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Review

The neurobiology of repetitive behavior: Of mice...

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ABSTRACT

Repetitive and stereotyped behavior is a prominent element of both animal and human behavior. Similar behavior is seen across species, in diverse neuropsychiatric disorders and in key phases of typical development. This raises the question whether these similar classes of behavior are caused by similar neurobiological mechanisms or whether they are neurobiologically unique? In this paper we discuss fundamental animal research and translational models. Imbalances in corticostriatal function often result in repetitive behavior, where different classes of behavior appear to be supported by similar neural mechanisms. Although the exact nature of these imbalances are not yet fully understood, synthesizing the literature in this area provides a framework for studying the neurobiological systems involved in repetitive behavior.

Contents

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1. Introduction

The wide variety of repetitive behavior that can be observed in typically developing young children has striking similarities to the ritualistic, stereotypic and compulsive behavior observed in certain neuropsychiatric syndromes such as obsessive–compulsive disorder (OCD) and autism spectrum disorders (ASD). However, whereas this behavior is adaptive in typical development, in many psychiatric disorders repetitive behavior forms a salient part of symptoms and causes prominent impairment in the daily life of affected individuals.

Similarly, repetition forms an important part of normal functioning in animal behavior. In invertebrates, birds and lower mammals, fixed, repeatedly performed action patterns are vital for survival of both individuals and species, and in higher mammals, repetitive actions such as highly skilled acts acquired through practice, occur as a part of normal behavior. However, *abnormal* repetitive behavior also occurs in animals and can take numerous forms, from pacing (birds, prosimians, large carnivores), jumping and somersaulting (mice) to crib- and bar-biting (horses, pigs, mice), rocking (primates) and self-injurious behavior (monkeys, parrots).

1.1. Scope of this review

The occurrence of similar behavior across species, in diverse neuropsychiatric and neurodevelopmental disorders, as well as in certain phases of typical development, raises a key question: Are these similar behaviors caused by similar neurobiological mechanisms or are different repetitive behaviors neurobiologically unique? Understanding which neuronal networks are involved in the development of repetitive behavior and related problems will improve insight into the pathogenesis of neuropsychiatric and neurodevelopmental disorders. This in turn will stimulate novel approaches to thinking about this behavior in these conditions, encouraging new therapeutic initiatives.

In order to understand neurobiology of repetitive behavior in psychiatric syndromes, animal work of repetitive behavior cannot be ignored. Therefore, in this paper we aim to investigate the neurobiological systems associated with various forms of repetitive behavior and co-occurring cognitive problems by discussing findings from the animal literature. In a separate review (Langen et al., 2010) we build on the findings from this paper in synthesizing *human* work of repetitive behavior across disparate neuropsychiatric disorders.

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 use the term repetitive behavior to describe a wide range of behaviors including stereotyped movements, manifestations of distress in response to minor changes of the environment, an insistence on following routines in precise detail, and preoccupation with narrow, circumscribed interests. Three characteristics unite these apparently disparate classes of behavior and define them as repetitive behavior: (1) a high frequency of repetition in the display of the behavior; (2) the invariant way the behavior or the activity is pursued; and (3) the behavior is inappropriate or odd in its manifestation and display (Turner, 1997). Repetitive behavior is observed across species and manifestations range from basic motor behavior to higher-level cognition.

2. Historical perspectives on repetitive behavior

Initially, repetitive behavior research was directed by fundamental animal studies and was mostly limited to motor stereotypies. Later, research advanced to developing translational animal models for human disorders, extending its scope to cognitive and emotional domains. In this section, we give an overview of what animal literature has taught us about repetitive behavior.

Traditionally, the basal ganglia have been a candidate for explaining repetitive behavior. In the 1920s, the striatum was directly implicated by studies of pharmacologically induced repetitive behavior in guinea pigs (Amsler, 1923) and since then many studies have used diverse techniques to confirm that damage to or dysfunction of the basal ganglia results in 'recurrent perseveration' or inappropriate response repetition (Garner, 2005; Norman and Shallice, 1986; Sandson and Albert, 1984; Turner, 1997). Many early studies focused on the development of repetitive *motor* behavior and largely ignored striatal influences on other, non-motor repetitive behavior. The reasons for this were threefold: First, motor stereotypies are more prominent than non-motor repetitive behavior and are relatively easy to model in animals. Second, higher-order repetitive behavior observed in animals with basal ganglia insults was thought to result from secondary neuropathological changes. Third and foremost, the leading theory of basal ganglia function at that time posed that basal ganglia output only targeted those areas of cerebral cortex that participated in the generation and control of movement (Middleton and Strick, 2000b). However, accumulating evidence led to a challenge of this belief and in a pivotal paper in 1986, Alexander and colleagues dramatically redirected basal ganglia theory and research (Alexander et al., 1986): they reviewed earlier ideas and studies of basal ganglia function (e.g. DeLong et al., 1984; Künzle, 1975, 1977, 1978; Nauta, 1979; Schell and Strick, 1984) and proposed that the basal ganglia should be viewed as components of multiple parallel, segregated circuits with outputs targeting not only primary motor areas, but also specific pre-motor and prefrontal cortical areas. Five parallel corticostriatal circuits were defined, although the authors noted at the time that this list was unlikely to be exhaustive. These circuits were named as (1) the motor circuit, (2) the occulomotor circuit, (3) the dorsolateral prefrontal circuit, (4) the lateral orbitofrontal circuit, and (5) the anterior cingulate circuit. The circuits were named after their cortical targets and not all circuits were initially functionally characterized. Later, Middleton and Strick (2000a) described two additional circuits between the basal ganglia and more posterior parts of the cortex (the inferotemporal and posterior parietal circuits). Each circuit was proposed to include discrete, essentially non-overlapping parts of the striatum (caudate nucleus, putamen and nucleus accumbens), globus pallidus, substantia nigra, thalamus, and cortex. Circuits are structured in a similar manner (Fig. 1), with each circuit receiving cortical inputs to the striatum, passing the input through the basal ganglia, via output nuclei (the substantia nigra pars reticulata and the medial globus pallidus) to a restricted area of the thalamus and from there back to a single cortical area (Ring and Serra-Mestres, 2002). Each corticostriatal circuit receives multiple inputs only from cortical areas that are functionally related and usually interconnected (Alexander et al., 1986). Furthermore, each loop consists of two distinct branches: the direct (or striatonigral) and the indirect (or striatopallidal) pathway. The net result of activity of the *direct* pathway is an increase in thalamic activity, whereas activity of the *indirect* pathway inhibits the thalamus. Thus, under normal circumstances, the direct pathway enhances behavior, whereas the indirect pathway inhibits it (Lewis et al., 2006). This dual system is thought to allow for fine-tuning of activity in large portions of frontal cortex responsible for movement, cognitive, and limbic function (Bradshaw, 2001).

