Catecholaminergic Neuron Electron Transport (CNET): A Neural Signaling Mechanism

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Abstract

The neural mechanism responsible for action initiation and selection for specific actions remains elusive. The CNET neural signaling mechanism hypothesis for action selection was first proposed in 2018 based on the available evidence at that time and made predictions about additional phenomena that should be present if the hypothesis was correct, as well as suggestions for how to test for them. Since that time, substantial evidence of the four core components of CNET has been obtained. First, it has been shown that high-energy triplet state electrons are generated from dopamine in large SNc dopamine neuron soma by chemiexcitation, which must be dissipated by some mechanism to protect the neurons. Second, it has been shown that the electrons can tunnel through ferritin structures that exist inside of and between large SNc dopamine neuron soma. Third, it has been demonstrated that post-synaptic activity at axon synapses of large SNc dopamine neurons depolarizes the axon membrane, promotes action potentials and provides an electromotive force for routing the tunneling electrons. Fourth, it has been shown that iron release that would be caused by the tunneling electrons interacting with ferritin at the target large SNc dopamine neuron(s) can promote calcium signaling and action potentials in those neurons. Thus, while tests to obtain direct evidence of a connection between the CNET neural signaling mechanism and action selection and initiation have not yet been conducted, this growing body of evidence of associated physical phenomena that are predicted by the CNET hypothesis indicates the need for such testing.

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Acronyms

- AFM atomic force microscopy
- ATP adenosine triphosphate

- BLG bilayer graphene
- Ca2+ calcium ion
- CNET catecholaminergic neuron electron transport
- EM electron microscope
- Fe2+ ferrous iron
- Fe3+ ferric iron
- H2O2 hydrogen peroxide
- LC locus coeruleus
- LIP labile iron pool
- NCC neural correlates of consciousness
- NMO neuromelanin organelle
- QD quantum dot
- ROS reactive oxygen species
- RyR ryanodine receptors
- SNc substantia nigra pars compacta
- SNr substantia nigra pars reticulata
- SPION superparamagnetic iron-oxide nanoparticle
- VTA ventral tegmental area

1. What is the CNET mechanism and why is it needed in the brain?

While there is a fairly large body of work directed to the neural correlates of consciousness (NCC) (Koch et al., 2016; Metzinger, 2000; Frith et al., 1999), an action initiation and selection mechanism that is consistent with how action initiation and selection is experienced has not been identified. The CNET hypothesis is an NCC for action initiation and selection and was defined in 2018 by the presence of substantial concentrations of ferritin and neuromelanin in catecholaminergic neurons (Rourk 2018). At that time, compelling evidence of electron tunneling through ferritin cores between electrodes at distances of up to 12 nm had been obtained. Neuromelanin was also known to be a nanoparticle having complementary electronic properties to those of ferritin. It was reasoned that if 1) these materials were present in the same neurons and had a structure that would allow energy to be transferred between those neurons, it would have to be for the purpose of the generation of action potentials, because that is the primary function of neurons and neural signaling. That would make sense, because the substantia nigra pars compacta (SNc) is at the head of what is called the direct pathway and is associated with action initiation and selection (Macpherson et al., 2014; Cui et al., 2013). Accordingly, 2) a source of energy to generate the electrons would be needed, in addition to 3) unusual electrical properties of the largest axons of those neurons to provide an electromotive force to route the electrons to a neuron or group of neurons that were best configured to receive them for the initiation and selection of an action. Finally, it was reasoned that 4) a previously-observed calcium release mechanism associated with the generation of reactive oxygen species (ROS) by the interaction of iron and hydrogen peroxide (H2O2) would promote calcium signaling. While some

evidence of each of these four components was available in 2018, there were notable gaps for which additional evidence would be needed if the hypothesis were to have predictive power. Since then, many of those gaps have been filled with additional evidence, as predicted. This paper will address that additional evidence, and identify the remaining gaps that still exist.

It is generally accepted that the initiation of a selected action is computed by cortical structures in the brain, which then provide afferent signals to the basal ganglia (Humphries and Gurney, 2021; Codol et al., 2022; Gurney et al., 2001; Gurney et al., 2004; Prescott et al., 2001; Gurney et al., 2001; Liu et al., 2018; Liu et al., 2021; Liu et al., 2022), but how these computations result in a specific action being initiated at a specific moment in time is not presently known. The CNET mechanism was first proposed as a neural signaling mechanism that could coordinate the initiation of a selected action by routing energy as a function of afferent cortical signals provided to the basal ganglia. The CNET mechanism is a hypothesized adiabatic energy routing mechanism associated with groups of catecholaminergic neurons, similar to the adiabatic energy routing mechanism used in photosynthetic systems (Ishizaki and Fleming, 2012; Cherepanov et al., 2017; Mohseni et al., 2008; Rebentrost et al., 2009). This energy routing is used to compute action initiation and selection as a function of sensory inputs, cortical afferents associated with cognitive processing and other neural signals, and assists with action potential generation in one or more neurons in the group for the purpose of initiating and selecting action. In the SNc, routing is associated with an action selection, and in the LC and possibly the ventral tegmental area (VTA) and other groups of catecholaminergic neurons, routing is associated with cognitive processing. CNET consists of four core components, as shown in Figure 1:

1. Somatic dopamine metabolism generates triplet electrons that can provide energy to the CNET mechanism.
2. The triplet electrons can tunnel through ferritin between soma.
3. Axon synaptic activity directs electron tunneling to one or more target neurons and promotes action potentials to mediate action selection.
4. Electrons received in somatic ferritin in the target neuron(s) cause iron release, which promotes calcium action potentials.

