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Research report

The disrupted basal ganglia and behavioural control: An integrative cross-domain perspective of spontaneous stereotypy

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HIGHLIGHTS

- Spontaneous stereotypy is a behavioural manifestation of poor welfare.
- We present a new model of basal ganglia dysfunction in spontaneous stereotypy.
- Taking a cross-domain approach informs us about the potential neurophysiological basis of stereotypy.

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ABSTRACT

Spontaneous stereotypic behaviour (SB) is common in many captive animal species, as well as in humans with some severe psychiatric disorders, and is often cited as being related to general basal ganglia dysfunction. Despite this assertion, there is little in the literature examining SB specifically in terms of the basal ganglia mechanics. In this review, we attempt to fill this gap by offering an integrative, cross-domain perspective of SB by linking what we currently understand about the SB phenotype with the ever-growing literature on the anatomy and functionality of the basal ganglia. After outlining current models of SB from different theoretical perspectives, we offer a broad but detailed overview of normally functioning basal ganglia mechanics, and attempt to link this with current neurophysiological evidence related to spontaneous SB. Based on this we present an empirically derived theoretical framework, which proposes that SB is the result of a dysfunctional action selection system that may reflect dysregulation of excitatory (direct) and inhibitory (indirect and hyperdirect) pathways as well as alterations in mechanisms of behavioural switching. This approach also suggests behaviours that specifically become stereotypic may reflect inbuilt low selection threshold behavioural sequences associated with early development and the species-specific ethogram or, low threshold behavioural sequences that are the result of stress-induced dopamine exposure at the time of performance.

1. Introduction

Stereotyped or stereotypic behaviours (SB) have historically been described as repetitive, topographically invariant response sequences that appear to lack any ultimate or proximal function [1]. SB can be either psychostimulant-induced [2–5,5–12], environmentally-induced [13] [14–18] and are often associated with human developmental disorders (e.g. autism [19]), neurological disorders (obsessive compulsive disorder, OCD; Giles de la Tourette's syndrome; GTS; [20–22]) and severe psychiatric disturbances (e.g. schizophrenia [23–25]). Non-human SBs include locomotor ('pacing' or 'route tracing') and oral ('sham chewing', 'bar mouthing' and 'cribbing') behaviour patterns (see [18]). Human SBs include minor repetitive motor actions, such as tics, full body SB such as 'rocking', or ritualised sequences of complex behaviours [26–30]. Whether non-human or human, SBs share the characteristics of being ritualised, habitual and often compulsive (in the sense that their performance often overshadows all competing behaviours) [21]. The three categories of SB (psychostimulant, spontaneous, human developmental/neuropsychiatric) although qualitatively quite different, may contain substantial morphological and neurophysiological overlap. Our main focus in this review is to present our thesis on environmentally-induced (spontaneous) SB in particular. However, in the interests of offering a cross-domain perspective, we will integrate discussion of translationally

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relevant comparative data from pharmacologically induced and neuropsychiatric models of SB.

Research to date identifies spontaneous animal SB as a multifaceted construct that has a substantial genetic component, is strongly predicted by assumed "chronic stress" associated with environmental restriction of species-typical behaviour (e.g. the more at variance the housing environment of captive animals is from their naturally free-ranging environment, the more likely they are to show SB), and is the result of altered basal ganglia physiology (see [31,32] for recent reviews). This account, however, cannot provide a convincing explanation of how and why a shift in neurophysiological function within the basal ganglia results in the development and manifestation of repetitive sequences of behaviour. The purpose of this review, therefore, is to consider:

(1) What are the key defining causal and neurophysiological characteristics of the spontaneous SB animal phenotype?
(2) What do we currently know about normal basal ganglia mechanics in producing behavioural control and what does the psychostimulant-induced SB literature tell us about how alteration of normal basal ganglia mechanics could lead to repeated sequences of behaviour (SB)?
(3) How does information from (Q2) inform us about the neurophysiological characteristics of the spontaneous SB phenotype?

In this review we will draw on studies and theories from ethology, neurology, psychology, pharmacology and neurobiology. The cross-domain integration of translationally relevant facets of these often-conflicting theoretical perspectives will expedite the development of biologically relevant causal models of spontaneous SB. For example, while psychology may inform us about general animal well-being, and neurology about potential differences in behavioural function, a clear understanding of the fine-motor control mechanisms that may be involved with complex SBs may come from pharmacologically-induced models. As such, by adopting a cross-domain approach, we hope to offer a very detailed insight into many aspects of SB, but also further insight into normal and disrupted basal ganglia functioning.

