Neurological components of parkinson's disease

My topic of choice is Parkinson’s disease (PD), a chronic neurodegenerative disease of the central nervous system. Its symptoms result in clinical manifestations of primarily the motor system, though non-motor symptoms do develop particularly in the disease’s later stages (Zhai, Tanimura, Graves, Shen, & Surmeier, 2018). This topic is of great significance as PD is the second most common neurodegenerative disease in the world, and affected 6. 2 million people in 2015, resulting in roughly 117, 400 deaths globally (GBD 2015). Its specific cause is currently unknown, and no cures have been found to date, thus it holds significant bearing in the field of scientific research. This topic is of particular importance to me as my uncle himself is a PD sufferer, and I would like to get a better understanding of what his symptoms will entail physiologically.

The PTEM element relevant to my topic is that biological entities harness potential energy stored in electrochemical gradients and released from chemical reactions. In humans, movement is produced by interactions between basal ganglia nuclei which send signals to the thalamus, relaying movement information to the motor cortex (Silverthorn, 2015). This process is controlled by striatal dopamine, and thus relies on energy produced by the electrochemical gradient of dopaminergic neurons in the substantia nigra (SN) from which the neurotransmitter is released. In PD, degredation of the SN results in fewer electrochemical gradients available from remaining neurons to be involved in the process of movement production by the basal ganglia-thalamo cortical pathway, giving rise to its clinical manifestations (Blandini, Nappi, Tassorelli & Martignoni, 2000).

The IFES element that relates to my topic is that information exists in many forms and is relayed within and across biological molecules, controlling processes at the cellular, tissue and organismal levels. For reasons not yet understood, PD elicits neurodegeneration of dopaminergic cells in the substantia nigra pars compacta (SNpc; Blandini et al., 2000). The majority of these cells undergo cell death and cannot produce or release their neurotransmitter, dopamine, resulting in a mitigated output of information from the neural tissue they comprise (Silverthorn, 2015). This has flow down effects on other components of the basal ganglia, who control their activity based off dopaminergic signals from the SNpc. These components of the basal ganglia alter the information release from their GABAnergic and Glutaminergic neurons accordingly, accruing as an excessive inhibitory input to the thalamus (Zhai et al., 2018). This results in suppression of the thalamo-corticospinal pathway which usually produces smooth movement, and thus gross motor symptoms onset in the sufferer (Blandini et al., 2000).

Two SF components relevant to my topic are that biological structures and their interactions are determined by chemical and physical properties that both enable and constrain function, and that these structures can be arranged into organized units to enable more complex functions. The chemical and physical properties of each component of the basal ganglia-thalamo cortical pathway result in activation or inhibition of their own or other biological structures, collectively giving rise to more elaborate physiological functions. The neurons comprising the SNpc act in unison to release dopaminergic signals to the striatum, whose binding has an excitatory or inhibitory effect on D1 and D2 GABA receptors respectively,

directly affecting the release of GABA from the GABAnergic neurons comprising the globus pallidus interna/externa (GPi/GPe) and substantia nigra pars reticulata (SNpr; (Blandini et al., 2000). These are inhibitory neurons which act on following neurons to constrain the function of the structure they comprise, and the strength of this effect is regulated by coordinating GABA release with signals from previous structures. Glutaminergic neurons comprising the subthalamic nuclei (STN) thus control their release of excitatory glutamate in accordance with GABA neuron activity, both of which input highly coordinated signals to the thalamus (Zhai et al., 2018). This signal dictates the level of inhibition placed on the thalamo-corticospinal pathway and hence the quality of movement produced (Blandini et al., 2000). In PD, structural changes in the degradation of the SNpc are visibly evident to the naked eye, due to the reduced density of dopaminergic neurons (Bear, Connors & Paradiso, 2016). From this we can see the resulting affect on the coordinated system of signals acting to enable and constrain function down the pathway.

PD incidences in humans have been seen to rise over time, which can be understood through an evolutionary perspective. Since phenotypes are subject to selective pressures, human evolution has been shaped by the environments in which our ancestors lived. These pressures lead to the generation of different phenotypes, resulting from the gain and loss of traits along an organism’s lineage in accordance with the differential rates of survival they confer within the environment. Since our ancestors survived as hunter-gatherers for thousands of years, our genome remains adapted to a prototypically physical way of life in which large expenditures of energy may

be made on a daily basis (O'Keefe, Vogel, Lavie & Cordain, 2011). Physical activity is known to have neuroprotective effects across all neurodegenerative diseases, including PD, which is supported by animal models (Ruiz & Espay, 2017). Additionally, moderate to vigorous physical exercise has been associated with more than a 30% reduction in the risk of PD (Yang et al., 2014). Technological advancement has resulted in a progressively dramatic reduction in physical exertion in the daily lives of humans, despite the evolutionarily unchanged physical demands of the human body, likely accounting for the increased risk and prevalence of PD over time (O'Keefe et al., 2011).

All components of the basal ganglia-thalamo cortical circuit have equally important roles in regulating the activity of each other in order to produce a coordinated response conducive to smooth movement. Changes in the density of dopaminergic neurons in the SNpc has profound effects on the rest of the system, leading to gross disorders in motor control (Blandini et al., 2000). These effects are evident in both the direct and indirect pathway of PD. In the direct pathway, limited dopamine release from the SNpc leads to reduced dopamine binding with D1 receptors in the Striatum. This limits excitation of inhibitory GABAnergic neurons from the striatum, dampening its effect on the GPi/SNpr (Zhai et al., 2018). This results in over-excitation of GABAnergic neurons travelling to the thalamus, which detects excessive inhibitory input, suppressing the thalamocorticospinal pathway necessary for producing movement (Bear et al., 2016). In the indirect pathway less dopamine is able to bind to D2 receptors in the striatum, limiting inhibitory signals to its GABAnergic neurons, which become overactive and excessively

inhibit GABAnergic neurons in the GPe (Zhai et al., 2018). These neurons then cannot sufficiently inhibit Glutaminergic neurons in the STN, resulting in over-stimulation of GABAnergic neurons in the GPi/SNpr, again sending excessive inhibitory signals to the thalamus (Bear et al., 2016).

Ultimately, PD is a disease of the central nervous system in which the loss of dopaminergic neurons in the basal ganglia profoundly affects ones motor control, and its pathophysiology can be linked with each of the biology core concepts we have explored so far this semester.

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