Studies investigating the functional and structural architecture of corticostriatal circuits have refined, but not fundamentally changed, this original model. It is now established that corticos-

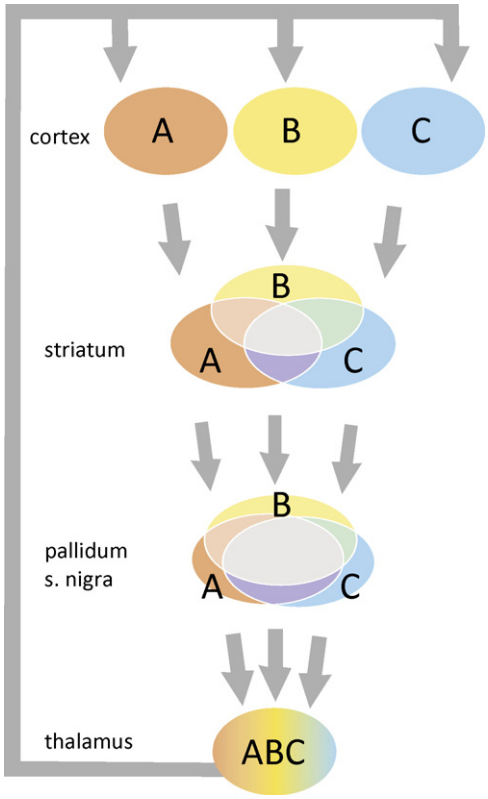

Fig. 1. Corticostriatal circuits as proposed by Alexander et al. (1986). Each circuit receives output from several functionally related cortical areas (A, B and C) that send partially overlapping projections to restricted parts of striatum. These striatal regions send converging projections to the globus pallidus (pallidum) and substantia nigra (s. nigra), which in turn project to specific regions of the thalamus. Each thalamic region projects back to one of the cortical areas that feed into the circuit, thereby completing the "closed loop".
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triatal loops can be functionally divided into three 'macro-circuits', related to the predominant cerebral cortical input to striatum. These are the sensorimotor circuit (comprising the motor and oculomotor loops), the associative circuit (dorsolateral prefrontal loop) and the limbic circuit (lateral orbitofrontal and anterior cingulate loops (Groenewegen et al., 2003). Within these macro-circuits, smaller (micro)-circuits can be recognized that subserve specific functions within the broader functional domain, i.e., sensorimotor (movements), associative (cognitive functions) or limbic (emotional–motivational behavior) (Groenewegen et al., 2003; Mason and Rushen, 2006). This level of detailed organization has been shown most convincingly for the sensorimotor macro-circuit, where specific microcircuits are related to different parts of the body and subserve various aspects of the movement, such as the direction of a movement, or the force exerted (Groenewegen et al., 2003). Furthermore it has become clear that the various functions subserved by these circuits are not independent, but rather that they follow a spiraling organization where information flows from higher-order circuits to lower-order ones (Haber, 2003; Haber and Calzavara, 2009).

Increasing understanding of corticostriatal loops has resulted in a re-evaluation of models of motor and non-motor repetitive behavior. In the original description of the five parallel circuits, Alexander described how damage to individual loops may lead to abnormal repetitive behavior. For example, he implicated the orbitofrontal circuit in behavioral inhibition and switching behavior, as studies in primates had shown that bilateral lesions to the lateral orbitofrontal area or to the portion of the caudate to which it projects result in perseverative behavior (Alexander et al., 1986). Now that corticostriatal loops have been functionally characterized, it is recognized that repetitive behavior may reflect a disruption of co-ordinated function within the basal ganglia or between striatal and forebrain structures (Robbins et al., 1990). As such, abnormal repetitive behavior may result from damage to any of the circuits, and the exact location of the disruption (i.e., which loop is affected) may determine what type of repetitive behavior is displayed (Mason, 2006). Many studies have suggested that the motor loop is primarily involved in abnormal stereotypical motor behavior: continuously repeating identical movements without pursuing a goal. Examples are studies demonstrating the stereotypy-inducing effects of direct administration of dopamine drugs to cortical and subcortical areas of the motor loop in rodents and primates (see Saka et al., 2004; Lewis et al., 2007 for an overview of studies), as well as direct association of stereotypies with gene-expression in midbrain structures of the motor loop (dorsal putamen) after cocaine exposure in squirrel monkeys (Saka et al., 2004), Involvement of the oculomotor loop in repetitive behavior has not often been described, but oculomotor perseveration has been shown in humans and animals (e.g. repetitive eye-rolling in calves and an inability to suppress eye movements in individuals with schizophrenia) (Mason, 2006). The prefrontal loop has been associated with inappropriate repetition of goal-directed behavior, often expressed in a relatively varied behavioral repertoire (as in some obsessive–compulsive behavior). This loop has particularly been implicated in human repetitive behavior (see Langen et al., 2010). In animal work, measures of perseveration and impaired extinction learning have been associated with damage to regions in the prefrontal loop (e.g. Dias et al., 1996; Birrel and Brown, 2000). 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). Animal studies investigating involvement of this loop in repetitive behavior have frequently used paradigms involving reward. In these studies, manipulating functionality (by drug administration or inflicting lesions) of brain regions in the limbic loop (e.g. nucleus accumbens, orbitofrontal cortex) results in changes in the motivational aspects of behavioral control. Examples are increased "reward wanting", displayed as strong preference for a small but immediate reward to a larger but delayed one (Cardinal et al., 2001) after nucleus accumbens lesions in rats, and as increased lever pressing in response to a reward predicting cue in rats after amphetamine injection into the nucleus accumbens (Wyvell and Berridge, 2000). This last effect continued when animals were in a drug-free state (Wyvell and Berridge, 2001), suggesting a robust alteration of limbic loop functionality.

