD symptoms. Especially the limbic or orbitofrontal circuit (orbitofrontal cortex, anterior cingulate cortex and caudate nucleus) has consistently been shown to be involved in symptoms. At the pharmacological level, the serotonin system is implicated, potentially via reduced serotonin transporter availability. However, the efficacy of augmentation using antipsychotic medication suggests there may also be a role for the dopamine system.

As in TS, not all evidence on the neurobiology underlying repetitive behavior in this disorder has been consistent. Potential factors contributing to the inconsistencies in results are described in Section 7 of this paper. For detailed reviews on the neurobiology and pathophysiology of OCD, see Graybiel and Rauch (2000), Aouizerate (2004), Menzies et al. (2008a,b).

## 5. Autism

Stereotypies, repetitive behavior and restricted interests form the third defining symptom cluster in autism (see DSM-IV-TR (American Psychiatric Association, 2000) for diagnostic criteria). A considerably body of work has investigated neurobiological mechanisms associated with the first two clusters of symptoms in this disorder (impaired social interaction and language development), but relatively few studies have investigated the neurobiology associated with this third cluster. This is surprising, given the prominence of these symptoms and the extent to which this behavior form a significant impairment for affected individuals and their families.

Structural MR studies of brain changes associated with repetitive behavior in autism have often focused on the basal ganglia. Results are somewhat ambiguous, as some studies have reported larger volumes (Haznedar et al., 2006; Hollander et al., 2005; Langen et al., 2007; Rojas et al., 2006; Sears et al., 1999; Voelbel et al., 2006), whereas others have not found changes (Gaffney et al., 1989) or have only found changes in line with overall increases in brain volume (Herbert et al., 2003; Sears et al., 1999). Several studies have related brain changes directly to repetitive behavior and have shown correlations between

symptoms and striatal volumes (Hollander et al., 2005; Langen et al., 2009; Rojas et al., 2006; Sears et al., 1999), lending confidence to involvement of striatum in repetitive behavior in this disorder. Turner et al. (2006) investigated functional connectivity in neural networks including caudate nucleus in a small sample of adult control subjects and adolescents and adults with autism. They found atypical caudate–cortical connectivity in autism. A later study linked repetitive behavior in autism to changes in activity of anterior cingulate and posterior parietal cortex, but not striatum (Shafritz et al., 2008). A recent study combined fMRI with diffusion tensor imaging (DTI) and suggested that repetitive behavior in autism may be related to deficient response monitoring in anterior cingulate cortex (ACC) in autism: subjects with autism made more errors on an anti-saccade task and showed reduced discrimination between errors and correct responses compared to controls. Furthermore, they had increased ACC activity on correct trials, while DTI showed structural changes in ACC white matter. Both the functional and structural changes related to the behavioral responses on the task and were correlated with repetitive symptoms in the subjects with autism (Thakkar et al., 2008).

There is limited neuropsychopharmacological evidence available on autism. However, conventional antipsychotic medication is commonly prescribed to individuals with autism spectrum disorders. There is some indication that this medication may be effective for reducing hyperactivity, aggression and repetitive behavior in this disorder, although no systematic studies are available (Barnard et al., 2002). SSRIs are also used. Here, most studies demonstrate significant improvement in global functioning and in symptoms of anxiety and repetitive behavior (Kolevzon et al., 2006). Although the evidence available is limited, it does suggest that both antipsychotic medication and SSRIs are beneficial in autism. As such, this putatively implicates the dopamine and serotonin systems here, as in other disorders with repetitive behavior.

In sum, although various studies have implicated corticostriatal circuitry in repetitive behavior in autism, results are not fully conclusive. Differences between studies may reflect differences in developmental stage between samples (Herbert et al., 2003; Hollander et al., 2005; Langen et al., 2009; McAlonan et al., 2002). More specifically: not the outcome of brain development but the developmental trajectory itself seems to be most disturbed in autism (Amaral et al., 2008). Furthermore, the heterogeneity in the autism phenotype forms a potential confound in itself: symptoms vary across individuals, in all three symptom-domains. For example, it has been shown that clusters of repetitive behavior in autism are associated with distinct profiles of other symptoms (Lam et al., 2008). As such, certain repetitive behaviors may be associated with distinct neural circuits. If different neural circuits indeed support different aspects of repetitive behavior, the relationships between structure and function could feasibly take different forms (Langen et al., 2009). This highlights the importance of detailed phenotyping in this disorder as well as of taking a dimensional approach to studying the neurobiological basis of heterogeneous disorders. Other potential factors contributing to the inconsistencies in results are described in Section 7 of this paper.

