Neuroscience - Analysis and discussion of the article: Cui *et al*. (2013)

Student's name

Institution

Neuroscience

Professor

December 2022

Article review: Cui, G., Jun, S., Jin, X. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation.

As we know, the differential connection between spiny neurons located in the matrix evidences the complex integration of motivational, sensory and motor signals coming from cortical and limbic afferents, and also suggests another level of functional segregation within the striatum. As a basis for understanding the work of Cui *et al*. (2013), it should be taken into account that to understand the functioning of neuronal assemblies it is necessary to be able to activate or inhibit with millisecond temporal precision a specific group of neurons with a similar function (e.g., neurons related to feeding), without affecting other neurons in charge of other functions (e.g., motor control) which may be spatially intermingled. Controlling neuronal activity selectively has been the most important technological challenge and the dream of many neuroscientists. In the last decade we have witnessed great advances in the understanding of brain functioning, however, these achievements have been limited due to the complex organization of the brain.

For example, dopamine is a monoamine that interacts with glutamate in approximately 95% of neurons in the striatum, and these neurons are of great importance in the regulation of both direct and indirect motor pathways. When there is an alteration in the direct and indirect pathways, the functional response of the internal circuits of the basal ganglia will also be affected. There is a bidirectional relationship between the basal ganglia and the cerebellum, so we believe that this interconnection could have been altered by a specific lesion (Zhang *et al*., 2009).

In the study by Cui *et al*., (2013) they evaluate a model to determine the in vivo activity of spiny neuronal projections by direct and indirect pathways using GCaMP3 in the dorsal body D1-Cre and mice. Therefore, making use of single photon counting and time-dependent fiber optics, with time-dependent mice running a tearea in an operant fashion.

In conjunction with the study by Cui *et al*., (2013), other studies have determined that evocation is a process involving the output of stored information and rapid decision making. Detecting that the blockade of muscarinic receptors in the anterodorsal striatum during the evocation process of the inhibitory avoidance task produces a deficit in the retention of this task. Evocation has been observed to induce changes in gene expression and protein synthesis. However, it is not yet known whether information retrieval produces structural changes in medium spiny neurons of the anterodorsal striatum.

In detail, as is known, in the basal ganglia, based on anatomical and physiological evidence, a model of interconnection between the basal ganglia has been proposed that is characterized by the presence of two specific output pathways of the striatum with different connectivity and functions, the direct and indirect pathways.

It has been determined then, that the neurons of the indirect pathway also have direct projections to the output nuclei, as proposed by Cui *et al*. (2013). Similarly, neurons of the direct pathway have projections to the external globus pallidus. Moreover, the existence of a connection from the cortex to the subthalamic nuclei that is transmitted directly to the output nuclei without passing through the striatum has also been proposed. The decrease in dopaminergic control over the striofugal neurons causes an imbalance in GABAergic neurotransmission of the direct and indirect pathways: The lack of stimulation produces a decrease in the signal of the direct pathway, while the lack of regulated inhibition causes an increase in the signal of the indirect pathway. Lack of direct inhibition and stimulation of the subalamic nucleus results in increased inhibition of the thalamus and a consequent decrease in cortical stimulation.

Particularly, to perform the study in Cui *et al*., (2013), they used indicator specifically as GCaMP3, which is a genetically modified calcium indicator of new appearance and is formed by the fusion of GFP, calmodulin, which is a protein that changes its conformation with the presence of calcium and M13 (synthetic peptide). These conformational changes occur in such a way that as the calcium concentration increases, GFP emits fluorescence, and as it decreases, it ceases to emit fluorescence. If GCaMP3 is bound to a synaptic protein called synaptophysin (syGCaMP3), GCaMP3 can be expressed together with this protein in the synaptic terminals in order to observe the calcium present. On the other hand, all fluorescent proteins show some sensitivity to the pH of the medium in which they are found, due to the effect produced by protons on the structure of the fluorophore (Sun *et al*., 2020). This sensitivity affects the excitation wavelength and produces small variations in fluorescence emission, variations that are barely perceptible in the range of pH values in which we move under physiological conditions. The pH sensitivity of GFP is a consequence of the protonation or deprotonation of certain important amino acids that are part of the core structure of the fluorophore.

In addition, with fluorescence, neurons can be grouped according to the similarity in their recorded activity, maximizing the similarity between the elements of a group and minimizing the relationship of them to other groups. Activation of the corticostriatal microcircuitry generates a greater number of groups of neurons with similar firing compared to those generated by thalamostriatal activation. In addition, the activity cycles of similarly firing neurons elicited by thalamic stimulation are fewer than those generated from the cortex (Tyssowski & Gray, 2019). We conclude that the impact to cortical or thalamic glutamatergic input generates important differences in the manner in which the striatal microcircuitry is activated.