Although this is a simplified classification of how functionality corresponds to anatomy, the literature does suggest that different frontal cortical areas and corresponding subcortical regions are involved in various and distinct aspects of motivation, cognition, and motor control (Haber and Calzavara, 2009) (Fig. 2).

3. Repetitive behavior induced by environmental deprivation

In animal behavior, repetition forms an important part of normal functioning. In invertebrates, birds and lower mammals, fixed behavioral patterns are vital for survival of both the individual and species. In higher mammals, repetitive actions also occur as a part of normal behavior and include highly skilled acts acquired through practice. However, abnormal repetitive behavior also occurs in animals and can take numerous forms, from pacing (birds, prosimians, large carnivores), jumping and somersaulting

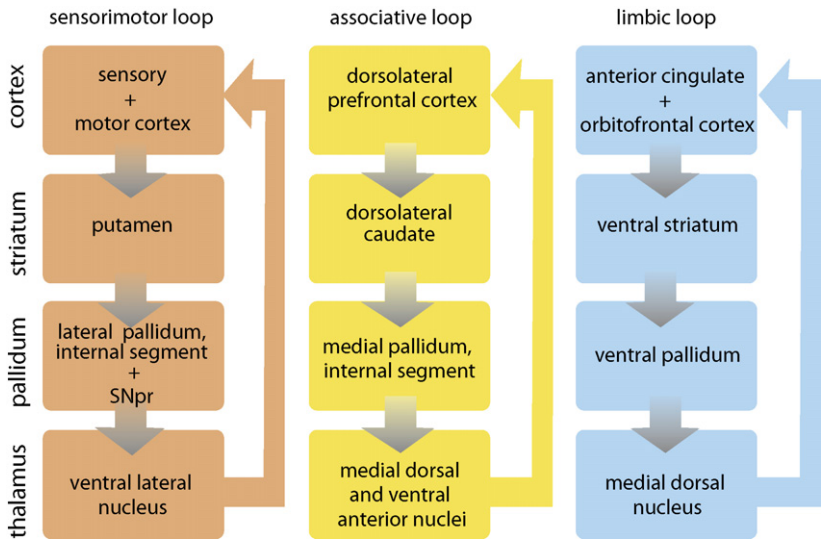

Fig. 2. Parallel corticostriatal macro-circuits with their main input, relay and output regions. Abnormal repetition of behavior can result from damage to any of the corticostriatal circuits, where the exact location of the disruption (i.e., which loop is involved) determines what type of repetitive behavior is seen.
SNpr = substantia nigra pars reticulata.

(mice) to crib- and bar-biting (horses, pigs, mice), rocking (primates) and self-injurious behavior (monkeys, parrots).

Adverse environmental circumstances can cause an animal to develop abnormal repetitive behavior. Confinement and environmental restriction are well-established risk factors; indeed, repetitive behavior is the most common category of abnormal behavior observed in confined animals (Lewis et al., 2007). Ridley (1994) hypothesized that in confinement, the environment shapes the patterns of behavior, as opportunities for behavior are so limited that only a repetitive pattern of responses can be formed. Others have argued that the stress induced by confinement is an important mediating factor in developing of repetitive behavior: Here, stereotypies are hypothesized to function as a coping mechanism to reduce the arousal level of the animal when it is exposed to stressful events or environments (for an extensive review on this theme: see Cabib, 2006).

3.1. Effects of environmental deprivation on brain development and brain chemistry

In the animal literature, a distinction has been made between maladaptive and malfunctional behavior. The first reflects a normal response to an abnormal environment, whereas the second is the product of abnormal psychology, brain development or neurochemistry and is induced by features of the restrictive environment (Garner, 2005; Mills, 2003). Although some authors have shown positive effects of environmental enrichment on repetitive behavior (see Swaisgood and Shepherdson, 2006), many have stressed the robustness of stereotypies in captive animals: As stereotypies develop, they become increasingly hard to abolish with environmental enrichment or neurochemical treatment (Garner, 2005; Garner et al., 2003; Swaisgood and Shepherdson, 2006). The difficulty in treating repetitive behavior induced by confinement and deprivation suggests that the underlying neurobiology may be permanently altered by such environmental restrictions.

Studies investigating the neurochemical effects of deprivation substantiate this hypothesis: Numerous studies have established that rearing rats in isolation leads to substantial dysregulation of forebrain catecholamine systems (Fulford and Marsden, 2007). For example, rats reared in solitude show increased stereotyped behavior in adulthood following administration of dopamine agonists. These results suggest that environmental deprivation may permanently affect brain biochemistry (Garner, 2006; Sahakian and Robbins, 1977; Sahakian et al., 1975). Taken together with other neurochemical data, this indicates that alterations in presynaptic dopaminergic function are a consistent effect of rearing animals in isolation (Powell et al., 2003). Other studies have directly demonstrated biochemical changes in the striatal system in deprived animals, including changes in dopamine and opiate metabolism (Fry et al., 1981; Kraemer et al., 1984, 1989; Lewis et al., 1996, 1990; Martin et al., 1991; Ödberg et al., 1987; Robbins, 1996; Sharman et al., 1982). Furthermore, some studies have been able to show structural and functional changes in striatal neurochemistry associated with environmental enrichment and relate this to prevention of developing stereotypies (Lewis et al., 2006), further implicating this system in this dysfunctional behavior.

Early social deprivation in particular has been shown to cause irreversible repetitive behavior (Mason and Rushen, 2006). The experiments by Harlow in the 1960s are well known for demonstrating the long-lasting effects of maternal and social deprivation on the behavioral repertoire (Harlow et al., 1965; Harlow and Harlow, 1962). In these studies, primates raised in partial or total social isolation displayed severely aberrant behavior with prominent repetitive behavior ('compulsive' sucking and stereotyped movements). The severity and robustness of the abnormal behavior was related to the degree of isolation and duration of the isolation period (Harlow et al., 1965; Harlow and Harlow, 1962). Stereotypies induced by deprivation are more common in monkeys and apes than in lower mammals. This suggests that humans may also be particularly vulnerable to this type of behavior. Indeed, severe effects of early social deprivation have been shown in humans, e.g. in adopted children from Romanian institutions (Groza, 1999; Hoksbergen et al., 2005; Rutter et al., 1999, 2007, 2001; Rutter and O'Connor, 2004). These children are at increased risk for behavioral and cognitive problems and show quasi-autistic features, including repetitive behavior. Even a year after adoption from Romania, half or more of these children still displayed stereotypies and self-injurious behavior (Beckett et al., 2002; Fisher et al., 1997; MacLean, 2004). Longer periods of deprivation (six months or more) had more severe and longer lasting effects (Beckett et al., 2002; Fisher et al., 1997; Rutter et al., 2001). These observations have led to the

speculation that institutionalization may set off 'some form of programming effect or neural damage' in these children (Rutter and O'Connor, 2004).