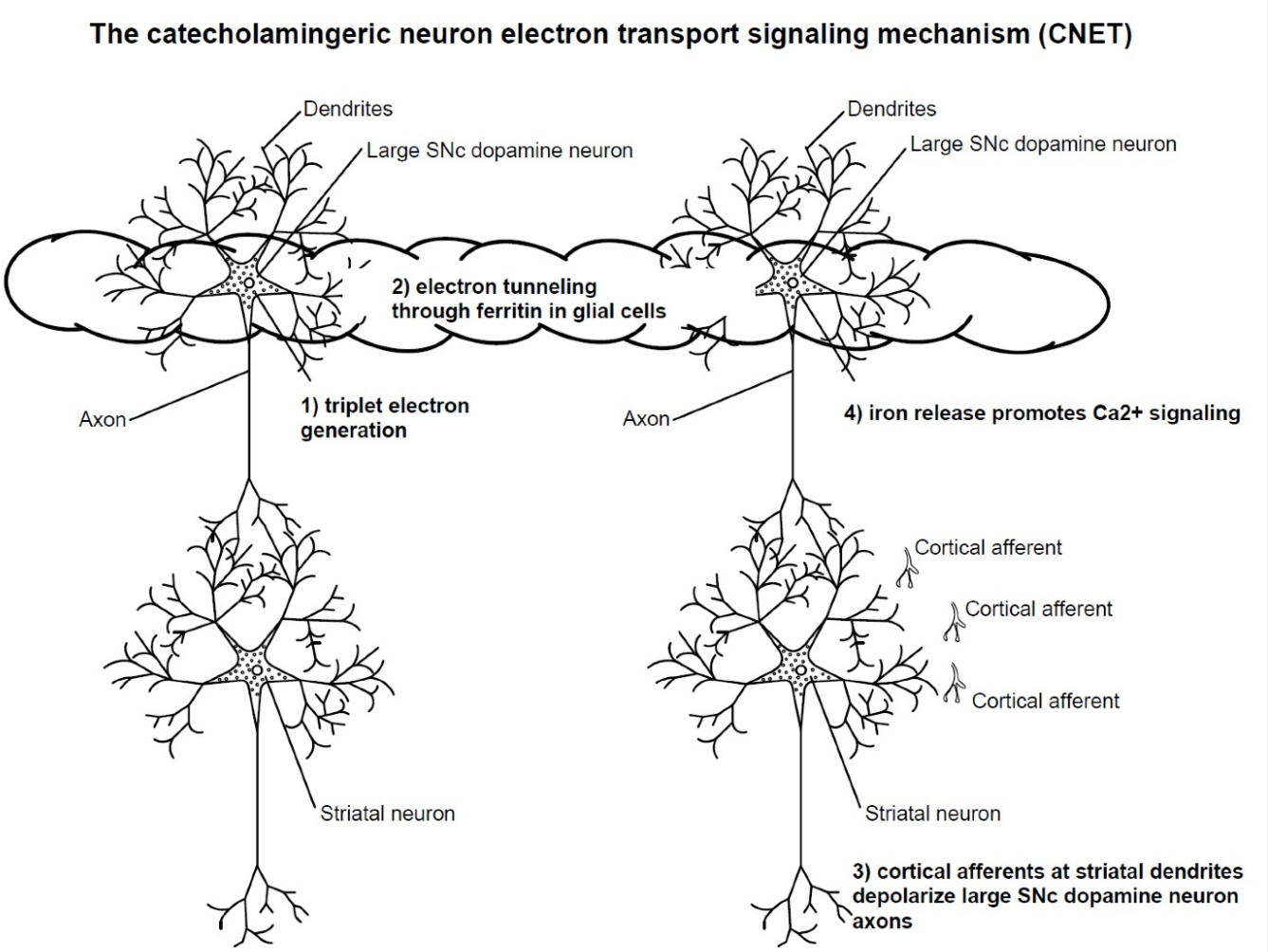

Figure 1. 1) somatic dopamine metabolism generates triplet electrons that can provide energy to the CNET mechanism (Brash et al., 2018; Brash and Goncalves, 2023; Gonçalves et al. (2023); 2) triplet electrons can tunnel through ferritin between soma (Rourk, 2019; Rourk et al., 2021); 3) axon synaptic activity directs electron tunneling and promotes action potentials to mediate action selection (Liu et al., 2018; Liu et al., 2021; Liu et al., 2022); 4) iron release in soma that receive the electrons causes iron release, which promotes calcium action potentials channels (Gleitze et al., 2021; SanMartín et al., 2014; Munoz et al., 2006; Munoz et al., 2011; Hidalgo et al., 2007; Hidalgo and Nunez, 2007)

When CNET was proposed in 2018, there was only partial evidence of each of these four components, but since then, a great deal of evidence has been obtained. This additional evidence is discussed below.

2. Somatic dopamine metabolism generates triplet electrons that can provide energy to the CNET mechanism.

The first component of CNET is the generation of high-energy electrons as a result of the chemiexcitation of dopamine from interaction with peroxidase (Brash et al., 2023). As discussed below, the chemiexcitation of dopamine provides a source of high-energy electrons that can be routed by the CNET. The high-energy electrons are generated as a function of normal neural activity in large SNc soma, which includes the production of dopamine. Ferritin provides a mechanism for neutralizing such high-energy electrons in other tissues. The number of high-energy electrons that are generated by the

chemiexcitation of dopamine and their associated effect on action potential generation would be less than the amount of energy needed for action potential initiation in large SNc soma, which would promote but not direct action potential generation. There is also a mechanism for neutralizing the high energy, chemiexcited electrons if they are not used for action potential generation.

2.a. Triplet electrons are generated as a function of dopamine production in large SNc soma and stored in ferritin

Dopamine is a catecholamine that functions as a neurotransmitter, and it is primarily produced in the SNc, the VTA and the hypothalamus in the brain (Juárez Olguín et al., 2016). It is also a precursor of norepinephrine, which is a neurotransmitter that is primarily produced in the LC in the brain. The biosynthetic pathway for dopamine is complex, and relies on iron to generate tyrosine, which is a rate-limiting enzyme in the production of dopamine (Kaushik et al., 2007). In addition to iron, hydrogen peroxide is produced in all cells by respiration in mitochondria (Bao et al., 2009), and due to the significant energy demands of large SNc dopamine neurons (Pissadaki), they also generate peroxidase (Ambani et al., 1975). Dopamine can be chemically excited to create triplet state electrons by exposure to peroxidase (Brash et al., 2018; Brash and Goncalves, 2023; Gonçalves et al. (2023)), which provides a source of high-energy electrons that must be neutralized by the cell to avoid causing damage. As discussed below, ferritin in large SNc dopamine neurons would be able to provide this neutralizing function.

Ferritin is a unique iron storage protein that self-assembles from 24 peptide subunits and which can oxidize ferrous (Fe2+) iron to ferric (Fe3+) iron for storage in the form of iron oxide nanoparticles (Zhang et al., 2020; Kumar et al., 2016). The outer diameter of the ferritin particle and the inner diameter of the iron oxide core is a function of the amount of iron that is stored, but they are approximately 12 nm and 8 nm, respectively. While the specific crystalline structure of the core can include ferrihydrite, magnetite and maghemite, the core is essentially an iron oxide nanoparticle, which at 8 nm or smaller is superparamagnetic. Superparamagnetic iron oxide nanoparticles are commonly referred to as SPIONS. The chiral structure of the helical peptide subunits of the ferritin may result in magnetization of the SPION cores of ferritin due to a transient charge dipole that can be generated along a chiral protein (Ozturk et al., 2023), which could also create transient magnetic polar effects as well as a transient spin dipole, and possibly both effects could be acting on the SPION core to cause it to become ferromagnetic (Koplovitz et al., 2019). The chiral helical structures of the peptide subunits of the ferritin shell form eight 3-fold pores, each having identical charge polarities, and six 4-fold pores, each having identical and opposite charge polarities from the 3-fold pores. This physical structure of ferritin provides it with electrical and magnetic properties that can influence chemical reactions.

While a thorough understanding of iron homeostasis is beyond the scope of this paper, a brief overview is helpful to the understanding of CNET. Iron is regulated systemically by the intestines, which absorb iron from food, and excess iron is stored in the liver (Gao, 2019). Blood then provides the absorbed iron to cells in the form of hemoglobin, which is also used for the transport of oxygen, and transferrin. Cells absorb iron from blood by a number of different membrane proteins, and the mitochondria regulate the production of those proteins. Once inside the cell, iron contributes to the labile

iron pool (LIP) of the cytosol, which contains iron bound to low-mass compounds such as peptides, carboxylates and phosphates, and a small amount in a free, hydrated form. Iron ions might also be present bound to specialized proteins known as metallochaperones (Philpott et al., 2017). The mitochondria can also code the production of ferritin proteins for iron storage, and ferroportin for reducing the amount of iron in the cell. Ferritin is produced by the cell in quantities sufficient to regulate the level of iron in the LIP, and overexpression of ferritin by the cell in the absence of elevated iron levels would be unrelated to cellular iron homeostasis.

