Research Article

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

Christopher Rourk[1]

1. Dallas Independent School District, Dallas, United States

[001] The neural mechanism responsible for action selection and initiation for specific actions remains elusive. The CNET neural signaling mechanism hypothesis for action selection and initiation was first proposed in 2018 based on 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 four core components of CNET have 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 protection 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.

Corresponding author: Christopher Rourk, crourk@jw.com

1. Introduction

[002] Quantum mechanics was discovered over 100 years ago, yet many life sciences professionals are unfamiliar with even the basics of quantum mechanics and how they apply to biological processes. For example, many life sciences professionals conceptualize "classical" approaches to chemical reactions that treat atoms and molecules as if they were solid objects, but in fact, the sub-atomic particles that form atoms and thus molecules are each defined by probability wave functions. These wave functions are responsible for the physical properties of atoms and molecules. A good example of these quantum mechanical properties is the bipolar nature of a water molecule, which has two off-diagonal hydrogen atoms attached to an oxygen atom. The reason why the two hydrogen atoms are off diagonal is because of the shape of the electron orbital wave functions of the oxygen. The behavior of electrons in orbitals differs from the behavior of electrons when they either dissociate from the atom or molecule to form an exciton or break free entirely, and can then hop or tunnel to another atom or molecule. A good introduction to the phenomenon of electron tunneling in molecules is provided by (Gray and Winkler, 2003). This article discusses a type of electron tunneling that appears to be different from electron tunneling associated with any other type of atom or molecule in a biological process, namely electron tunneling associated with the protein complex ferritin. The distinction between classical electron transfer and electron tunneling associated with ferritin should be kept in mind when reviewing this article, because CNET depends on electron tunneling, as opposed to electron transfer associated with electrons in the orbitals of iron atoms. If this distinction is not understood, it will not be possible to understand the CNET mechanism.

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

[003] 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 selection and initiation mechanism that is consistent with how action selection and initiation is experienced has not been identified. The CNET hypothesis is an NCC for action selection and initiation, 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 selection and initiation (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 selection and initiation 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.

[004] 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 selection and initiation 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:

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

[005] The triplet electrons can tunnel through ferritin between soma.

[006] Axon synaptic activity directs electron tunneling to one or more target neurons and promotes action potentials to mediate action selection.

[007] Electrons received in somatic ferritin in the target neuron(s) causes iron release, which promotes calcium action potentials.