## 6. Parkinson's and Huntington's disease

Research on the function of human corticostriatal circuitry has been strongly influenced by descriptions of the clinical phenomenology of human basal ganglia disorders, such as Huntington's and Parkinson's disease (Albin et al., 1989). Although the changes in motor behavior associated with Parkinson's disease (PD) and Huntington's disease (HD) are not classified as repetitive behavior, we do include them here, as they have greatly contributed to our understanding of the neurobiology of repetitive behavior.

Parkinson's disease (PD) results from degeneration of the substantia nigra pars compacta, minimizing dopamine release in the midbrain. Decreased dopamine stimulation of striatum then results in inhibition of the direct pathway and stimulation of the indirect pathway, leading to an overall decrease in motor behavior. The opposite mechanism (overactivity in the direct pathway and underactivity in the indirect pathway) is thought to be involved in repetitive behavior. In Huntington's disease (HD), a degeneration of neuronal cells, especially in the frontal lobes and caudate nucleus, astrogliosis and loss of medium spiny neurons occurs. This results in a reduced dopamine modulation via the indirect and direct pathways: the remaining dopamine signals within striatum are too weak to inhibit the appropriate target regions. The only exception is the globus pallidus externa, which over-inhibits when activated, and thereby alters the flow of excitation from the subthalamic nuclei, contributing to the lowered function and loss of movement control. This creates the characteristic jerky uncontrolled movement associated with HD (Kandel et al., 1991).

In addition to overall motor disturbances, individuals with Parkinson's and Huntington's disease suffer from behavior that is characterized by repetition and perseveration. One frequently reported deficit in PD and HD concerns the ability to shift set, the ability to alter behavior according to changes in dimensional relevance of stimuli (Cools et al., 2001). This ability has often been related to frontal lobe function (Dove et al., 2000; Mecklinger et al., 1999; Rogers et al., 1998; Sohn et al., 2000; Stablum et al., 1994), although more recent studies suggest that disrupted interactions between striatum and the frontal cortex may cause these deficits in PD and HD, ultimately resulting in perseverative behavior (Cools et al., 2001).

Repetitive behavior and disturbed impulse control are highly prevalent in PD patients treated with dopamine agonists (Voon and Fox, 2007; Voon et al., 2007). This behavior includes pathological gambling, hypersexuality, compulsive shopping and compulsive eating and is thought to result from aberrant or excessive dopamine receptor stimulation. A related phenomenon seen with dopamine replacement therapy is punding, an intense fascination with repetitive tasks such as collecting or arranging objects, developing from pre-potent idiosyncratic habits. This has been linked to dopamine dysregulation syndrome (Evans and Lees, 2004), caused by excessive dopamine stimulation of the striatum. Punding was first described in amphetamine addicts and is thought to represent the culmination of a continuous process of psychomotor stimulation (mediated by ventral striatal structures) and behavioral competition (mediated by dorsal striatal structures). The stereotyped behavior seen in punding is likely homologous to the complex stereotyped behavior seen in animals with amphetamine-stereotypies, cage stereotypies and isolation-induced stereotypies (Evans et al., 2004).

In sum, studies of PD and HD have contributed greatly to our understanding of the role of corticostriatal circuitry in repetitive behavior. Compared to the other disorders described in this review, PD and HD allow for a unique approach, as their neuroanatomical substrate is known. This field has shown us how the balance between the direct and indirect pathways in striatum modulates behavior. Moreover, observations of the effects of dopamine replacement therapy in PD indicate the significance of the dopamine system and the interplay between the ventral and dorsal striatal system in repetitive behavior.

## 7. Discussion and conclusions

### 7.1. Repetitive behavior across disorders

The term repetitive behavior refers to broad and often disparate classes of behavior linked by repetition, rigidity, invariance, and

inappropriateness (Turner, 1999). Repetitive behavior is characteristic of many psychiatric disorders, as well as of stages of typical development. Categorizations into ‘higher order’ or ‘cognitive’ and ‘lower order’ or ‘motor’ repetitive behavior do not always hold: these behaviors are often correlated and are mediated by similar or connected circuitries, at least in part (Langen et al., 2010). Furthermore, distinct types of repetitive behavior are often comorbid (e.g. obsessions and stereotypies in autism, stereotypies and obsessive/compulsive behavior in OCD (Garner, 2006)), and family studies suggest a genetic relationship between different types of repetitive behavior (Hollander et al., 2003). In this paper we sought to explore to what extent these phenomenologically related behaviors are mediated by overlapping versus distinct neural substrates?