Recent evidence indicates that during the execution of automated movement sequences, the striatum, the main input nucleus of the basal ganglia, encodes complex variables such as speed,

time or space. The way in which these representations are constructed during learning and the specific contribution of these representations to behavior remain to be determined.

In turn, the particularities of neuronal morphology require that neurons maintain sophisticated but fluid communication between their different subcellular compartments. This is particularly important to maintain proper communication between the information encoded at the synapses and the neuronal nucleus, so as to translate this into effective short- and long-term changes. Nuclear Ca2+-mediated signaling connects neuronal activity with a transcriptional response, which ends up globally affecting different neuronal functions, involving metabolic, energetic and morphological changes, adapting them to the new conditions (Reese & Kavalali, 2015).

Particularly, the basal ganglia, having direct connections with the cerebral cortex, regulate their activity through subcortical circuits in which the subthalamic nuclei and substantia nigra are specifically involved.

It is clear that the basal ganglia themselves are directly involved in the generation of functions indispensable for the elaboration and execution of the complex program of voluntary motor function. Thus, the functions of initiation, planning, sequencing and regulation of voluntary movements can be attributed to the gray nuclei. It remains to be clarified whether these functions are properly the direct product of their functioning or whether, on the contrary, the gray nuclei provide an indispensable component for these functions to operate correctly, the function as such remaining outside the nuclei, or being the product of the joint work of a distributed network of structures. However, this is a question that could hardly be resolved from empirical research. Not only insightful experimental designs but also a good deal of discussion and reflection on the concept of brain function are needed. It has been pointed out that it is interesting insofar as it can be shown that the basal ganglia may be related to praxis. However, he emphasizes his criticism on the consideration that it is the alteration of the gray nuclei itself that generates the apraxia and not the direct or indirect affectation on the functional scaffolding that is established with the thalamus and the frontal and parietal cortical regions. It has been determined that one should be more cautious when attributing the origin of apraxias to basal ganglia lesions. For him, the effect of basic movement alterations (in speed, strength, control) may lead to confusion in clinical diagnoses of apraxia with basal ganglia origin.

Negative feedback encompasses the involvement of pre- and postsynaptic dopaminergic receptors. The neuronal circuits of the rat and human basal ganglia are very similar, so the use of animal models is essential for the study and understanding of human pathophysiopathological, biochemical and molecular mechanisms.

For example, information from the visual field reaches the visual cortex, which together with the other areas of association and visual processing corresponds to 55% of the entire cerebral cortex. Because of its multiple cortical and subcortical connections, it is reported that half of all information stored in the brain is directly or indirectly related to vision. The V1 cortex corresponds to Brodmann's area 17. It is also called striate cortex because it presents Gennari's stria, formed by

highly myelinated axons in its fourth cytoarchitectonic layer. This cortex is made up of six laminae, of which the IV is subdivided into IVA, IVB, IVC-alpha and IVC-beta.

On the other hand, in reference to optogenetics, the bases are found in the study of a unicellular organism, the alga Chlamydomonas reinhardtii, and its ability to move towards a light source. In such a way that the controlled application of light beams provokes action potentials, which makes it possible to study the function of those neurons previously chosen by the experimenter and, importantly, without affecting those in the environment, since they are not sensitive to the light beam. Through genetic strategies, genes from microbial opsins, can be introduced to genetically defined neurons (Cole *et al*., 2018). These opsins are unique (do not require the addition of cofactors) light-sensitive components either ion-permeable channels (e.g., ChR2) or anion pumps (NpHR) with activation-inactivation kinetics in the millisecond range.

It has been determined that optogenetic inhibition of cholinergic neurons during the change in contingency makes individuals less sensitive to identify this change, thereby regulating behavioral adaptability to a change in contingency.