There is substantial evidence that ferritin can absorb high-energy triplet electrons from dopamine and release them at a later time to neutralize ROS. It has been observed that ferritin has an iron-independent ROS neutralization mechanism, which appears to result from its ability to store electrons and subsequently make them available to neutralize ROS (Alkhateeb et al., 2013; Alsyamy et al., 2022; Ruddell et al., 2009; Watt et al., 1985; Wolszczak and Gajda, 2010; Saenz et al., 2016). Ferritin is overexpressed in response to ROS/inflammation (Koorts and Viljoen, 2007; Orino et al., 2001; Epsztejn et al., 1999; Wang et al., 2016), even when the source of ROS/inflammation is not iron. It has been proposed that ferritin is an antioxidant (Mumbauer et al., 2019; Shesh and Connor, 2023; Becana et al., 2000), which indicates that ferritin has the ability to donate stored electrons from antioxidants to neutralize ROS. Mitochondrial ferritin may also help to control ROS by absorbing electrons leaked by complexes I and III of the electron transport chain (Koundouros and Poulogiannis, 2018). These biological functions of ferritin may be related to the reason why ferritin is overexpressed in large SNc dopamine neurons and forms layers outside of NMOs (Sulzer et al., 2018; Rourk, 2019), which would render it capable of buffering high energy electrons for use in neutralizing ROS. Thus, considerable evidence suggests that ferritin can receive and store high-energy triplet electrons from chemiexcited dopamine.

The interaction of ferritin with electron donors such as the ascorbate anion, the ascorbate free radical and superoxide has been studied extensively, and those studies have shown that ferritin can receive electrons from these and other compounds that are commonly found in cytosol, to cause iron to be released from the core under the proper conditions (Badu-Boateng and Naftalin, 2019). In contrast, H2O2 is associated with iron uptake into ferritin, but not iron release. It has also been shown that ferritin can store electrons for hours in the absence of a chelator (Watt et al., 1985; Wolszczak and Gajda, 2010; Saenz et al., 2016). The complex interaction between compounds like ascorbic acid and ferritin in the cytosol appears to stabilize the iron that is stored in ferritin *in vivo*, as a function of other cytosolic components of the iron homeostasis system such as the LIP (Bridges and Hoffman, 1986; Badu-Boateng and Naftalin, 2019). It has been suggested, apparently without evidence, that what appears to be stabilization of iron storage could instead be an indication that ascorbate increases the exchange of cytosolic iron with the iron core of ferritin (Badu-Boateng and Naftalin, 2019). Regardless of whether ascorbate and other antioxidants cause iron to be stabilized in the ferritin core or exchanged between the core and the cytosol, it is not depleted from the core as is observed when ferritin and ascorbate are combined *in vitro*. There are several possible reasons for these contrasting observations. One is that the cellular environment includes iron regulatory proteins that may return the released ferrous iron back to the ferritin. A second is that the LIP creates a higher concentration of ferrous iron outside of the ferritin, and that ferritin does not release ferrous iron until the number of electrons stored in the ferritin results in a ferrous ion concentration that is greater than that of the LIP, because as noted, ferritin has the ability to store a large number of electrons in the absence of a chelator for periods of

time as long as hours (Watt et al., 1985; Wolszczak and Gajda, 2010). A third is that the ferritin may act as a buffer for electrons received from antioxidants, and those electrons may tunnel out of the core to neutralize ROS in the vicinity of the ferritin *in vivo* that is not present *in vitro*, thus depleting the stored ferrous iron in the core of the ferritin.

Because ROS carry a net charge, they also have a magnetic field, and may be attracted to ferritin cores due to either superparamagnetic or ferromagnetic properties of the ferritin cores (Ermakova et al., 2013; Nie et al., 2021; Sharmin et al., 2021; Wu et al., 2023). Ascorbic acid and other antioxidant ions interact with ferritin, and would also carry a charge and associated magnetic field. Thus, it is possible that the electrical and magnetic properties of ferritin may be a component of the mechanism that results in chemical interactions between ROS, antioxidants and ferritin *in vivo*.

In dopamine neurons, the creation of the hydroxyl radical from the interaction of iron and hydrogen peroxide is needed for the production of dopamine (Kaushik et al., 2007). Peroxidase, an enzyme that catalyzes various oxidative reactions that use hydrogen peroxide, is also present in dopamine neurons (Ambani et al., 1975), and the interaction of dopamine and peroxidase generates triplet state electrons through a process called chemiexcitation (Brash et al., 2018; Brash and Goncalves, 2023; Gonçalves et al., 2023). The electron triplet state is an unstable molecular state where two electrons in different molecular orbitals have parallel spins, which forces one electron to a higher energy molecular orbital where it is weakly held, because two electrons with the same spin state cannot occupy the same orbital. Triplet-state electrons have longer lives compared to singlet-state electrons, which can enable chemical reactions that would not otherwise be possible (Gonçalves et al., 2023). Other cellular mechanisms in dopamine neurons can also generate triplet electrons, such as the processes that generate neuromelanin, but the rate-determining process for the CNET mechanism would likely be associated with the interaction of dopamine and peroxidase or other reactions associated with the production of dopamine.

2.b. The number of triplet electrons generated by the interaction of dopamine and peroxidase in the soma is independent of action potential propagation in large SNc neurons

Action potential propagation in large SNc dopamine neurons requires high energy demands (Pissadaki and Bolam 2013; Bolam and Pissadaki 2012). Large LC noradrenaline neurons are also complex, have high energy demands and also interface with highly-branched Purkinje cells in the cerebellum, which requires extensive axon arbors (Wang et al., 2020; Hoffer et al., 1973; Loughlin et al., 1986). While it appears that there are many similarities between large SNc neurons and large LC neurons, the LC has not been studied as extensively as the SNc, most likely due in part to its distributed structure and diversity of neuron types. However, because dopamine is a precursor of norepinephrine, triplet electron generation will occur in both types of neurons. It is noted that peroxidase is also present in the noradrenaline neurons of the LC (Moreno et al., 1995).

The SNc contains a large percentage of dopamine neurons, most of which are small but a few percent of which are large (Rudow, 2008). These large SNc dopamine neurons only generate phasic action potentials associated with calcium channel signaling, which are action potentials that occur at irregular intervals, whereas smaller dopamine neurons can fire tonically or in a sustained series of bursts, which is associated with sodium channel signaling (Pissadaki and Bolam 2013;

Bolam and Pissadaki 2012; Grace 1991). The large SNc dopamine neurons innervate the striatum, and can have over 1 million synapses (Pissadaki and Bolam 2013; Bolam and Pissadaki 2012), although recent studies indicate that as few as 20% of those synapses might be active for any one neuron (Liu et al., 2018; Liu et al., 2021; Liu et al., 2022). Many of those synapses are in the form of varicosities, and activation of such varicosities may be associated with the memory function of neurons (Bailey et al., 2015).

