The role of the indirect pathway of the basal ganglia in the amplification of spontaneous stereotypy in a deer mice model

Introduction [shorter: establish topic, significance, allusion to lit review]

Stereotypical behaviors, or random, repetitive movements that serve no apparent function, are important for the diagnosis of autism and other neurological disorders[1-10]. These movements are often predictable, rhythmical, and maladaptive to the environment[5-7,9,11]. Thus far, many studies have implicated the basal ganglia as crucial for the manifestation of stereotypic behaviors[1,4,8,10,14]. Specifically, imbalances between the direct and indirect pathways of the basal ganglia could be responsible[1,4,8]. Despite the evidence supporting the involvement of the basal ganglia, the exact neurobiological basis of these movements remains undetermined. Studies performed **with animal models** could offer insight into the fundamental mechanisms of stereotypy, revealing how we can manipulate **the two pathways of the basal ganglia**, the **amount of dopamine transmitted**, and **the activity of the three receptors** to alter the amount of stereotypy present, which could then potentially have clinical applications[2,3,9].

The importance of the deer mice animal model [keep subheadings – they still make sense in terms of content; remove critique – in a research report, every question or gap has to be answered by the research, so only want a single question at end of Intro; remove recommendations – some may go in Discussion]

Deer mice provide one example of a possible animal model that can be used to study the stereotypic movements seen in a variety of animals, such as birds, pigs, horses, minks, monkeys, and humans[3]. Deer mice exhibit high rates of spontaneous stereotypic behaviors, which typically include vertical jumping and backwards somersaulting, after being raised in standard laboratory conditions[2-4,7-10,12,13]. This standardized housing is thought to represent an environmental

Commented [SS1]: First subheading matches the information in the intro paragraphs, staying in parallel order of mention, and covering topics the reader would expect to have explanation on given the title.

restriction in comparison to their natural habitat[2-4,7-10,12,13]. The environmental constraint that causes stereotypy in deer mice can be likened to the deprivation experienced by children with autism who have social and communication deficiencies[3]. Both populations are lacking traditional experiences that could be crucial for typical development. Therefore, it is possible that the early deprival of conventional experiences plays a role in the induction of stereotypy in both deer mice and children with autism[3]. The spontaneous occurrence of these behaviors due to their environmental conditions makes deer mice a particularly good model because the lack of pharmacological intervention mirrors the case of children with autism[9,13]. Stereotypy in humans also occurs spontaneously and as a result of the surrounding environment[9].

The basal ganglia and its direct and indirect pathways

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Stereotypic behaviors have been connected to dysfunction in cortico-basal ganglia circuitry[3,4,7-10]. The basal ganglia, which have been cited as key structures for the development of these repetitive behaviors, are made up of the striatum (which consists of the caudate nucleus and the putamen), the pallidum, the subthalamic nucleus, and the substantia nigra[15]. This group of nuclei is located in the forebrain, and their position allows them to affect the executive operations of this structure, thereby giving the basal ganglia the ability to change the way the brain plans movement[15]. …[content removed to shorten this document!]

The importance of the neurotransmitter dopamine

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Stereotypic behaviors can be increased by amplifying the amount of dopamine transferred to the striatum, and can conversely be decreased by preventing dopamine from reaching the striatum[1,16]. However, the ability to induce stereotypic behaviors is specific to the striatum, and injection of dopamine extrastriatially does not increase these movements[11]. Researchers have found several different ways to manipulate the amount of dopamine reaching

the striatum to determine the effect that this neurotransmitter has upon stereotypic behaviors. For instance, it has been hypothesized that the restricted conditions of standard laboratory housing for deer mice cause stereotypic behaviors because these environments cause stress to the animal[7]. This stress subsequently changes the way that dopamine is transmitted in the brain[7]. Further studies performed with different species of mammals have also indicated the importance of dopamine by showing that dopamine agonists and other drugs that enhance dopamine's actions have the ability to induce stereotypic behavior[2,3,5,9]. Another way to increase the amount of dopamine would be to apply a central nervous system stimulant, such as amphetamines or cocaine, which cause dopamine to be released into the striatum[6,7,11]. Conversely, administration of a dopamine receptor antagonist would block dopamine from reaching the striatum and thereby prevent these stereotypic movements from occurring[11]. [content removed to shorten doc]

The interaction of dopamine, adenosine, and metabotropic glutamate receptors in the indirect pathway

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In addition to the D_2 dopamine receptors found on the striatopallidal neurons of the indirect pathway, adenosine A_{2A} receptors are also selectively present[16]. These two receptors are co-localized on neurons of the indirect pathway, and both are found in high concentrations in the striatum[16]. D_2 and A_{2A} receptors interact with one another in several ways, and they have an antagonistic relationship[4,16]. For example, A_{2A} receptor antagonists are able to amplify the effect of D_2 agonists to decrease overall indirect pathway activity and thereby increase movement[16]. These direct interactions occur when A_{2A} receptors are activated which then causes D_2 receptors to decrease their attraction to agonists while their affinity for antagonists remains the same[16]. This finding is important because it shows that a selective D_2 agonist alone is not enough to intensify stereotypy[10]. Therefore, it can be assumed that the indirect pathway changes made by

the A_{2A} antagonist are necessary for an increase in stereotypy to occur. [content removed to shorten doc]

Goals of the Present Project [this is no longer a conclusion! Instead, it introduces the gap and research question]

Although the exact neurobiological mechanism behind stereotypic movements remains elusive, numerous studies have established the importance of the basal ganglia and the imbalance of the activity of its direct and indirect pathways. These structures are crucial for understanding stereotypy, and prior examination has already pointed out the importance of dopamine. An increased influx of this neurotransmitter into the striatum has the ability to increase stereotypy. However, the ability of dopamine to reach the striatum is modulated by several receptors located on the striatopallidal neurons of the indirect pathway. Adenosine and metabotropic glutamate receptors combine to antagonize the dopamine receptors found on these neurons, and their overall affect can lead to the alteration of indirect pathway activity.

Therefore, each structure in the basal ganglia, both of the pathways, and all of the neurons and receptors play important roles in the induction of stereotypic behavior. The interactions of each of these different components are very important, and further research is needed to entirely map out the activation process and to understand the neurobiology behind these movements. To this end, our lab/I **[add research question/s]…**

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