2. What are the key defining causal and neurophysiological characteristics of the spontaneous SB animal phenotype?

In the first section of this review, we describe the putative causal factors and general environmental conditions that are proposed to constitute risk factors for SB development. As part of the cross-domain approach, we will discuss ethological models of behavioural motivation and give an overview of some human models of SB to further deconstruct the role of risk factors in eliciting SB, but also to provide a mechanistic framework upon which neurophysiological evidence can be critically analysed.

2.1. Stress as a mediator of SB: Beyond the 'coping' hypothesis

Spontaneous SBs rarely occur in feral or semi-feral populations of animals, suggesting that their development is an artefact of the captive or domestic environment [33–35]. Restricted or sub-optimal housing conditions, particularly involving marked incongruity from the species' feral environment, represent a significant risk factor in the development of SB (e.g. [35–37]). Thus, spontaneous SB in captive animals is associated with stress and often perceived as an indicator of existing or previous poor welfare, and has previously been described as a 'coping mechanism' in this context [1,33].

In its most general form, stress refers to the physiological response to a psychological or physical 'stressor' [38]. In other words, stress can be operationally defined as any event or perception that leads to a physiological stress response. Although 'stress' is frequently referred to when describing the aetiology of spontaneous SB [1,39–42], there are limitations in using this term. First, it is a complex and heterogeneous construct [43] and as a result there is variation in how it is interpreted. Second, stressors differ both qualitatively (psychological or physical) and quantitatively (e.g. chronic, acute, chronic intermittent) [45–47], and different individuals respond (physiologically and behaviourally) to the same stressors in quite disparate ways [47,48]. As a consequence, not all stressors will cause SB, and some stressors will be significant risk factors for SB in some species, but not in others. For example, although food restriction, social isolation and restricted locomotion have all been linked to SB development, cold, immobilisation and inescapable electric shock have not (see [49] for review). In addition, not all individuals that share the same environment develop SB [50,51], whereby stress and propensity for SB development is highly influenced by genotype [52–54]. Cabib et al. [102,103], for example, reported a significant genotype-dependent effect of different stressors on SB development in mice that was mediated through dopaminergic (DAergic) activity (to be discussed in Section 2.4).

Although stress may be considered too ambiguous a term, specific *stressors* have been consistently linked to the development of SB in several species. For example, restricted food intake reliably causes stereotypic pecking in poultry [57–59], whilst for pigs, this together with restriction of locomotion causes stereotypic headweaving, chain manipulation, bar-biting and sham chewing [50,60]. Prevention of locomotion causes stereotypic jumping by bank voles [61], whilst in similar conditions mink perform stereotypic pacing and rearing [48]. Also in mink, feed-restriction is reported to have a similar effect [62]. Cows tongue-roll when food is restricted [63,64] or when they are confined [65], restricted feeding or social isolation induces SB in sheep [66] and social isolation has the same effect in dogs [67].

To summarise, while there is significant overlap between the effects of different stressors on the risk to develop SB, there is certainly much variation at both a species and stressor level with genotypic predisposition playing an important role.

2.2. An ethological framework for SB development

Ethological models of behavioural motivation have been used to determine the relationship between internal and external stimuli in eliciting and terminating behaviours [68]. Such models are therefore important in understanding the causal and functional aspects of SBs since they are characterised by non-termination of behaviour sequences. Here we revisit some of these models in the context of SB as a platform for critical analysis within the neurophysiological domain.

Many of the motivation models originate from Lorenz's psychohydraulic model [69] (water pressure symbolising motivation within a threshold-based system) and von Holst's Sollwert–Istwert model [70] (discrepancy between perceived states [current and desired] determining and directing motivation). These models suggest that for continual repetition of a behavioural sequence to exist, the respective level of motivation must (a) always be above threshold and (b) perpetually outcompete other prospective behavioural sequences. Conversely, SBs rarely constitute 100% of the time budget and thus, within this framework, motivational levels of SBs must vary sufficiently for other competing behaviours to emerge.

One of the most pertinent models of motivation in respect to SB is that that proposed by Hughes and Duncan [71]. This model was aimed primarily at explaining the concept of animal 'behavioural needs' but also to explain the motivational basis of SBs. The model is based on the premise that goal-directed behaviours