Large dopamine neurons of the SNc have a number of unusual characteristics. One is that the axon originates at a dendritic site (Gentet and Williams, 2007; Tepper et al., 1997). The spike-generating region of the axon/dendrite is also functionally compartmentalized from the spike-generating region in the soma (Grace, 1990). One *in silico* study of these neurons indicates that calcium signaling may be the only way that neurons having 10 or more branches can reach action potential (Pissadaki and Bolam 2013), which is also consistent with observations of tonic and phasic activity in SNc dopamine neurons (Floresco et al., 2003). Mitochondrial calcium signaling is important as part of the ignition and propagation of calcium action potentials in these neurons (Zampese et al., 2022), and calcium homeostasis is tightly regulated by mitochondria (Vilas-Boas et al., 2023).

The production of somatic dopamine in large SNc dopamine neurons is associated with the delivery of dopamine from axon synapses to the striatum, and is highly correlated to axonal signaling (Azcorra et al., 2022). Only a fraction of dopamine in any one neuron would interact with peroxidase to produce triplet electrons, such that the contribution of electrons from other neurons would be a small fraction of what is available in each neuron. Routing these electrons to a neighboring neuron would thus help to prevent excessive electron buildup in ferritin and an associated local release of iron when it is not needed, while assisting neighboring neurons to reach action potential when it is.

In summary, there is substantial evidence of the first core component of CNET, that large SNc dopamine neurons generate high-energy triplet electrons that are stored in somatic ferritin, and that these electrons are available to move between soma if there is a suitable medium for them to move over. They will also require an electromotive force to cause them to move.

3. The triplet electrons can tunnel through ferritin between soma

Evidence of the second component of CNET - a medium over which the high energy electrons that are generated by chemiexcitation from the interaction of dopamine and peroxidase can be transported between large SNc dopamine neuron soma – has been recently obtained (Bera et al., 2019; Rourk et al., 2021). The signaling pathway begins inside the soma, where layers of ferritin outside of NMOs accumulate electrons. Glial cells interface with the soma and provide ferritin to the soma, creating a pathway between soma for sequential tunneling of electrons.

3.a. Ferritin and neuromelanin structures within the soma of catecholaminergic neurons allow electron tunneling to occur

Because ferritin particles are ~12 nm in diameter, it can be very difficult to see the formations of these particles *in vivo*.

Electron microscope (EM) images provide some of the highest resolution, but when the scale changes from microns to even tens of microns, essential details can be lost. An example of this can be seen in (Plum et al., 2013), which has a set of EM images ranging in magnification from x18,000 to x60,000, all with 1-micron scale bars. Even though ferritin is known to be present around the NMOs from (Sulzer et al., 2018), small electron-dense particles are only slightly visible at the highest magnification levels. Likewise, the small electron-dense particles surrounding NMOs in (Tribl et al., 2009) are likely ferritin, but only a few are associated with immunogold markers that have been tagged with anti-ferritin. More recent work, such as (Everett et al., 2023), confirms not only the presence of ferritin-sized iron particles inside of the cell but also in the cell membrane of large SNc dopamine neurons, using Scanning Transmission X-ray Microscopy. Thus, while evidence of ferritin particles in these neurons and their formations is difficult to obtain, the composite of data from different sources indicates that such structures are present.

In order to determine whether electron tunneling could occur in SNc tissue, (Rourk 2018) suggested performing tests on that tissue using electrical atomic force microscopy (AFM) techniques that can detect tunneling. To that end, fixed human SNc tissue was tested by EAG Labs using conductive AFM, and evidence of electron tunneling was obtained, as discussed further in (Rourk 2019). In brief, the measured currents show large dynamic variations with electron flow from a grounded sample into a -10V probe tip electron source, with only a small net current flow to the ground over the entire measurement cycle. These currents make sense if there is widespread electron tunneling caused by the dislocation of pi-orbital electrons from NMOs into ferritin as a result of the high dV/dt caused by the oscillating conducting AFM probe tip, and the eventual return of those electrons to their source when the electric field oscillation ceases. An electrochemical reaction between the AFM probe tip and the tissue sample can be ruled out on a number of grounds, namely, because the AFM probe tip is designed not to be chemically reactive, and there are no significant chemical reactions that could generate a potential sufficient to force electrons into the AFM probe tip against the -10 V probe tip bias. For example, the largest theoretical electrochemical single-cell battery potentials are in the range of 7 volts, based on standard rate reduction potentials (Rumble 2020), but practical configurations of such cells have potentials of less than 5 volts (Wu et al., 2017). Thus, no known electrochemical reaction could explain the measured currents, because an electrochemical reaction would need to generate in excess of 10 volts of electromotive force to push electrons into a probe biased at -10 V. Also, as noted in (Rourk 2019), the net current over the AFM probe measurement cycle was essentially zero, which establishes that all electron movement was dynamic with a return to its original state, other than a small amount of positive current reflecting current flow to the grounded substrate. Thus, there is no evidence of any electrochemical reaction in the test results.

Likewise, the currents could not be a result of ferrihydrite or any other substance “leaking” from ferritin and interacting with the probe. As discussed, ferritin is formed from 24 protein subunits that self-assemble to form a hollow shell that has 6 pores that are formed from the intersection of 4 protein subunits and 8 pores that are formed from the intersection of 3 protein subunits (Zhang et al., 2020). The size of these pores is 3-5 angstroms, and molecular dynamics models demonstrate that the movement of individual iron atoms through the pores is a complex molecular process (Sala et al., 2017). The ability of ferritin to store water-soluble Fe2+ iron for hours in solution and in the absence of a chelator has been demonstrated (Watt et al., 1985; Wolszczak and Gajda, 2010). The test results were also reviewed by a staff

scientist for the equipment manufacturer (Bruker), and no evidence of fouling of the probe tip with contaminants was found (Rourk 2019).

The data from the conductive AFM current measurements also correlate to electron spectroscopic evidence of layers of ferritin outside of neuromelanin organelles (NMOs) in SNc dopamine neurons (Sulzer et al., 2018). These layers correspond to layers of electron tunneling indications that were approximately 12 nm thick outside of spherical electron tunneling indications that were approximately 300 nm in diameter, within the size range of NMOs. Thus, there is strong evidence that was subsequently obtained after the initial publication of the CNET hypothesis in 2018 of ferritin and neuromelanin structures within the soma of catecholaminergic neurons that are sufficient to allow electron tunneling to occur. Additional testing of SNc tissue to map the extent of such tunneling and the mesoscopic structures associated with such tunneling, as well as testing of catecholaminergic neurons from the locus coeruleus (LC), ventral tegmental area (VTA) and other nuclei should be performed, though.

For example, one limitation of the tests reported in (Rourk 2019) is that only 4 areas were scanned. While each scan included 3 current measurements at each of 262,144 locations for a total of 786,432 current measurements, the size of the scanned areas ranged from 76 x 76 microns to 2 x 2 microns. These relatively small areas only provided a small window into the structures that are present in these neurons, and a more extensive survey could be performed to obtain a better understanding of the structures. In addition, while fixed SNc tissue provides some indication of the physics of electron transfer in that tissue, live or fresh tissue would provide a better indication. The thickness of the samples tested was 5 microns, which means that the large SNc neuron soma were sectioned, and a sample with a thickness sufficient to observe whole large SNc dopamine neuron soma, which have diameters of 30 microns or greater, would be of interest. Other AFM test techniques could also be used, such as electrostatic force AFM, Kelvin probe AFM, magnetic AFM or others. It would also be useful to obtain electron microscope (EM) images or other imaging of the samples with sufficient resolution to allow correlation between the AFM and EM data.