In the Sections 3–5 we discussed the neurobiology of repetitive behavior in human developmental neuropsychiatric conditions that count repetitive behavior among their core symptoms. Clearly, corticostriatal circuitry is implicated in this behavior, across disorders and methods. However, the literature is not always consistent in terms of the direction of effects. For example, imaging studies have reported both smaller and larger volumes, as well as both increases and decreases in activity in corticostriatal regions. Within disorders, these discrepancies may in part reflect confounders, including (pharmacological) treatment, comorbid disorders or symptoms, and methodological issues, such as limited sample size, differences in gender or intellectual level, and non-uniformity in the classification of repetitive behavior across studies. Furthermore, corticostriatal circuits have a protracted developmental trajectory (Durstun and Casey, 2006) and neurobiological changes associated with repetitive behavior may change over development.

## 7.2. Classification of repetitive behavior across and within disorders

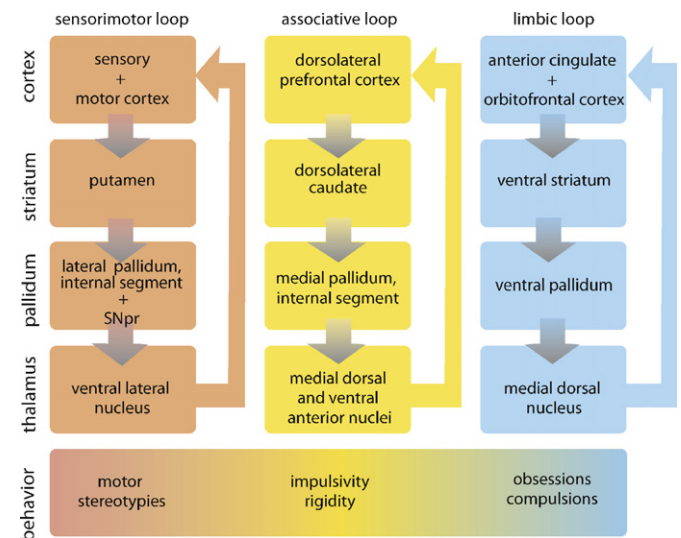
Discrepancies between disorders may also reflect some of these issues. However, they may additionally result from real differences in repetitive behavior and its underlying neurobiology across clinical domains. In all, the evidence seems to point to a distinct but connected neurobiology for different classes of repetitive behavior. Qualitative differences in human repetitive behavior may then principally result from the localization of brain changes. In primates, the anatomical distinctions between corticostriatal circuits (sensorimotor circuit, associative or cognitive circuit, and the limbic circuit) relate to different types of behavior and lesions to each of these circuits will result in a type of repetitive behavior that corresponds to the system affected (Haber and Calzavara, 2009; Francois et al., 2004; Langen et al., 2010). Translation of these findings of animal work to repetitive behavior in humans is a complicated matter. The reasons for this are two-fold: first, invasive studies cannot be performed in humans, as in primates. Second, human repetitive behavior has often been studied from the viewpoint of specific disorders and this has resulted in only limited integration of the findings.

However, a synthesis of findings from developmental neuropsychiatric and neurodegenerative disorders (as discussed in Sections 3–5) has shown that repetitive behavior may result from dysfunction at the subcortical or cortical level, or by faulty exchange of information within the circuit. Subtle variations in corticostriatal pathology across individuals may account for variations in the expression of the symptoms associated with a given disorder (Osmon, 2005), as the contribution of each node in a loop to the behavior it supports is unique (Schmahmann and Pandya, 2008). For several disorders, associations between symptoms and a specific corticostriatal circuit have been suggested: for example, neuroimaging data suggest that motor and vocal tics in TS correspond to changes in the sensorimotor loop

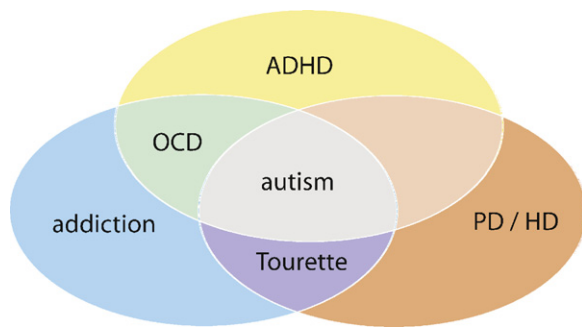
through putamen, whereas obsession and compulsion in OCD are associated with the limbic loop (Graybiel and Rauch, 2000; Menzies et al., 2008a,b). In addition, the dorsolateral frontal circuit has been implicated in comorbid ADHD symptoms in TS, while the orbitofrontal circuit is implicated in comorbid OCD symptoms in TS (Osmon, 2005). Some studies have gone one step beyond and have identified how specific repetitive behavior symptoms within a disorder correspond to distinct anatomical regions (e.g. in OCD, see Mitterschiffler et al., 2006 for an overview; in autism: Langen et al., 2010).