3.2. Cognitive changes following environmental deprivation

In addition to behavioral stereotypies mediated by the motor corticostriatal circuit, environmentally deprived animals show specific cognitive abnormalities. These include poor extinguishing of learnt responses (Garner et al., 2003; Lutz et al., 2004; Mason and Rushen, 2006; Vickery and Mason, 2003, 2005) and disinhibition of response selection (Garner and Mason, 2002). These cognitive problems are related to stereotyped behavior: One study showed a correlation between cage stereotypies and performance on a cognitive perseveration task in parrots (Garner et al., 2003). Others have shown that blue and marsh tits (Garner et al., 2003), bank voles (Garner and Mason, 2002), and bears (Vickery and Mason, 2005) that spontaneously exhibit stereotypic behavior also have a perseverative response pattern on a gambling task; in reversal learning; or in the extinction of stimulus–response learning (Tanimura et al., 2008). Overall, captive animals with high levels of stereotypy show a strong tendency to repeat responses or behavior: In every species looked at, the most stereotypic individuals also showed the most persistent, repetitive responding in a variety of cognitive tasks (Mason and Rushen, 2006). These findings suggest a fundamental similarity between deprivation-induced stereotypies and specific cognitive abnormalities and suggest that a common pathway may underlie both. Some studies have used cognitive tasks to relate behavioral stereotypies directly to the basal ganglia. For example, Garner and Mason (2002) correlated stereotypies in rodents with their performance on a cognitive task that reflects basal ganglia function (a spatial extinction task). They showed a strong correlation between task performance and cage stereotypies. Their findings suggest that deprivation results in general striatal disinhibition of response selection, reflected by motor stereotypies as well as cognitive problems. Tanimura et al. (2008) followed a similar approach: They investigated the relationship between stereotypies and cognitive ability mediated by corticostriatal circuitry (cognitive flexibility, as assessed by reversal learning) in mice. Their results showed a strong association of high stereotypy levels with cognitive rigidity, but not with other cognitive measures. These findings substantiate the hypothesis that distinct types of repetitive behavior (motor stereotypies, cognitive rigidity) are inter-correlated and are mediated by corticostriatal dysfunction. However, it remains unclear what the exact mechanism behind common motor and cognitive problems is. Are problems in one system secondary to dysfunction in another? If so, what is the direction of this effect? Or are the neurobiological changes induced by environmental deprivation so widespread that they affect all corticostriatal circuitry?

In sum, repetitive behavior is common in animals faced with environmental deprivation, particularly when they are exposed to it early in development. The repetitive behavior induced by environmental deprivation includes motor stereotypies and cognitive rigidity, where these are related and may therefore be mediated by similar circuitry. Repetitive behavior induced in this manner does not seem to reflect an adaptive coping mechanism. Rather, it seems to reflect robust and possibly permanent changes in brain development. This is supported by the difficulty in treating this behavior; resulting changes in striatal neurochemistry; and by findings of cross-sensitization between environmental factors and psycho-stimulants. However, the effects of environmental deprivation are not on an on/off scale. Rather, they are modulated by factors such as quality and duration aspects of deprivation, genetic make-up and other individual characteristics.

4. Translational studies of repetitive behavior

In the previous section, we discussed how repetitive behavior can result from environmental conditions. In this section, we consider studies that have deliberately induced repetitive behavior. Whereas confinement and deprivation studies implicate striatal systems in the development of repetitive behavior indirectly, work inducing stereotypies by drugs, lesions or gene manipulation can relate this brain circuitry to repetitive behavior more directly, as the system can be manipulated to uncover the relative contribution of its various components. Furthermore, lesions and pharmacological manipulations can be applied in young animals to assess their impact in the development of repetitive and stereotyped behavior and gene-manipulation can be used to assess the effect of up- and down-regulating some of the genes involved in the developing animal.

4.1. Pharmacological modulation of repetitive behavior

Fig. 3 is a simplified diagram illustrating the complex nature of how the basal ganglia system is modulated by endogenous neuropeptides. As described earlier, the direct pathway enhances behavior, whereas the indirect pathway is inhibitory. Generally speaking, activating the indirect pathway or suppressing the direct pathway will alleviate stereotypies, whereas suppressing the indirect pathway will induce them. In contrast, activating the direct pathway leads to hyperactivity, not stereotypy; and inhibiting only the direct pathway suppresses *all* behavior (including stereotypy) (Garner, 2006; Lewis et al., 2006). The main neurotransmitters in striatum, pallidum, and thalamus are GABA and glutamate, as these are the neurotransmitters used by most neurons in this region. Corticostriatal circuitry is further modulated by dopamine, opiates (dynorphin, enkephalin), serotonin and several other neurotransmitters (Albin et al., 1989; Mason and Rushen, 2006). Studies investigating the role of neurotransmitters in repetitive behavior are faced with a number of complications: First, these systems do not function in isolation, but are interactive, meaning that manipulating one system may influence another. Second, when exogenous pharmacological agents are administered to affect these systems, it is relevant *how* this is done: the effects of direct injection into a brain region may be very different from the effects of oral administration or subcutaneous or intravenous injection. Third, the effects of exogenous agents are often dose-dependent, complicating the generalization of findings relating to drug-induced behavior (Mills and Luescher, 2006).