Other testing could also be performed that would provide additional data regarding the electron tunneling properties of ferritin and NMOs in catecholaminergic neurons. For example, patch clamp recording of live SNc dopamine neurons in live tissue slices could be used to test whether electron tunneling can occur between the neuron cell bodies by using high-frequency electrical stimulation and observing current and voltage waveforms as a function of frequency. Another test would be to use quantum dot (QD) or nitrogen-vacancy nanodiamond sensors to detect electron tunneling activity in real-time in slices of live SNc neuron tissues. Thus, while unusual and predicted evidence of electron tunneling has been obtained that makes sense in the context of CNET, additional testing and investigation would help to obtain a better understanding of ferritin and neuromelanin structures in catecholaminergic neurons, which could help to explain the behavior of these neurons.

3.b. Ferritin structures between the soma of large SNc neurons allow electrons to tunnel between them

In addition to demonstrating that electron tunneling was occurring in association with structures that correlate to NMOs inside of catecholaminergic neurons, the tests in (Rourk 2019) also provided evidence of electron tunneling outside of the

cell bodies, because the electron tunneling indications were present throughout the 76 x 76 micron sample that included several structures that corresponded to large soma and the intervening cells and extracellular matrix. Subsequent tests using microparticle-induced X-ray emission of SNc tissue provided further evidence of ferritin structures in glial cells (Friedrich et al., 2021). In addition, testing with a nuclear microprobe and scanning proton-induced X-ray emission spectrometry was used to quantify ferritin levels in neurons and glial cells, with the surprising finding that glial cells such as astrocytes and oligodendrocytes have significantly higher concentrations of ferritin than neurons (Reinert et al., 2019). This evidence is consistent with earlier EM data that showed accumulations of electron-dense particles in SNc glial cells that were not identified, either as ferritin or anything else (Xiong et al., 2009), but which are very similar to electron-dense particles in EM data from macrophages that was subsequently confirmed to be ferritin (Mykhaylyk et al., 2004; Perez et al., 2023). This is not surprising, because glial cells and macrophages are both phagocytes, which are known to provide iron to cells in response to ROS generation by the cells. For example, an iron-independent mechanism has been observed that protects cancer cells by providing ferritin to them (Alkhateeb et al., 2013; Salatino et al., 2019), which is consistent with the observation that ferritin is overexpressed in response to infection and ROS (Orino et al., 2001; Epsztejn et al., 1999; Wang et al., 2016). It has also been shown that macrophages facilitate electrical conduction in the heart and help to regulate heartbeats, although that study did not include any consideration of ferritin (Hulsmans et al., 2017). There are indications that tunneling actin microtubules can provide ferritin directly to cells (Ljubojevic et al., 2021; Infante et al., 2007; Goldfarb et al., 2021), which would explain the iron-independent mechanism that allows macrophages to stimulate cancer cells, as well as why extensive indications of electron tunneling between soma were observed in (Rourk 2019). Electron tunneling through ferritin would also explain at least part of the mechanism for functional coupling between neurons and glia (Alvarez-Maubecin et al., 2000) and ephaptic coupling between neurons (Anastassiou et al., 2011; Martinez-Banaclocha 2018; Ruffini et al., 2020). It has been observed that SNc and LC neurons have pacemaker modes of function, which implies the presence of a coordination mechanism (Branch et al., 2014; Courtney et al., 2012; Howells et al., 2012). As discussed further below, calcium signaling promoted by iron release could be associated with higher levels of ferritin in astrocytes (Schipke et al., 2002).

Additional evidence demonstrates that ferritin structures in macrophages exhibit small-angle neutron scattering due to aligned magnetic moments of the ferritin in a manner similar to that of self-assembled monolayers of ferritin on insulating substrates (Mykhaylyk et al., 2004; Yuan et al., 2006). Ferritin exhibits lower levels of neutron scattering in bulk (Stuhrmann et al., 1976; Seehra et al., 2000), but the degree of neutron scattering of ferritin as ordered in macrophages was greater than when the ferritin was removed. Neutron scattering due to aligned magnetic moments has also been observed in quantum dot solids (Murray et al., 2001; Murray et al., 1995), which can also conduct electrons by sequential tunneling (Chandler et al., 2007). Aligned magnetic moments may result from the influence of induced electric dipoles from chiral-induced spin-selectivity of ferritin protein segments around the iron oxide nanoparticle core (Koplovitz et al., 2019; Ozturk et al., 2023).

Subsequent to the publication of (Rourk 2018), independent tests were reported that demonstrated the ability of ferritin to transport electrons over distances as great as 40 microns (Bera et al., 2019), confirming one of the predictions made by CNET of previously unobserved and unusual electron tunneling behavior associated with ferritin. These tests used self-

assembled ferritin multilayers between two electrodes that were spaced apart by 40 microns, and measured a maximum current of.3 microamperes at an applied voltage of 3 volts. Based on the size of individual ferritin cores, that corresponds to over 3000 ferritin cores placed side by side in layers. The behavior of individual ferritin cores typically shows little or no current below 0.5 applied volts, so this behavior was inconsistent with the electrical behavior of individual cores but was consistent with electron transport through QD solids. In addition, these tests measured less than one nanoampere of current using AFM across the layers for up to 4 layers, and no current above 4 layers. Taken as a whole, these tests indicate that ferritin can support sequential tunneling when there is sufficient order, such as a stack of self-assembled monolayers, but that in the absence of such order, electron tunneling currents are limited, likely due to Coulomb blockade formation, as discussed below.

Based on these tests, additional tests were designed that used a similar electrode configuration and layer-by-layer assembly of self-assembled monolayers, but with 4 electrodes and electrode spacing of 20, 40 and 80 microns, to allow for a parametric study of electron transport to be performed (Rourk et al., 2021). A number of important observations were made from these tests. First, the ability of self-assembled ferritin multilayers to conduct up to 3 microamperes at an applied voltage of 3 volts was observed, confirming long-distance electron tunneling through the multilayered ferritin structures. Those structures are similar to the ferritin structures observed in glial cells and macrophages, thus indicating that electron transport through such ferritin structures over long distances between SNc neuron soma is physically possible. Second, the yield rate of the dies made for these tests was approximately 25%, which demonstrates that ferritin will not conduct electrons over long distances without sufficient order. Simply placing ferritin between electrodes is not sufficient to conduct electrons through sequential tunneling. Third, a number of dies exhibited non-linear behavior consistent with the formation of Coulomb blockades, an observation that was subsequently confirmed (Labra-Muñoz. et al., 2022). A Coulomb blockade occurs when electrons stored on different nanostructures create negatively-charged repulsive forces that prevent electron movement, such as tunneling. Coulomb blockade formation is consistent with electron transport through QD solids (Roest et al., 2004; Vanmaekelbergh and Liljeroth, 2005).