From the increasing body of work emphasizing the etiological overlap between separate disorders (Hollander et al., 2007; Kas et al., 2007; Fineberg et al., 2009; Marsh et al., 2009), we suggest a functional and neuroanatomical classification of human repetitive behavior (Fig. 1) and of how these behaviors may group together in symptom clusters as seen in various psychiatric disorders (Fig. 2). In sum, the motor loop is primarily involved in abnormal stereotypical motor behavior: continuously repeating identical movements without pursuing a goal. The prefrontal loop is likely associated with inappropriate repetition of a goal, expressed in a relatively varied behavioral repertoire (as in some obsessive-compulsive behavior). The limbic loops (lateral orbital loop and anterior cingulate loop) are implicated in motivational aspects of behavioral control, including impulsive behavior (difficulty in suppressing behavior even when consequences are negative), response to reward, and obsessive and compulsive behavior (including compulsive drug-taking).

To conclude, our understanding of the neurobiology of repetitive behavior has vastly expanded in recent years. However, there are still gaps in our knowledge. For example, what are the neurobiological mechanisms that mediate the transition from repetitive behavior common to typically developing children to the



**Fig. 1.** Parallel corticostriatal macro-circuits with their main input, relay and output regions. Abnormal repetition of behavior can result from damage to any of the corticostriatal circuits, where the exact location of the disruption (i.e. which loop is involved) determines what type of repetitive behavior is seen. Both animal and human studies have suggested that the sensorimotor loop is primarily involved in abnormal stereotypical motor behavior: continuously repeating identical movements without pursuing a goal. The associative loop is likely to be associated with inappropriate repetition of a goal, expressed in a relatively varied behavioral repertoire (as in obsessive-compulsive behavior). The limbic loops (lateral orbital loop and anterior cingulate loop) are implicated in motivational aspects of behavioral control, including impulsive behavior (difficulty in suppressing behavior even when consequences are negative); response to reward; and obsessive and compulsive behavior (including compulsive drug-taking). (SNpr = substantia nigra pars reticulata).



**Fig. 2.** Schematic representation of how behavior resulting from problems in one of the three macro-circuits (sensorimotor, associative or limbic; see Fig. 1) may group together in symptom clusters as seen in various psychiatric and neurological disorders. (ADHD = attention deficit hyperactivity disorder; OCD = obsessive–compulsive disorder; PD = Parkinson's disease; HD = Huntington's disease).

developmentally inappropriate, persistent, fixed, and habitual repetitive behavior in clinical disorders (Lewis et al., 2007)? We also know little about the development of repetitive behavior over time within individuals and how the waxing and waning of symptoms is supported by changes in neurobiology (Ödberg, 1993). Furthermore, the systematic comparison of repetitive behavior between studies is complicated by inconsistent labeling and categorization across disorders and fields. Recently, investigators have been advocating a more etiological approach of defining behavior as domains of disorder-related traits, rather than separable categories (Kas et al., 2007). By focusing on features that connect behaviors across disorders and species, rather than distinguish them from one another, we will be able to further advance our knowledge.

A connected approach involves the concept of endophenotypes: heritable, quantitative traits associated with genetic risk for a disorder. Stimulated by findings of segregated abnormalities in brain and behavior of sufferers and their unaffected relatives (e.g. in OCD: Chamberlain et al., 2008 (fMRI data and reversal learning performance); Menzies et al., 2007, 2008b (sMRI and DTI data and inhibition task performance)), many recent studies have now taken up the challenge to search for endophenotypes for specific disorders. Endophenotypes are considered more proximal to genetic effects than clinical phenotypes and so may facilitate identification of specific genes predisposing to a disorder or a symptom (Menzies et al., 2007). In addition, endophenotypes may have a role in identifying how closely disorders are associated with other mental disorders with which they share major comorbidity (Fineberg et al., 2007). Examples of endophenotypic studies are for OCD: Menzies et al. (2007, 2008b), Chamberlain et al. (2008), and Viswanath et al. (2009) and for autism: Duvall et al. (2007); Viding and Blakemore (2007); De Jonge et al. (2009); Saresella et al. (2009). Some have even suggested that studying a certain aspect of a disorder (e.g. the repetitive behavior phenotype in autism) and searching for an endophenotype are interchangeable (Abramson et al., 2005).

Regardless of the gaps that still need to be filled, fundamental biological knowledge of repetitive behavior will increasingly be integrated in the daily clinical practice of neuropsychiatric disorders in the coming decades.

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