Optogenetics makes it possible to manipulate the activity of neurons with millisecond temporal precision thanks to the controlled application of light flashes that affect the function of light-sensitive sodium channels expressed in defined neuronal populations, in order to control neuronal activity it is necessary that neurons contain in their entire membrane, To achieve this, a virus capable of infecting and incorporating the genetic material necessary for the neurons to express this channel can be used, or transgenic animals that already express the channel constitutively as part of their genome, and these animals have been used to study the neuronal circuit involved in Parkinson's disease, the relationship between the motor cortex and the somatosensory cortex, among others (Elizabeth *et al*. , 2011). In such a way that the controlled application of light beams provokes action potentials, which makes it possible to study the function of those neurons previously chosen by the experimenter and, importantly, without affecting those found in the environment, since they are not sensitive to the light beam. This method will serve to identify cell populations involved in various diseases and will help in the search for new therapeutic targets. Moreover, the method itself promises therapeutic utility (Seeger-Armbruster *et al*., 2015). For example, the group of neurons that responds to Parkinson's treatment by deep electrical stimulation was recently identified with optogenetic strategies. In addition, optogenetics has been used to control epileptic seizures in experimental animal models. Likewise, the primary role played by dopaminergic neurons in generating substance addictive behaviors has been discovered (Yazdan-Shahmorad *et al*., 2016).

In conclusion, this type of research is of great relevance, and to evaluate the direct pathways and indirect pathways, to study the different pathologies, and to elucidate, the different conditions and neural mechanisms through different models and studies. In relation to the loss of the control exerted by the substantia nigra in the striatum and the subthalamic nucleus on the globus pallidus will produce anomalies that will derive in dysfunctions associated to the basal ganglia and, therefore, to the production of voluntary movement. The subthalamic nuclei form, then, the

indirect pathway in the basal ganglia circuit and, consequently, receive afferences from the lateral globus pallidus. However, their efferents go back to the medial globus pallidus and the substantia nigra reticulata. Studies show that the subthalamic nuclei receive direct afferents from the cerebral cortex. The substantia nigra contains dense nuclei of dopamine-producing neurons and establishes the nigrostriatal system with the striatum by providing it with dopaminergic inputs.

References

Cole, S.L., Robinson, M.J.F., Berridge, K.C. (2018). Optogenetic self-stimulation in the nucleus accumbens: D1 reward versus D2 ambivalence. *PLoS One* 13, 1–29. https://doi.org/10.1371/journal.pone.0207694

Cui, G., Jun, S., Jin, X. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature* 494, 238–242 (2013). https://doi.org/10.1038/nature11846

Elizabeth, A., Sabens, K. Steller, J. (2011). Mieyal Levodopa activates apoptosis signaling kinase 1 (ASK1) and promotes apoptosis in a neuronal model: implications for the treatment of Parkinson's Disease. *Chem Res Toxicol;* 24 (10): 1644-1652.

Hagenston, A., Bading, H., Bas-Orth, C. (2019). Functional Consequences of CalciumDependent Synapse-to-Nucleus Communication: Focus on Transcription-Dependent Metabolic Plasticity. *Cold Spring Harbor Perspectives in Biology*: a035287.

Kwon, T., Sakamoto, M., Peterka, D., Yuste, R. (2017). Attenuation of Synaptic Potentials in Dendritic Spines. *Cell Reports* 20:1100–1110.

Luo, L., Hina, B., McFarland, B., Saunders, J., Smolin, N., von Reyn, C. (2022). An optogenetics device with smartphone video capture to introduce neurotechnology and systems neuroscience to high school students. *PLoS ONE* 17(5): e0267834.

Reese, A. & Kavalali, E. (2015). Spontaneous neurotransmission signals through store-driven Ca2+ transients to maintain synaptic homeostasis. *eLife* 4:1–15.

Seeger-Armbruster, S., Bosch-Bouju, C., Little, S., Smither, R., Hughes, S., Hyland, B. (2015). Patterned, but not tonic, optogenetic stimulation in motor thalamus improves reaching in acute drug-induced Parkinsonian rats. *J Neurosci*; 35(3):1211–6.

Sun, X., Bernstein, M., Meng, M., Rao, S., Sørensen, A., Yao, L., Zhang, X., Anikeeva, P., Lin Y. (2020). Functionally Distinct Neuronal Ensembles within the Memory Engram. *Cell* 181:410-423.e17.

Tyssowski, K. & Gray, J. (2019). The neuronal stimulation–transcription coupling map. *Current Opinion in Neurobiology* 59:87–94.

Yazdan-Shahmorad, A., Diaz-Botia, C., Hanson, T., Kharazia, V., Ledochowitsch, P., Maharbiz, M. (2016). A Large-Scale Interface for Optogenetic Stimulation and Recording in Nonhuman Primates. *Neuron*; 89(5):927–39.

Zhang, S., Zou, M., Lu, L., Lau, D., Ditzel, D., Delucinge-Vivier, C., Aso, Y., Descombes, P., Bading, H. (2009). Nuclear calcium signaling controls expression of a large gene pool: Identification of a gene program for acquired neuroprotection induced by synaptic activity. *PLoS Genetics* 5.