In summary, there is substantial evidence of the second core component of CNET, namely, that ferritin structures in the SNc, both in and between large SNc soma, can transport high-energy electrons generated by chemiexcitation of somatic dopamine over long distances by sequential electron tunneling through ferritin. An electromotive force would be needed to cause them to move. Because electrons carry a negative charge, they will be repelled by other electrons or a neuron cell membrane at rest potential of -70 mV, and would be repelled less by neuron cell membrane potentials that are depolarized, because they are less negative.

4. Axon synaptic activity of large catecholaminergic neurons directs electron tunneling and promotes action potentials to mediate action selection

Evidence of the third core component of CNET, depolarization of large SNc dopamine neuron axons by afferent cortical signals, has been recently obtained (Liu et al., 2018; Liu et al., 2021; Liu et al., 2022). The most basic function of a neuron is to receive incoming, or afferent, signals at dendrites, which depolarize the cell membrane to the point at which an action

potential is generated. The action potential initiates a cascade of sodium, potassium and/or calcium channels in the cell membrane that causes the axon to deliver an outgoing, or efferent, signal to the dendrites of other neurons. A large body of work into the phenomenon of predictive reward signaling of SNc dopamine neurons has demonstrated that those neurons can also function in a reverse or antidromic manner, and can be depolarized to the point of action potential by afferent signals from cortical neurons that are received at dendrites of the striatum, which are in close proximity to axon synapses to those dendrites. A similar structure and function have also been observed in LC neurons (Behl et al., 2022).

4.a. Axon membrane potentials of large SNc neurons are depolarized by afferent cortical signals in the striatum

Studies of SNc dopamine neurons have revealed an unusual behavior - they are activated by rewarding events that are better than predicted, they remain uninfluenced by events that are as good as predicted, and they are depressed by events that are worse than predicted (Schultz 1998; Smith et al., 1994; Yao et al., 2008). This observation was somewhat confusing, though, because the afferent cortical signals that provide the information about whether a rewarding event was better or worse than predicted form synapses with the striatal dendrites that the dopamine neuron axons provide efferent signals to in an unusual three-way synaptic structure, and are not provided to the dendrites of the SNc dopamine neurons.

The axon synapses of the large SNc dopamine neurons contain a large number of varicosities that can be used to provide dopamine to boutons on striatal dendrites where afferent cortical signals are also received (Schultz 1998; Smith et al., 1994; Yao et al., 2008). Pioneering work performed by Prof. Pascal Kaeser demonstrated that signals such as these afferent cortical signals are capable of depolarizing the large SNc neuron axons to the point of action potential, and can cause ectopic action potential generation (Liu et al., 2022). These ectopic action potentials are similar to localized action potentials generated in highly-branched Purkinje neuron dendritic trees (Llinás and Sugimori, 1980; Raman and Bean, 1999). As such, while they are unusual, they are not without precedent. Similar observations of this unusual behavior in SNc neurons have also been made (Albarran and Ding, 2022; Kramer et al., 2022).

The electrical properties of the extensive axon arbors of large SNc neurons are part of the CNET electron transport mechanism - cortical afferents at striatal dendrites depolarize some of the axon cell membranes of the large SNc neurons more than others and provide an electromotive force that causes triplet electrons from other large SNc neurons to move towards the SNc neurons with the most depolarization. This unusual axon behavior of large SNc neurons was predicted in 2018 and was contrary to any prior observations and the generally accepted way in which neurons are understood to operate. In order for electrons to tunnel between neurons, there must be an electromotive force that directs their movement. The CNET circuit includes all of the participating SNc neurons that are connected by a medium that conducts electrons by tunneling. Seen from the perspective of an electron in a soma, it will travel to an adjacent one that is less electronegative, because like charges repel each other. Thus, if the membrane potentials of large SNc neurons, which are primarily in the extensive axon arbors, are depolarized by cortical afferents, as has been observed, electrons in the adjacent neurons will tunnel through ferritin structures towards the neuron with the most depolarized axon membrane.

4.b. Action potentials in large SNc neurons are associated with action selection

As noted by (Liu et al., 2021), “[f] or movement control, dopamine modulates moment-by-moment activity in the striatum to mediate action selection.” Furthermore, as noted by (Liu et al., 2018), “dopamine secretion is mediated by sparse, mechanistically specialized active zone-like release sites. This architecture supports spatially and temporally precise coding for dopamine and provides molecular machinery for regulation.” These findings were surprising, as it had previously been understood that “the phasic dopamine response does not code movement” (Ljungberg et al., 1992; Schultz, 2016). However, while Ljunberg did not observe a correlation between movement and dopamine signaling for most SNc dopamine neurons, it is noted that it did, in fact, show clear evidence of movement following a strong activation of a dopamine response in at least some neurons (Fig. 8), which would correspond to the action initiation signals generated by the small number of very large dopamine neurons in the SNc. As such, while the results of Kaeser’s research were viewed as surprising, they merely confirmed what had been previously observed but which was not recognized. In addition, a number of other researchers have reached the same conclusion based on different evidence and reasoning, namely, that the SNc gates action initiation and action selection (Girard et al., 2021; Da Silva et al., 2018).

Furthermore, because of the compartmentalization of the soma from the axon/dendrite of large SNc neurons, even if the contribution to the action potential from electrons transferred by the CNET mechanism was sufficient to cause spiking, it would not result in action potential propagation unless it was also coordinated with synaptic activity at the axon/dendrite. This is consistent with observations that electrical stimulation of anterior substantia nigra pars reticulata (SNr) neurons, which are adjacent to SNc neurons, has an anticonvulsive effect, whereas electrical stimulation of posterior SNr neurons has no such effect (Velíšek et al., 2002). Electrical stimulation of the CNET mechanism would be expected to disrupt action initiation and selection. Likewise, studies of the effect of electrical stimulation on the SNc show that it results in head-turning and circling behavior, consistent with the effect of natural sensory stimuli (Piazza I et al., 1989; Piazza II et al., 1989). Thus, rather than causing movement, electrical stimulation of the SNc can either disrupt convulsions or contribute to voluntary action initiation and selection, but does not cause convulsions. Furthermore, stimulation of the VTA can alleviate depressive behavior (Friedman et al., 2009), which suggests that more subtle action initiation and selection effects occur than could be identified from animal movement tests.

In addition to the SNc, the VTA and LC contain large neurons that have extensive axon arbors (Alm, 2021; Matchett et al., 2021). There is also evidence of switching by the LC for the delivery of noradrenalin to select groups of cortical neurons, similar to the switching function performed by the SNc to provide spatial and temporal coding for cognitive processing. (Breton-Provencher et al., 2021; Breton-Provencher et al., 2022). There is evidence that this cognitive processing generates a large number of channels of action initiation and selection information that are provided to the SNc/striatal junctions (Humphries and Gurney, 2021; Codol et al., 2022; Gurney et al., 2001; Gurney et al., 2004; Prescott et al., 2001; Gurney et al., 2001). In this regard, the different switching mechanisms in the SNc and LC are integrated through various cognitive processing loops, such as corticostriatal loops (Hoffman et al., 2011; Seger 2009), cortico-striatal-thalamic loops (Peters et al., 2016; Fettes et al., 2017); hippocampal-striatal loops (Chersi and Pezzulo, 2012), cerebro-cerebellar loops (Salmi et al., 2010) and others. Coordination between these loops would be essential to ensure synchronized neural

processing, and the hypothesized switching mechanisms of the LC and SNc are in a central location to all of these loops and are able to perform that function (McHaffie et al., 2005; McCutcheon et al., 2018; - Janacsek et al., 2022).