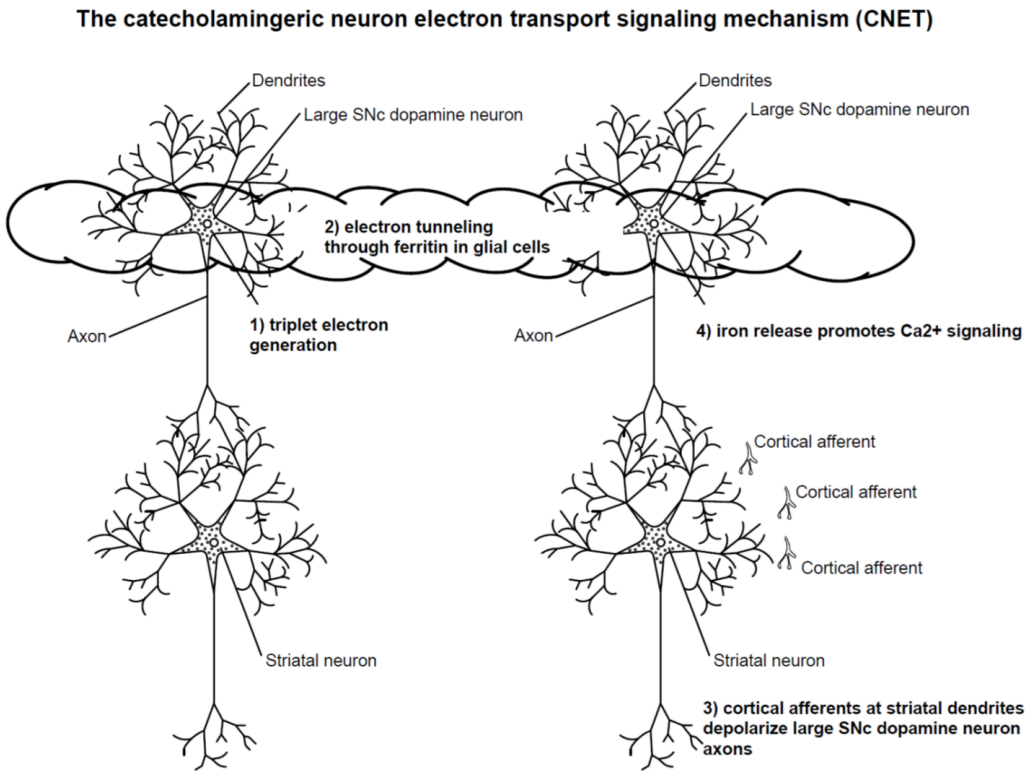


Figure 1. The CNET mechanism includes four core components. 1) somatic dopamine metabolism generates triplet electrons that can provide energy to the CNET mechanism (Brash et al. 2018; Brash and Goncalves, 2023; Gonçalves et al. (2023); 2) triplet electrons can tunnel through ferritin between soma (Rourk 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)

[008] 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

[009] The first component of CNET is the generation of high energy electrons as a result of chemiexcitation of dopamine from interaction with peroxidase (Brash et al., 2023). As discussed below, 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 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.

[0010] 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 and Bolam 2013; Bolam and Pissadaki 2012)., 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.

[0011] 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, which could create a magnetic field having the form of a modified Hopf soliton. In addition, it has recently been shown that an electron beam can create Hopf solitons in an isotropic chiral magnet (Zheng et al., 2023), and it has previously been shown by numerical simulations that static Hopf solitons can be formed in magnetic nanostructures with perpendicular magnetic anisotropy, which in conjunction with confinement can stabilize the Hopf solitons, and also that the stability of Hopf solitons in chiral colloidal ferromagnets is enhanced by chirality (Tai and Smalyukh, 2018). Perpendicular magnetic anisotropy has been observed in sintered thin films formed from magnetic nanoparticles (Erdem et al. 2016), which would be structurally similar to self-assembled ferritin formations. It has also been observed that self-assembled monolayers of ferritin have aligned magnetic moments (Yuan et al. 2006), if these arise from aligned Hopf solitons in the ferritin, they could support electron transport based on the same principle by which electron beams generate Hopf solitons in Zheng et al. This physical structure of ferritin provides it with electrical and magnetic properties that can influence chemical reactions.

[0012] 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 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 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.

[0013] There is substantial evidence that ferritin can absorb high energy triplet electrons from dopamine and release them at a later time them 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 to 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.

[0014] 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 iron the 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.

[0015] 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*.

[0016] 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 the 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.

[0017] 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

[0018] 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).

[0019] 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).

[0020] 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 compartmentalization 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 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).

[0021] The production of somatic dopamine in large SNc dopamine neurons is associated with 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 against 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.

[0022] 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.

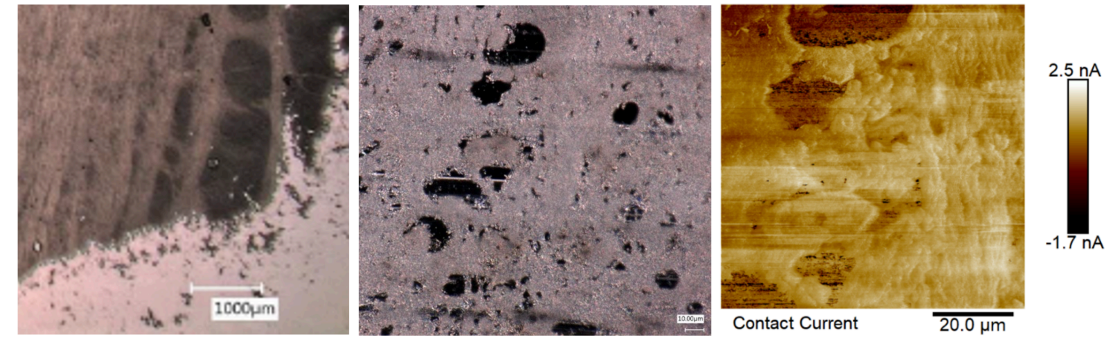
[0023] 3) The triplet electrons can tunnel through ferritin between soma

[0024] 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 of 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.