4.2. Pharmacological modulation of repetitive behavior: GABA and glutamate

The targeted administration of agents that bind to inhibitory GABA-receptors or excitatory glutamate sites can be used to manipulate the activity of distinct elements of corticostriatal circuitry. In this way, positive feedback to the cortex can be affected to reduce or stimulate repetitive behavior. Inhibiting the output nuclei of the basal ganglia facilitates activation of thalamocortical relay neurons and consequently provides positive feedback to the cortex. As such, administering GABA agonists to the substantia nigra pars reticulata induces stereotypy in rats (Scheel-Kruger et al., 1980). Intracortical manipulation of the activity of excitatory cortico-striatal projections also affects stereotypic behavior: Administering GABA-agonists or antagonists to the frontal cortex in rats, respectively, attenuates or exacerbates stereotypic behavior (Karler et al., 1995). However, distinct behavioral effects following GABAergic drug administration have been observed, affected by topographical variations (site of

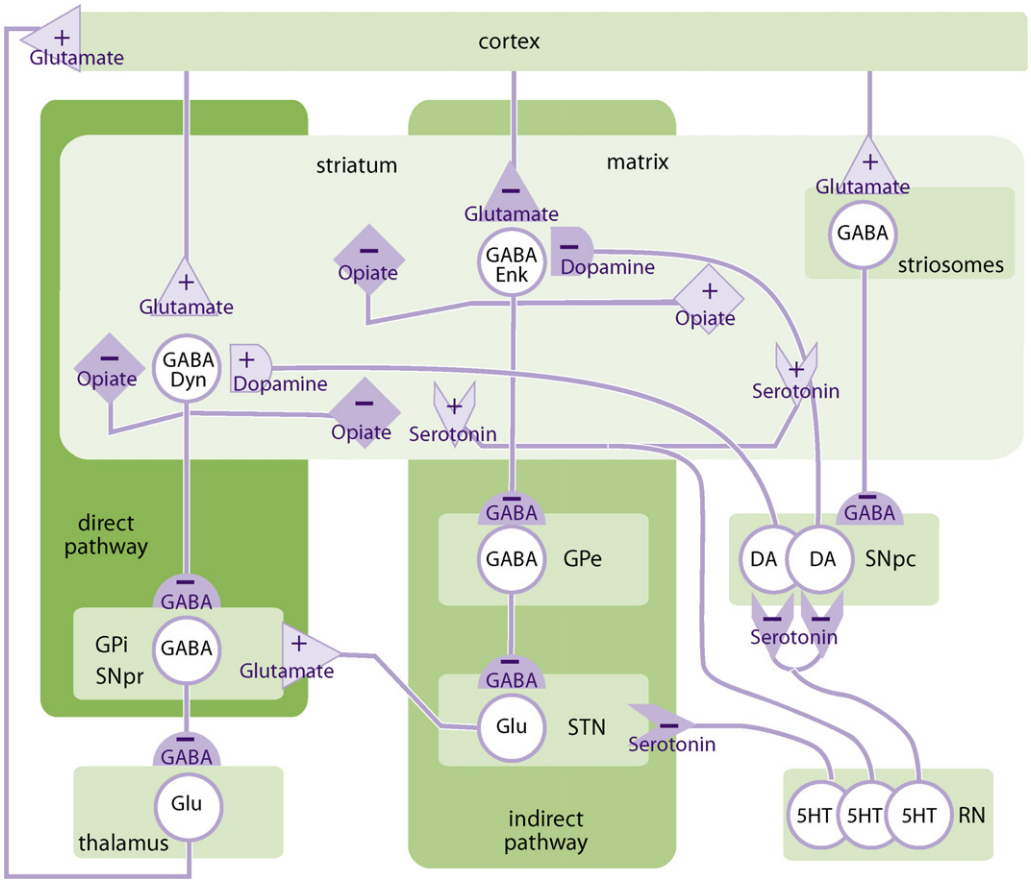

Fig. 3. Schematic representation of corticostriatal circuitry, showing direct and indirect pathways and endogenous neurochemistry involved.
Figure adapted with permission, from G. Mason & J. Rushen (eds.); 2006; Stereotypic Animal Behaviour. Fundamentals and Applications to Welfare (2nd Edition); CAB International, Wallingford, UK.

injection) or dose differences (Scheel-Kruger et al., 1980), stressing the neurochemical complexity of the corticostriatal feedback loops. Finally, manipulating striatal activity by administering glutamatergic agents modulates repetitive behavior: glutamate receptor agonists, such as NMDA agonists, can induce stereotypic behavior, whereas striatal administration of an NMDA-receptor antagonist can attenuate drug-induced stereotypy (Bedingfield et al., 1997). Similarly, transgenic mice with potentiated cortical and limbic glutamate output to the striatum show increased stereotyped behavior after increasing glutamate release as compared to control litter-mates (McGrath et al., 2000). Elevated glutamate levels may produce a depolarizing effect, eventually enabling striatal NMDA-receptors to be activated. Ultimately, neuronal activity of striatum disinhibits feedback to the cortex, inducing stereotypic behavior (Presti, 2004).

4.3. Pharmacological modulation of repetitive behavior: dopamine

The dopamine system was the first system to be associated with repetitive and stereotyped behavior. In 1874, Harnack demonstrated 'compulsive gnawing' in rabbits after injection of apomorphine, an observation replicated by Amsler in 1923 and many others since. Further experiments in guinea pigs showed that repetitive gnawing after apomorphine administration originated from striatum (Amsler, 1923). At the time that Harnack and Amsler conducted their studies, the concepts of chemical neurotransmission and transmitter receptors were unknown and therefore it was not until the 1960s that the neuronal mechanisms underlying apomorphine-induced stereotypy were established (Kuschinsky, 2006). By then, apomorphine was recognized as a dopamine agonist, with its main site of action in the neostriatum. Apomorphine administration was shown to activate dopamine receptors in the neostriatum, resulting in compulsive gnawing behavior (Ernst and Smelik, 1966). The stereotypy-inducing effects of apomorphine and related stimulants have been replicated in numerous studies and across species since (for an extensive overview: see Saka et al., 2004). Striatal dopamine is thought to modulate the balance between the direct and indirect pathways and, consequently, the level of basal ganglia output (Groenewegen et al., 2003). As such, dopaminergic *drugs* may modulate the prevalence of stereotypy through stimulating the direct pathway and inhibiting the indirect pathway (Mason and Rushen, 2006). How these agents affect these circuits is illustrated in Fig. 3: In the direct pathway, post-synaptic D1 receptors are targeted by dopamine projections from the substantia nigra pars compacta. Activation of these D1 receptors increases the overall excitability of the post-synaptic neuron, resulting in amplification of excitatory corticostriatal input and subsequently increased GABA-ergic inhibition of the substantia nigra pars reticulata and the medial globus pallidus, the major inhibitory output nuclei of the basal ganglia. This in turn facilitates activation of thalamo-cortical relay neurons and consequently provides positive feedback to the cortex. Conversely, blocking these dopamine D1 receptors suppresses the direct pathway, and decreases feedback to the cortex, resulting in less stereotypic behavior (Joel and Doljansky, 2003; Presti, 2003). In the indirect pathway, activation of post-synaptic dopamine D2 receptors in the striatum reduces excitatory cortical input and thereby decreases inhibition of the globus pallidus externa. This leads to stronger inhibition of the subthalamic nucleus, thereby decreasing activation of the sub-