Integration of numerous cortical processing loops in the SNc and LC could also be associated with phenomenal consciousness, as it is well known that readiness potential lags phenomenal consciousness (Budson et al., 2022). The SNc and LC thus form an important part of the neural mechanism required to compute action initiation and selection, recognizing that action selection is often preceded by extended periods of cortical processing during which no action is taken. Executive control of data processing is an essential component of biological computing systems (Horsman et al., 2017; Horsman et al., 2014).

4.c. Coulomb blockade formation in ferritin provides a routing mechanism that can control that tunneling

A number of quantum mechanical electron transport mechanisms associated with CNET were proposed in (Rourk 2018) based on the earlier observations of electron tunneling in ferritin (Kumar et al., 2016; Awschalom et al., 1992; Axford and Davis, 2007; Choi et al., 2005), such as coherent electron transport, electron tunneling and electron hopping. Because it was uncertain which of these might be present, one non-limiting example of a routing mechanism was provided that would use coherent transport and localization, but it was recognized that other mechanisms might also or alternatively be present. However, as discussed above, the formation of Coulomb blockades was observed in self-assembled ferritin multilayers, which indicates that it is the likely routing mechanism (Rourk et al., 2021). Those tests were designed to detect coherent tunneling and localization, but the data from the tests was instead consistent with Coulomb blockade routing.

A Coulomb blockade routing mechanism would allow electron transfer between neurons to be controlled by a number of factors, including the number of glial cells between the neurons, the amount of iron in the glial cells, the number of electrons stored in ferritin in the soma, and electrical activity of the cell membrane, among others. As electrons build up in ferritin in a soma, a Coulomb blockade would start to form that would prevent additional electron transport to that soma, unless the number of ferritin cores between the soma and the number of electrons stored in ferritin of other soma were configured to support such transport. Coordination between the mechanism and the LIP of the soma, as well as other signaling activity of the neuron, would also be needed to result in a sufficient number of transferred electrons to cause iron release and assist with the generation of an action potential. As discussed, the complex interaction of ferritin with the LIP in iron homeostasis controls iron release and prevents cellular damage.

In summary, there is substantial evidence of the third core component of CNET, namely, that cortical afferents received at axon synapses of large SNc dopamine neurons, where they form a 3-way connection with striatal dendrites, can depolarize the axon cell membranes, even to the point of generating ectopic action potentials. These neurons would appear to be less electronegative than a neuron with less associated stimulation from cortical afferents, consistent with the routing hypothesis of CNET, namely, that large SNc dopamine neurons use CNET as a signaling mechanism to coordinate action potential generation as part of the action initiation and selection mechanism of the SNc. It has been shown that large SNc dopamine neurons provide dopamine in a manner that is temporally and spatially precise to mediate

action initiation and selection. Because thousands of these neurons have that capability, a mechanism is needed to prevent them from firing simultaneously.

5. Iron release in soma that receive the electrons causes iron release, which promotes calcium action potentials

The fourth core component of CNET is the promotion of calcium signaling that is caused by the release of iron from ferritin, in response to the transported electrons that are received in the ferritin. Substantial evidence has been obtained that indicates that released iron promotes the emergence of Ca2+ signals via the activation of redox-sensitive Ca2+ channels (Gleitze et al., 2021; SanMartín et al., 2014; Munoz et al., 2006; Munoz et al., 2011; Hidalgo et al., 2007; Hidalgo and Nunez, 2007). A sufficient number of electrons tunneling to a single neuron or group of neurons would be able to cause the release of iron and promote the emergence of Ca2+ signals/action potentials in those neurons.

5.a. Providing electrons to ferritin causes iron release

It has been established that ferritin will release iron when it receives electrons from different sources. One of the earliest observations of this release was by (Watts et al., 1985), who showed that reduction of ferritin with $S_2O_4^{2-}$ resulted in nearly complete retention of iron in the core of ferritin after 20 minutes. Likewise, (Wolszczak and Gajda, 2010) demonstrated that ferritin is capable of storing for hours electrons that are received from electron beam implantation as well as electrons from the protein shell that are energized by UV light exposure, in the absence of a chelator. Electrons stored in ferritin that are generated by UV were shown to be released relatively slowly in the presence of a chelator (Saenz et al., 2016). As such, while electrons do result in the release of iron from ferritin, a relatively large number of electrons need to be received or a relatively long period of time needs to elapse before that occurs.

In the large SNc neurons, ferritin forms layers outside of neuromelanin organelles (Sulzer et al., 2018; Tribl et al., 2009; Rourk, 2019). Neuromelanin is formed from eumelanin and pheomelanin, which have low ionization potentials (4.4 to 4.8 +/1 0.2 eV and 3.8 +/- 0.2 eV, respectively) (Peles et al., 2009). These values fall within the range of ionization potentials for bilayer graphene (BLG) (De Corato et al., 2014), and ferritin placed in contact with BLG has been demonstrated to shift the Fermi level of the BLG, by receiving electrons from the BLG (Gupta et al., 2022). Thus, ferritin layers outside of NMOs may effectively be “pre-loaded” with electrons that sensitize the release of iron from ferritin, although it is noted that iron homeostasis is complex and that iron release from ferritin would involve the interaction of the LIP. The large amounts of ferritin outside of NMOs in large SNc neurons are greatly in excess of what would be necessary for normal iron homeostasis, relative to other cells. Iron is needed for dopamine synthesis, and there is a crosstalk relationship between iron and Ca2+ signaling in neurons (Gleitze et al., 2021; Kadian et al., 2022).

5.b. The release of iron from ferritin increases the LIP and the amount of iron that interacts with H2O2 in the cytoplasm, which generates ROS

Cellular processes in catecholaminergic neurons generate a variety of harmful byproducts that must be used or otherwise neutralized to prevent damage to the cell. One of the key cellular processes is the production of adenosine triphosphate (ATP) by mitochondria, which provides the energy source for many cellular functions. An important part of that process is the mitochondrial electron transport chain, a series of four protein complexes that couple redox reactions, creating an electrochemical gradient that leads to the creation of ATP in a complete system named oxidative phosphorylation. The element iron is an essential part of the mitochondrial electron transport chain, and regulation of cellular iron is performed by the mitochondria.

Fe2+ is water soluble and reacts with H2O2, which is also a byproduct of ATP production as well as a non-radical ROS (Avshalumov et al., 2005; Boveris and Chance, 1973; Dugan et al., 1995; Liu et al., 2002). This reaction is known as Fenton's reaction, and results in the production of the damaging hydroxyl free radical, •OH, which has a single unpaired electron. Cells use antioxidants to neutralize the hydroxyl free radical. Thus, while iron is an important part of the cellular processes for creating ATP, it can also contribute to the generation of the hydroxyl free radical, which must be neutralized by the cell to prevent damage. H2O2 is generated in all cells by mitochondrial respiration (Boveris and Chance, 1973; Dugan et al., 1995; Liu et al., 2002). Endogenous H2O2 also regulates the excitability of dopamine neurons by its interaction with ATP-sensitive potassium channels, and is thus also able to serve as a signaling agent in addition to ATP to link excitability to energy demands.