[0025] 3.a) Ferritin and neuromelanin structures within the soma of catecholaminergic neurons allow electron tunneling to occur

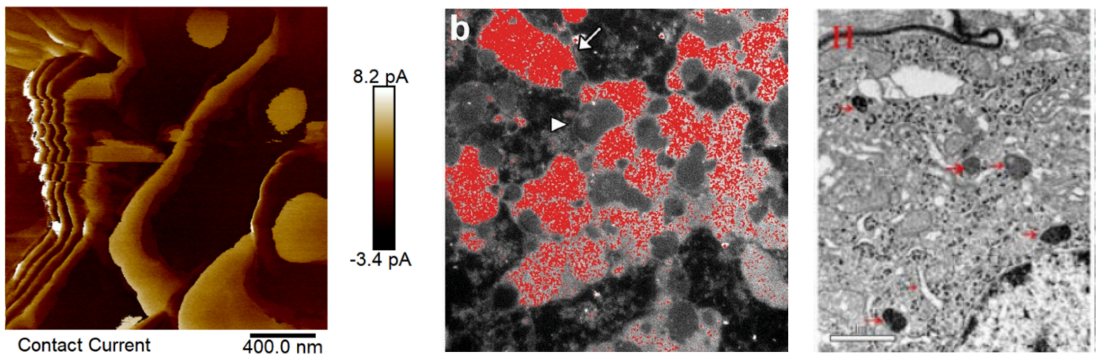
[0026] Because ferritin particles are ~12 nm in diameter, it can be very difficult to see formations of these particles *in vivo*. Electron microscope (EM) images provide some of the highest resolution, but when the scale changes from microns to even tens of microns, essential details can be lost. An example of this can be seen in Fig. 2, as well as 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.

[0027]



[0028]

doi.org/10.32388/PZJNJP.2



[0029] Figure 2 caption. Evidence of ferritin and biosystems associated with ferritin can be difficult to see and can require a combination of different imaging techniques. A) is an optical image of an unstained, 5-micron thick slice of fixed SNc tissue with a 1 mm scale bar. At this scale, no identifying features can be made out. B) is an optical image of the fixed SNc tissue on foil with a 10 micron scale bar. At this scale, it can be seen that soma (the round black objects) are within 10-20 microns of each other. C) is a CAFM data set of tunneling currents measured in the fixed SNc tissue with an 20 micron scale bar. It can be seen that tunneling currents are widespread, but with no apparent mechanism associated with the currents. D) is a CAFM data set of tunneling currents in the fixed SNc tissue with a 400 nm scale bar. At this scale, it can be seen that the tunneling currents correlate to layers of ferritin outside of neuromelanin organelles. E) is an electron spectroscopic image of iron layers (red) outside of an NMO with a 1 micron scale bar (from Sulzer et al., 2018). Other data establishes that the iron is stored in ferritin. F) is an electron microscope image of a glial cell with a 100 nm scale bar (from Xiong et al., 2009). The electron dense dots are ferritin, and it can be seen that they form nearly continuous structures across the glial cell.

[0030] 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 ground over the entire measurement cycle. These currents make sense if there is widespread electron tunneling caused by 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.

[0031] 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).

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 3.b) Ferritin structures between the soma of large SNc neurons allow electrons to tunnel between them

[0036] 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 micro particle 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 oligodendrites 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 the higher levels of ferritin in astrocytes (Schipke et al., 2002).

[0037] 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-

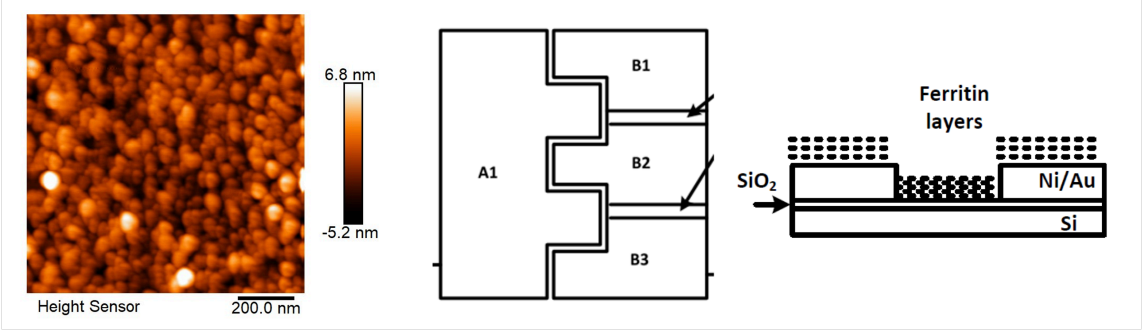
assembled monolayers of ferritin on insulating substrates (Mykhaylyk, et al. 2004; Yuan et al. 2006). Ferritin exhibits lower levels of neutron scattering in bulk (Stuhrmann et al. 1976; Seehra et al. 2000), but the degree of neutron scattering of ferritin as ordered in macrophages was greater than when 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).