stantia nigra pars reticulata and the globus pallidus interna. When these major inhibitory output nuclei are inhibited, the thalamus becomes *dis*inhibited, resulting in increased activity of the cortex (Lewis et al., 2006). Dopaminergic drugs such as apomorphine and amphetamine act on dopamine D2 receptors (Garner, 2006). As such, they suppress the indirect pathway and disinhibit behavior. Conversely, dopamine antagonists, such as haloperidol, reduce or block stereotypies by blocking dopamine D2 receptors (Kjaer et al., 2004).

4.4. Pharmacological modulation of repetitive behavior: serotonin

It is well established that pharmacological stimulation of postsynaptic serotonin receptors in rodents leads to complex behavioral symptoms including stereotyped and repetitive behavior (Curzon, 1990). How exactly this effect is mediated is not well understood. One hypothesis is that spontaneous stereotypic behavior is associated with hypo-activity in serotonin (and dopamine) pathways (Korff et al., 2008). This was also suggested by a study showing stereotypy-reducing effects of citalopram, a serotonin agonist (Schoenecker and Heller, 2003) in bank voles. Other studies have implicated higher serotonin release or turnover or overactivity of serotonin receptors in the development of repetitive behavior. For example, primates reared in isolation that exhibited abnormal repetitive behavior also had higher levels of 5-hydroxyindoleacetic acid (5-HIAA), the major brain metabolite of serotonin when compared to socially reared controls (Kraemer et al., 1989). Interestingly, environmental stress seems to be an important factor in the involvement of serotonin in repetitive behavior: stress-induced increases in stereotypies are more dependent on serotonin than dopamine functioning (Schoenecker and Heller, 2001, 2003). This may relate to why serotonergic medication is especially effective for relieving stress-related repetitive behavior in anxiety disorders, such as OCD (Schoenecker and Heller, 2003; and see Soomro et al., 2008 for a review). However, another hypothesis states that serotonin may affect the development of stereotypies by modulating the dopamine system (Curzon, 1990; Mason and Rushen, 2006; Schoenecker and Heller, 2001). Some findings have suggested an interaction between dopamine and serotonin systems, as dopamine-induced motor stereotypies can be alleviated by drugs that act on serotonin-receptors (Elliott et al., 1990) and motor stereotypies in rats given large doses of amphetamine have been shown to be dependent on serotonin release (Lees et al., 1979).

In sum, much of what is known about the neurobiological basis of repetitive behavior comes from studies of drug-induced behavior. Pharmacological experiments have established the importance of the basal ganglia in the mediation of repetitive behavior and have elucidated the biochemical mechanisms underlying it. However, future work is needed to further explore how exactly repetitive behavior is mediated by these complex systems.

4.5. The impact of lesions on the development of repetitive behavior

A more limited number of studies have studied the effects of brain lesions on the development of repetitive behavior. Unfortunately, in these studies, the stereotypies associated with such models are often not well described. Additionally, the extensive nature of the lesions caused by toxins and infectious agents and the wide variety of abnormal behavior displayed by the animals limit the specificity of these findings. Some studies have investigated the effects of more localized, mechanically induced insults to the CNS on the development of repetitive behavior. Some have targeted the striatum (Antoniou et al., 1998), whereas others have focused on connected cortical and subcortical structures. Enhancements in stereotyped behavior have been associated with lesions in the substantia nigra pars reticulata, supposedly by disinhibition of dopamine neurons in the substantia nigra pars compacta (Koch et al., 2000). Interestingly, changes in stereotyped behavior have also been reported after lesions to the nonstriatal structures within the medial temporal lobe (hippocampus, amygdala). From these studies, it follows that the timing of lesions is crucial for the eventual behavioral abnormalities (stereotypies). Applying such lesions in very young non-human primates resulted in behavioral abnormalities (Bachevalier, 1996; Bauman et al., 2008) that were more pronounced than following similar lesions in adults (Málková et al., 1997), although others have suggested that early lesions are generally associated with more functional sparing (Wood et al., 1997). Interestingly, the results of other studies in rats indicate that a similar lesion to the hippocampus induced in adulthood results in qualitative differences in behavioral abnormalities compared to lesions induced early in life, where repetitive behavior is potentiated after early lesions, but reduced after lesions inflicted in adulthood (Wood et al., 1997; Lipska and Weinberger, 1993). These findings are suggestive of specific developmental windows in the development of repetitive behaviors.

In sum, studies investigating effects of brain lesions on repetitive behavior confirm a central role for striatum in repetitive behavior, but suggest that other areas in the medial temporal lobe may also play a role, possibly by their connections to corticostriatal loops. One hypothesis is that early lesions to the limbic system affect the development of other brain regions, such as the medial prefrontal cortex, that are involved in the regulation of striatal dopamine function (Lipska and Weinberger, 1993; Bauman et al., 2008).

4.6. Genetic modulation of repetitive behavior

In addition, to administering pharmacological agents or inducing lesions, a third way to affect central nervous system function is by genetic modification. Studying behavior of transgenic animals (often mice), such as gene knockouts, can enhance our understanding of the role of those genes in the development of (abnormal) behavior.

4.7. Genetic modulation of repetitive behavior through dopaminergic genes

Consistent with pharmacological studies, genetic models have implicated the dopamine system in repetitive behavior. These models include the dopamine transporter (DAT) and dopamine receptor D3 (DRD3) knockout mice and the dopamine receptor D1 (D1) mutant mouse. These models may be particularly informative on the spontaneous development of repetitive behavior in that (1) they take critical developmental periods into account and (2) they mimic the complex interplay of the integrated development of associated neurobiological structures.