Iron promotes the emergence of Ca2+ signals via activation of redox-sensitive Ca2+ channels (Gleitze et al., 2021). As discussed in Gleitze, the translation of iron-related proteins involved in the absorption, storage and recycling of iron is controlled by iron regulatory proteins that bind to iron-responsive elements of mRNA to control the cytoplasmic LIP so as to provide a concentration of redox-active iron ranging from 0.5 to 1.5 μM, which represents less than 5% of the total intracellular iron levels (Cabantchik 2014). A sudden increase in redox-active iron resulting from the release of ferrous iron from ferritin due to an influx of electrons would thus temporarily increase ROS through interaction with H2O2, but would subsequently be sequestered back into the ferritin by iron chaperones (Philpott et al., 2017).

5.c. Ryanodine receptors (RyR) release calcium in response to ROS, which can contribute to the generation of calcium action potentials

Recent work has shown that iron promotes the emergence of calcium signals via activation of redox-sensitive Ca2+ channels by RyR, which are central to cytoplasmic calcium signaling in the central nervous system (Gleitze et al., 2021; Dulhunty et al., 2018; Fill and Copello, 2002; SanMartín et al., 2014). Altered functional interactions between plasma membrane voltage-operated Ca2+ channels, RyR and the abnormal Ca2+ buffering capacity of aged neurons has been identified as a contributing mechanism to neurodegenerative disease (Kraus and Koulen, 2020; Murchison and Griffith, 2007), underscoring the importance of those interactions to normal neuron function.

Neurons maintain a large intracellular Ca2+ concentration gradient between the extracellular environment and the cytosol at rest. Calcium signaling begins with the opening of membrane calcium channels, allowing calcium to flow from outside of the cell into the cytosol. While those signals are damped by calcium-buffering proteins, they are sustained by the rapid

release of calcium from calcium stores in a process known as calcium-induced calcium release (CICR), which is mediated by calcium acting on RyR channels (Belan et al., 1993; Verkhratsky & Shmigol, 1996; Usachev & Thayer, 1997, 1999a, b; Verkhratsky & Petersen, 1998; Akita & Kuba, 2000; Buchholz et al., 2007).

In conclusion, substantial evidence exists that the four core components of CNET can provide a signaling mechanism in large SNc dopamine neurons:

1. chemiexcitation of dopamine in large SNc dopamine neurons creates high-energy electrons,
2. ferritin provides a substrate that allows these electrons to tunnel between neurons,
3. cortical afferents associated with action initiation and selection computations are received at striatal dendrites that form unusual 3-way synapses with large SNc dopamine neuron synapses and can depolarize the axons, and
4. iron release from ferritin can promote calcium signaling and associated action potentials.

Evidence of these four core components obtained since the CNET hypothesis was first proposed in 2018 establishes the predictive power of the CNET hypothesis, and justifies further research to determine whether evidence that CNET provides an action initiation and selection mechanism in catecholaminergic neurons can be obtained.

6. Discussion

Action initiation and selection is one of the hard problems of consciousness, sometimes referred to as free will. Why do we “choose” to act, not to act, or to wait to act? The study of consciousness was entirely metaphysical until the discovery of neurons in 1740 by Emmanuel Swedenborg (Fodstad 2002). At present, with one foot in physics and one in metaphysics, the study of consciousness is avoided by many neuroscientists (Kitchener and Hales, 2022). As a result, some of the people with the most value to add to the scientific study of consciousness are not even engaged.

The metaphysical concept of free will is often viewed as being in opposition to determinism (Kane, 1998). Part of the reason for this perceived dichotomy may be the lack of understanding of how action selection and initiation function in the brain. While much progress has been made toward understanding the neural correlates of action selection and initiation, the mechanism responsible for the selection and initiation of a specific action has not yet been acknowledged.

CNET provides this mechanism, and if it is also part of the physical mechanism for the experience of phenomenal consciousness, it would explain why it can appear to the actor that actions are “chosen” and why the concepts of “free will” and “determinism” are not mutually incompatible. As a preliminary matter, if CNET is associated with phenomenal consciousness, that would be consistent with observations of readiness potential. Cortical decision-making computations result in action initiation and selection before the actor has phenomenological awareness of those processes, and arise from a large number of competing neural channels. The strength of the signals associated with these different channels would control the influence they have on the CNET mechanism, with a “decision” being experienced when the signals associated with that channel are stronger than the signals associated with other channels.

Cognitive processing loops are continuously updated as a function of the interactions between neurons and changes in

sensory inputs. The outputs from these loops are provided to neurons in other loops as well as the SNc, the LC and other catecholaminergic neurons, where they would contribute to the generation of the phenomenological conscious experience as a function of their strength relative to other signals. This effect would explain the separate experiences of the “inner dialog,” action selection, and the ability to distinguish and prioritize different sensory inputs, such as listening and looking for salient events and being aware of physiological changes (e.g., sharp pains, a tap on the back). You can take a sip from your drink at an event while listening for someone to call your name, and also while you are thinking about your vacation next week. These separate functions would be associated with different catecholaminergic switches, which could explain why there is a limit to the number and type of functions that can be multitasked. In addition, damage to the SNc but not the LC or VTA could explain locked-in syndrome, where phenomenal consciousness exists without the ability to initiate voluntary actions.

Actions that fall closer to the realm of “free will” are ones that are preceded by time to cognitively process or “contemplate” facts, sensory inputs and possible outcomes, whereas actions that fall closer to the realm of “determinism” are those that are associated with well-developed neural structures that process facts and sensory inputs that do not require as much cognitive processing. Thus, it is an act of “free will” to eat a donut if you contemplate whether you can afford the calories based on your diet and what you have eaten today, and it is “determinism” if you have structured your cognitive processing either eat or not eat a donut under any circumstances. However, in this example, there is no such thing as true determinism – whether you initiate an action to select a donut and to take a bite still requires you to select which donut, to evaluate whether it is a real donut, to evaluate whether someone else has already started to eat it and so forth. To some extent, free will and determinism are constructs formed from cognitive processing and neural structures that can be changed, even if that change requires substantial time and effort.

7. Conclusion

The CNET hypothesis, as published in 2018, made a number of predictions about unusual and unexpected phenomena that would be needed to provide evidence that it exists. A source for high-energy electrons that could tunnel between neurons would be needed. A medium over which they could tunnel would be needed. Depolarization of the axons of large SNc neurons would be needed to create an electromotive force and direct tunneling. A mechanism for promoting Ca2+ action potentials in large SNc neurons in response to the release of iron from ferritin in those neurons would be needed. Evidence of all four of those core components of CNET was subsequently obtained from independent sources, demonstrating the predictive power of the CNET hypothesis. Additional research should be conducted to better understand these phenomena and to determine whether the CNET mechanism could provide answers to some of the many questions that exist regarding action initiation and selection, both for neurology and psychology.

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