[0038] 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.

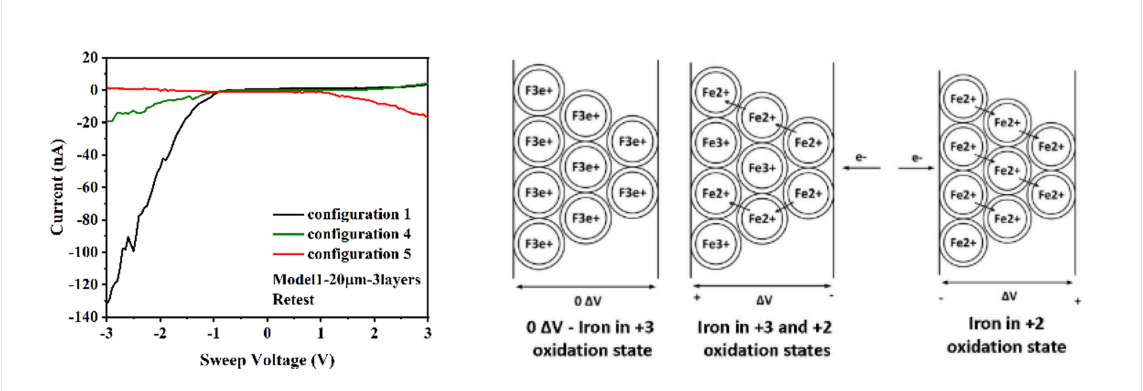
[0039] Based on these test, additional tests were designed that used a similar electrode configuration and layer-by-layer assembly of self-assembled monolayers, but with 4 electrodes and electrode spacing of 20, 40 and 80 microns, to allow for a parametric study of electron transport to be performed (Rourk et al., 2021). Some results from those tests are shown in Figure 3. 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).

[0040]



[0041]



[0042] Figure 3 caption. A) is an AFM height data set of a self-assembled layer of ferritin on an insulated silicon wafer substrate. The relative disorder within the layer can be seen, but the layer-by-layer deposition process creates at least one degree of order in each layer. B) is a diagram of the test die configuration, showing the electrode placements (A1 and B1-B3) and the spacing between

doi.org/10.32388/PZJNJP.2

electrodes. C) is a diagram of a side view of a test die showing the arrangement of the self-assembled ferritin layers on top of the electrodes and in the spaces between electrodes. D) is a diagram of the current-voltage characteristics for one of the tested die configurations with 3 deposited layers and a 20 micron spacing between electrodes. The configurations refer to the placement of the positive and negative leads and whether the current through electrodes B1-B3 was measured separately or in parallel. E) is a diagram showing the Coulomb blockade effect that could explain the nonlinear current-voltage characteristic. Electrons can tunnel from the electrode on the right to the electrode on the left, but in the reverse direction they fill the ferritin cores and create a counter-EMF that blocks electron flow.

[0043] 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.

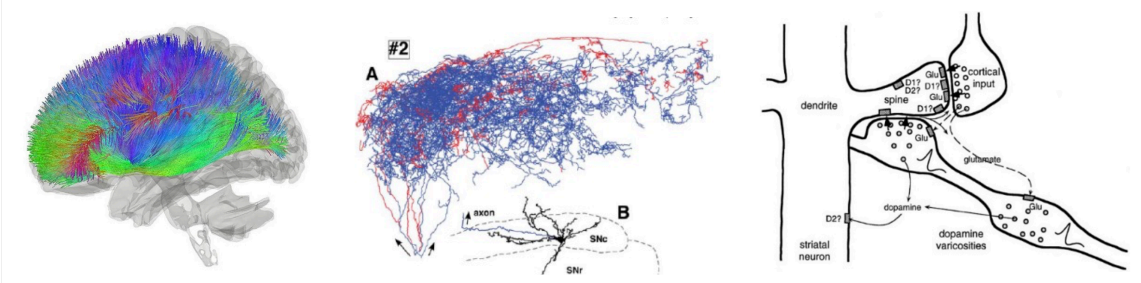
[0044] 4) Axon synaptic activity of large catecholaminergic neurons directs electron tunneling and promotes action potentials to mediate action selection.