The dopamine transporter regulates the extra-cellular dopamine concentration by the re-uptake of dopamine into the presynaptic terminal following release of the transmitter. The effects of knocking out the DAT-gene are two-fold. First, it results in hyperdopaminergia, increases in extracellular dopamine levels in neostriatum of up to 170% (Berridge et al., 2005). Second, it causes an imbalance between the dopamine and serotonin systems in the basal ganglia (Pogorelov et al., 2005). The hyperdopaminergic DAT knock-out mice display behavior known as superstereotypy: excessively strong and rigid manifestations of complex and fixed action patterns (Berridge et al., 2005).

Unlike the profound and diverse behavioral effects observed in a DAT-knockout, the effects of knocking out the dopamine D3 (DRD3) receptor gene are more specific and lead to narrowly defined changes in behavior. Joseph and colleagues showed an

increase in spontaneous stereotypic behavior of DRD3-knockout mice compared to the wild type (Joseph et al., 2002). Furthermore, these mice exhibited more locomotor activity, but not stereotypy, in response to amphetamine, suggesting a more limited role for the DRD3 in modulating drug-induced stereotypy (McNamara et al., 2006).

A potential problem with knock-out translational models is that modifications affect the entire organism, generating widespread, non-specific results on the one hand and possibly initiating compensatory mechanism on the other. This can complicate interpretation of the data. In contrast, if genetic modification can be targeted to specific brain regions, this may provide valuable additional information on the modulatory effects of the genes involved. Campbell et al. (1999) applied such an approach to investigate behavioral abnormalities in transgenic mice after they had potentiated regional subsets of dopamine D1 neurons (in cortical and limbic regions). These mice displayed episodes of perseverance and repetition of any and all normal behavior, such as repetitive non-aggressive biting of siblings during grooming, and repetitive leaping. The cortical and limbic neurons manipulated are thought to control stimulating glutamate output to the striatum. This study suggests that genetic modification of specific elements of the dopamine system can induce complex compulsive behavior in mice by stimulating regional activity within corticostriatal loops.

4.8. Genetic modulation of repetitive behavior through other genes

The number of genes that may potentially affect pathological repetitive behavior is large and the field of neuroscience is only now beginning to identify some of the players involved. Thousands of genes are expressed during brain development and are involved in regulating and shaping the function and structure of the brain. While modification of dopamine genes is clearly important to the development of repetitive behavior, other genes may also be of interest. Examples include the GABA A-receptor beta-3 gene (GABRB3), the serotonin receptor 2C gene (HTR2C or 5-HT2c), and the disks large-associated protein-3 gene (DAP-3 or SAP90/PSD-95-associated protein 3 or SAPAP3). Translational studies have demonstrated repetitive behavior in knockout models of these genes: The 5-HT2c knockout mouse shows intensified and stereotyped chewing and reduced habituation of responses (Chou-Green et al., 2003); SAPAP3 knockouts display increased repetitive grooming (Welch et al., 2007); and knocking out the GABRB3 gene has bee shown to result in intense circling and tail-chasing (DeLorey et al., 2008; Homanics et al., 1997). These knock-out models are of particular interest, given that (association) studies have linked all three genes to neuropsychiatric disorders, where repetitive behavior is one of the core features: The GABRB3 gene has been linked to autism (DeLorey, 2005), the HTR2C to autism and OCD (Veenstra-VanderWeele et al., 2000) and the DAP3 to trichotillomania (pathological repetitive hair-pulling, an Axis-I impulse control disorder, DSM-IV) and OCD (Züchner et al., 2009).

In sum, data from gene knock-out studies suggest that specific genes may directly and specifically affect or induce repetitive behavior. Candidate genes include dopamine and serotonin genes but also a number of other genes, that have been implicated by whole-genome association studies. These are particularly interesting when they can inspire knock-out models where the behavioral phenotype shows repetitive behavior. Such models may hold clues to the etiology and pathophysiology of this behavior (Lewis et al., 2007).

5. How basal ganglia loops may modulate repetitive behavior

Several hypotheses have been posed to explain how basal ganglia circuitry may modulate repetitive behavior. It is important to note that these models are not mutually exclusive, but may constitute parallel processes, with additive or interactive effects. Here we describe three well-established hypotheses for the neurobiological mechanisms underlying repetitive behavior.

5.1. The direct versus the indirect pathway

In a normally functioning system, the basal ganglia select and amplify desired movements and behavioral patterns via the direct (striatonigral) pathway, while they inhibit unwanted actions via the indirect (striatopallidal) pathway. This balancing of activity by facilitation and suppression occurs at all levels of behavior (Bradshaw, 2001). In general, activating the indirect pathway or suppressing the direct pathway will alleviate stereotypies, whereas suppressing the indirect pathway will induce them. Repetitive behavior has been associated with an imbalance between activity in the direct and indirect pathways, and can thus be seen as a result of decreased inhibition and/or increased facilitation of behavior (Lewis et al., 2006, 2007). Pharmacological and gene-expression studies and models of neuropsychiatric disorders have provided support for this hypothesis, as is described in section III (Translational studies of repetitive behavior) and in Langen et al. (2010).

5.2. Dorsal versus ventral striatum

As described earlier, the striatum is comprised of sensorimotor, associative and limbic areas (Parent, 1990). Sensorimotor and associative cortex projects predominantly to dorsal striatum (putamen and caudate nucleus), whereas limbic areas project predominantly to ventral striatum (including nucleus accumbens, deep layers of olfactory tubule and ventral parts of caudate and putamen). This functional–anatomical arrangement suggests a large degree of segregation between these circuits. However, several studies have shown that exchange of information between corticostriatal circuits takes place (Groenewegen et al., 1994; Haber et al., 2000; Joel and Weiner, 1994; Zahm and Brog, 1992) and it has been suggested that this exchange follows a ventral-to-dorsal path (Haber et al., 2000). These connections allow activity in one cortical–subcortical circuit to influence information processing in another. For example, information in ventral striatum is thought to influence the dorsal striatum, allowing emotional and motivational information to direct sensori-motor behavior. Dorsal striatum is known to be pivotal to habit formation. According to this model, the ventral loop, connecting ventral striatum to orbitofrontal cortex, might therefore affect the expression of habits, once they have become firmly established, or even affect the formation of habits in dorsal striatum (Groenewegen et al., 2003). In this manner, an imbalance between dorsal and ventral striatum might result in the abnormal repetition of (fragments of) behavior or in exhibiting behavior in inappropriate contexts (Groenewegen et al., 2003).

