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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

1. Introduction . . . 346
   1.1. Scope of this review . . . 346
2. Historical perspectives on repetitive behavior . . . 346
3. Repetitive behavior induced by environmental deprivation . . . 347
   3.1. Effects of environmental deprivation on brain development and brain chemistry . . . 348
   3.2. Cognitive changes following environmental deprivation . . . 349
4. Translational studies of repetitive behavior . . . 349
   4.1. Pharmacological modulation of repetitive behavior . . . 349
   4.2. Pharmacological modulation of repetitive behavior: GABA and glutamate . . . 349
   4.3. Pharmacological modulation of repetitive behavior: dopamine . . . 350
   4.4. Pharmacological modulation of repetitive behavior: serotonin . . . 351
   4.5. The impact of lesions on the development of repetitive behavior . . . 351
   4.6. Genetic modulation of repetitive behavior . . . 351
   4.7. Genetic modulation of repetitive behavior through dopaminergic genes . . . 351
   4.8. Genetic modulation of repetitive behavior through other genes . . . 352
5. How basal ganglia loops may modulate repetitive behavior . . . 352
   5.1. The direct versus the indirect pathway . . . 352
   5.2. Dorsal versus ventral striatum . . . 352
   5.3. Striosomes versus the matrix . . . 352
6. Discussion and conclusions . . . 353
   Acknowledgements . . . 353
   References . . . 353

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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-