[0045] 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 has also been observed in LC neurons (Behl et al., 2022).

[0046] 4.a) Axon membrane potentials of large SNc neurons are depolarized by afferent cortical signals in the striatum

[0047] 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, see Figure 4.

[0048]



[0049] Figure 4 caption. The interaction of cortical, sensory and other neuron afferents with the basal ganglia requires analysis of data from multiple scales and different imaging techniques. A) is population-averaged diffusion MRI data showing the corticostriatal pathways. This data shows how cortical columns provide afferents to the striatum. B) is a camera lucida drawing of the axon arbor of a single large SNc neuron, which primarily innervates the striatum. It can be seen that the axon arbor is very extensive, but the specific branching structure is not apparent in this view. C) is a drawing based on observations of the three-way synapse formed by cortical afferents and SNc axonal varicosities with striatal dendrites. One SNc axon can have over 1 million of these varicosities, but may only have 20% that are active, the rest being presumably dormant until activated. Signals from the cortical afferent can locally depolarize the SNc axon.

[0050] 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 backfiring/antidromic action potentials observed in LC neurons (Arakawa et al. 1997) and 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).

[0051] The electrical properties of the extensive axon arbors of large SNc neurons is 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 some 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.

[0052] 4.b) Action potentials in large SNc neurons are associated with action selection

[0053] 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 Kaeser's research were viewed as surprising, they merely confirm 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).

[0054] 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 selection and initiation. 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 selection and initiation, but does not cause convulsions. Furthermore, stimulation of the VTA can alleviate depressive behavior (Friedman et al., 2009), which suggests that more subtle action selection and initiation effects occur than could be identified from animal movement tests.

[0055] 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 delivery of noradrenalin to select groups of cortical neurons, similar to the switching function performed by the SNc to provide spatially and temporally 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 selection and initiation 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).

[0056] Integration of numerous cortical processing loops in the SNc and LC could also be associated with phenomenal consciousness, as it is well know 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 selection and initiation, 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).

[0057] 4.d) Coulomb blockade formation in ferritin provides a routing mechanism that can control that tunneling

[0058] 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.

[0059] 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 amount 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 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.

[0060] 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 selection and initiation 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 selection and initiation. Because thousands of these neurons have that capability, a mechanism is needed to prevent them from firing simultaneously.

[0061] 5) Iron release in soma that receive the electrons causes iron release, which promotes calcium action potentials

[0062] 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 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 release of iron and promote the emergence of Ca2+ signals/action potentials in those neurons.

[0063] 5.a) Providing electrons to ferritin causes iron release

[0064] 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 electrons for hours 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.

[0065] 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).

[0066] 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

[0067] 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.

[0068] 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 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.

[0069] Iron promotes the emergence of Ca2+ signals via activation of redox-sensitive Ca2+ channels (Gleitze et al., 2021). As discussed in Gleitze, 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).

[0070] 5.c) Ryanodine receptors (RyR) release calcium in response to ROS, which can contribute to the generation of calcium action potentials

[0071] 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.

[0072] 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).

[0073] In conclusion, substantial evidence exists that the four core components of CNET can provide a signaling mechanism in large SNc dopamine neurons:

[0074] chemiexcitation of dopamine in large SNc dopamine neurons creates high energy electrons,

[0075] ferritin provides a substrate that allows these electrons to tunnel between neurons,

[0076] cortical afferents associated with action selection and initiation computations are received at striatal dendrites that form unusual 3-way synapses with large SNc dopamine neuron synapse and can depolarize the axons, and

[0077] iron release from ferritin can promote calcium signaling and associated action potentials.

[0078] 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 selection and initiation mechanism in catecholaminergic neurons can be obtained.