5.3. Striosomes versus the matrix

The corpus striatum is the main input station of the basal ganglia. Cortical input to the striatum is received through the medium spiny neurons, inhibitory neurons with large and extensive dendritic trees. Within the striatum, there are at least two different types of medium spiny neurons. Small clusters of medium spiny neurons of the first type (called "patches" or "striosomes") are embedded in a "matrix", which contains medium spiny cells of the second type (Kandel et al., 1991). The matrix compartment occupies 80–90% of striatal volume, whereas striosome compartments represent only 20–10% of the volume. The two types of spiny neuron are neurochemically distinct and differ in their ontogenetic origin (van der Kooy and Fishell, 1987)

and cortical afferents. Projections from the striosomal and matrix compartments to the substantia nigra are organized compartmentally (Saka and Graybiel, 2003).

Given the distinct anatomic connections of the striosomes and matrix, it seems likely that they are involved in different forms of information processing (Saka and Graybiel, 2003). One hypothesis is that neurons in the matrix are preferentially involved in sensorymotor function and that neurons in striosomes are more involved in motivational aspects of behavior (Leckman, 2002; Saka and Graybiel, 2003). Some studies have indeed suggested that a shift in activity from matrix to striosomes reflects a shift toward more motivationally driven behavior with a consequent narrowing of focus and escalation of repetitive behavior (Canales and Graybiel, 2000; Leckman, 2002; Lewis et al., 2007; Saka et al., 2004). A second hypothesis has arisen from a series of studies on the expression of immediate-early genes in animals exposed to psychomotor stimulant drugs that induce behavioral stereotypies (Saka and Graybiel, 2003). Expression of these genes is a marker of neuronal activity. In one such study, activation of striosome and matrix compartments was related to the level of drug-induced stereotypy in rats: The relative hyper-activation of striosomes compared to matrix activation predicted the degree of induced motor stereotypy (Canales and Graybiel, 2000). These results suggest that an imbalance between striosome and matrix activity may represent a neural correlate of motor stereotypy. Another study reported similar findings in primates: striosome predominance in activity predicted stimulant-induced stereotypy levels. This finding is particularly relevant to human behavior, as the striatum and corticostriatal loop systems in primates are more differentiated than those in rodents (Saka et al., 2004).

In summary, the findings discussed in this section demonstrate how imbalance both *within* and *between* the motor, cognitive and limbic corticostriatal circuits can modulate repetitive behavior. Three complementary models of (1) direct and indirect pathways, (2) ventral and dorsal striatum and (3) striosome and matrix compartments of striatum illustrate how imbalance between these may relate to the development of these behaviors.

6. Discussion and conclusions

This review sought to provide insight in the neurobiology of repetitive behavior. To that end, we have provided an overview of findings from fundamental animal research and translational models.

From early studies on, the basal ganglia have been implicated in repetitive behavior, although initially this was limited to *motor* behavior. In the 1980s, it became clear that the basal ganglia should be viewed as components of multiple parallel, segregated feedback circuits with outputs targeting not only primary motor areas, but also pre-motor and prefrontal cortical areas. Initially, five structurally and functionally distinct parallel loops were proposed, which were later regrouped into three 'macro-circuits': the sensorimotor circuit, the associative or cognitive circuit and the limbic circuit. Respectively these involve the motor and premotor cortex, the dorsolateral prefrontal cortex, and the lateral orbitofrontal and anterior cingulate cortex. Recently, it has been argued that the various functions that are subserved by the macrocircuits cannot be executed independently and it has become clear that information is exchanged between circuits, likely in a ventral-to-dorsal path (Haber et al., 2000). The primary function of corticostriatal circuits is to control and select goal-directed motor, cognitive and motivational behavior. Eventual actions result from coordinated inhibition and disinhibition of the cortical and subcortical structures involved.

Disruption of co-ordinated function within the basal ganglia or between striatal and forebrain structures results in abnormal behavior, often including repetitive behavior. When striatal feedback to fronto-cortical areas becomes dysfunctional, it results in the inappropriate repetition of a behavioral set, an inability to switch to other behavior or the facilitation of inappropriate behavioral sets. Knowledge of the neurobiological mechanisms underlying repetitive behavior comes from studies of environmentally deprived animals and from translational studies, using pharmacological interventions, lesion approaches and gene manipulation. These studies have taught us that environmentally induced repetitive behavior often reflect robust and perhaps even permanent changes in brain development. Furthermore, different types of repetitive behavior are often correlated and seem to be mediated – at least partly – by similar circuitries. The majority of neurons in the basal ganglia use GABA and glutamate as neurotransmitters, whereas especially dopamine and serotonin have important modulatory effects on corticostriatal circuitry, thereby affecting development of repetitive behavior. Gene manipulation is yet in its infancy, but early studies confirm the pivotal role of particularly the dopamine system.

Several hypotheses have been posited to explaining how dysfunction in basal ganglia circuits may induce abnormal repetitive behavior. All involve imbalance between aspects of corticostriatal circuits, and they have focused on models of the direct versus indirect pathway, the ventral versus dorsal striatum or the striosomes versus matrix compartments. These models are not mutually exclusive, but more likely occur in parallel, with different additive or inter-active effects explaining different subtypes of repetitive behavior. One topic only briefly touched upon in this review is the translation of animal work to humans, both in typical development and neuropsychiatric conditions. This is the topic of a separate paper (Langen et al., 2010).

Future research will further target the integration of findings from separate research fields, across techniques and species. As such, it will enhance our understanding of the modulation of repetitive behavior by corticostriatal systems. One of the problems faced today is that animal models of repetitive behavior do not map one-to-one onto the complex behavior observed in humans. Shifting focus from complex syndrome studies to inter-species trait studies may enable the definition of cross-species behavioral clusters. This will facilitate the identification of biological substrates underlying the behavior that characterizes these disorders (Kas et al., 2007). Valuable steps are for example recent papers discussing the validity of translational models for obsessive compulsive spectrum disorders (Boulougouris et al., 2009; Wang et al., 2009), aiming to develop a cross-species model for obsessive compulsive clinical features. Finally, detailed phenotyping and consensus in the definitions applied is indispensable to systematic research efforts investigating repetitive behavior across species and clinical conditions (Lewis and Bodfish, 1998).

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