[0079] 6. Discussion

[0080] A main assumption of the computational model of the basal ganglia developed by Gurney, Prescott, and Redgrave (Gurney et al., 2001) is that actions are represented in the basal by neural signals associated with sensory, cognitive, and emotional information called a “channel.” The model posits that the channels are organized in parallel, which is supported by physiological and histological evidence, and that the basal ganglia selects one of the channels and suppresses the others. This model was further developed by (Codol et al. 2022), which showed that the selected channel can lock out the other channels as a function of differential (rather than equal) sensitivity of the two types of dopaminergic receptors to dopaminergic input. This behavior was assumed to be the action selection mechanism by Codol et al., but one problem with that conclusion is that it does not prevent seizures if two or more competing channels simultaneously lock out other channels. This could happen frequently when multiple channels are equally strong, such as when there is a great deal of important

sensory data being received, such as when driving a car through a parking lot. In order to prevent simultaneous lock outs that result in seizures, an additional mechanism is needed that would initiate one and only one channel at a time.

[0081] The CNET mechanism is based on physical observations of ferritin levels in and between large catecholaminergic neuron soma, which are closely grouped. These neurons have additional unusual properties. The axons of both the largest SNc and LC soma are very long, with extensive branching that results in unusual electrical properties. As observed by Kaeser et al., those properties include the ability to form ectopic action potentials in the axon arbor of SNc neurons that can arise from afferents to striatal dendrites, similar to backfiring/antidromic action potentials observed in LC neurons. In the SNc, functional compartmentalization of the spike generating region of the axon/dendrite from the spike generating region in the soma would require activation of both spike generating regions in order to result in successful action potential generation that invades the entire axon arbor. This would require simultaneous depolarization of the axon as well as the soma, where one without the other would not result in successful action potential. Electron tunneling to the soma as a result of depolarization of the axon would help to coordinate such simultaneous depolarization, and would require cortical afferents that are provided to the striatal neurons associated with the strongest channel. In other words, cortical cognitive processing would need to be coordinated with sensory signals to result in action selection.

[0082] Returning to the parking lot example, a person driving a car in a parking lot needs to depress the accelerator or depress the brake – two potentially conflicting actions, both of which require some cognitive preprocessing to perform (i.e. spatial alignment of the foot with the accelerator and brake pedals). The accelerator needs to be pressed periodically to keep the car moving, but not continuously because the car would move too fast. In addition, any one of the cars that are parked could start backing out or a pedestrian could emerge as the driver progresses along a row of parking spaces, so the driver needs to be prepared to step on the brake when sensory data demands. A person getting out of their car would generate sensory data, but would not 1) pose a risk of injury that requires brake activation or 2) present a potential parking opportunity that would require brake activation or prevent accelerator activation. However, brake lights from a car associated with a person who the driver cognitively observed walking to the car would suggest a need for brake activation. Seizure events – where a person continues to press the accelerator when they want to press the brake or vice versus – are rare, suggesting that close temporal correlation between sensory inputs and cognitive processing

for action selection is required, as opposed to just sensory inputs. This comports with many other experiences, such as where a person fails to act quickly because they were unprepared, i.e. lacked the prerequisite cognitive processing and associated cortical afferents to be able to act when the sensory input was received.

[0083] With both CNET and the locking mechanism of Codol et al. required for channel selection and lock out, the risk of a seizure would be greatly reduced, as that would require near-simultaneous activation of both the spike generating region of the axon/dendrite and the spike generating region in the soma in two or more neurons. Thus, the CNET mechanism does not need to control action potential generation in all SNc neurons, and would help to reduce the risk of simultaneous lock out events by enabling activation of the two spike forming regions of large SNc dopamine neurons that mediate action selection and initiation.

[0084] 7. Conclusion

[0085] The CNET hypothesis as published in 2018 made a number of predictions about unusual and unexpected phenomena that would be needed to provide evidence of 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 to 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 selection and initiation, both for neurology and psychology.

References

- Akita T, Kuba K (2000) Functional triads consisting of ryanodine receptors, Ca2+ channels, and Ca2+-activated K+ channels in bullfrog sympathetic neurons: plastic modulation action potential. J. Gen. Physiol. 116, 697–720.
- Albarran, Eddy, and Jun B. Ding. "W'axon, wax off: Striatal cholinergic synapses instruct dopamine axon activity." Neuron 110.18 (2022): 2889-2890.

- Alkhateeb, Ahmed A., Bing Han, and James R. Connor. "Ferritin stimulates breast cancer cells through an iron-independent mechanism and is localized within tumor-associated macrophages." Breast cancer research and treatment 137 (2013): 733-744.
- Alm, Per A. "The dopamine system and automatization of movement sequences: a review with relevance for speech and stuttering." Frontiers in human neuroscience 15 (2021): 661880.
- Alsyamy, Amaar, et al. "Role of Ferritin in Immunity, Inflammation and Malignancy." (2022).
- Alvarez-Maubecin, Veronica, et al. "Functional coupling between neurons and glia." Journal of Neuroscience 20.11 (2000): 4091-4098.
- Ambani, Lalit M., Melvin H. Van Woert, and Sean Murphy. "Brain peroxidase and catalase in Parkinson disease." Archives of neurology 32.2 (1975): 114-118.
- Anastassiou, Costas A., et al. "Ephaptic coupling of cortical neurons." Nature neuroscience 14.2 (2011): 217-223.
- Arakawa, S., et al. "Antidromic burst activity of locus coeruleus neurons during cortical spreading depression." Neuroscience 78.4 (1997): 1147-1158
- Avshalumov, Marat V., et al. "Endogenous hydrogen peroxide regulates the excitability of midbrain dopamine neurons via ATP-sensitive potassium channels." Journal of Neuroscience 25.17 (2005): 4222-4231.
- Awschalom, D. D., et al. "Macroscopic quantum tunneling in magnetic proteins." Physical review letters 68.20 (1992): 3092.
- Axford, Danny N., and Jason J. Davis. "Electron flux through apo-and holoferritin." Nanotechnology 18.14 (2007): 145502.
- Azcorra, Maite, et al. "Dopaminergic axons track somatic signaling in behaving mice." bioRxiv (2022): 2022-06.
- Badu-Boateng, Charles, and Richard J. Naftalin. "Ascorbate and ferritin interactions: Consequences for iron release in vitro and in vivo and implications for inflammation." Free Radical Biology and Medicine 133 (2019): 75-87.
- (Bailey, Craig H., Eric R. Kandel, and Kristen M. Harris. "Structural components of synaptic plasticity and memory consolidation." Cold Spring Harbor perspectives in biology 7.7 (2015)
- Bao, Li, et al. "Mitochondria are the source of hydrogen peroxide for dynamic brain-cell signaling." Journal of Neuroscience 29.28 (2009): 9002-9010.
- Becana, Manuel, et al. "Reactive oxygen species and antioxidants in legume nodules." (2000): 372-381.

- Behl, Tapan, et al. "The Locus Coeruleus–Noradrenaline system: Looking into Alzheimer's therapeutics with rose coloured glasses." Biomedicine & Pharmacotherapy 151 (2022): 113179
- Belan P, Kostyuk P, Snitsarev V, Tepikin A (1993) Calcium clamp in isolated neurons of the snail Helix pomatia. J. Physiol. (Lond.) 462, 47–58.
- Bera, Sudipta, et al. "Long-range solid-state electron transport through ferritin multilayers." Journal of Materials Chemistry C 7.29 (2019): 9038-9048.
- Bolam, J. Paul, and Eleftheria K. Pissadaki. "Living on the edge with too many mouths to feed: why dopamine neurons die." Movement Disorders 27.12 (2012): 1478-1483.
- Boveris A, Chance B (1973) The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. Biochem J 134:707–716.
- Branch, Sarah Y., Ramaswamy Sharma, and Michael J. Beckstead. "Aging decreases L-type calcium channel currents and pacemaker firing fidelity in substantia nigra dopamine neurons." Journal of Neuroscience 34.28 (2014): 9310-9318.
- Brash, Douglas E., Leticia CP Goncalves, and Etelvino JH Bechara. "Chemiexcitation and its implications for disease." Trends in molecular medicine 24.6 (2018): 527-541.
- Brash, Douglas E., and Leticia CP Goncalves. "Chemiexcitation: Mammalian photochemistry in the dark." Photochemistry and Photobiology 99.2 (2023): 251-276.
- Breton-Provencher, Vincent, Gabrielle T. Drummond, and Mriganka Sur. "Locus coeruleus norepinephrine in learned behavior: anatomical modularity and spatiotemporal integration in targets." Frontiers in Neural Circuits (2021): 46.
- Breton-Provencher, Vincent, et al. "Spatiotemporal dynamics of noradrenaline during learned behaviour." Nature 606.7915 (2022): 732-738.
- Bridges, Kenneth R., and Kim E. Hoffman. "The effects of ascorbic acid on the intracellular metabolism of iron and ferritin." Journal of Biological Chemistry 261.30 (1986): 14273-14277.
- Buchholz, John N., et al. "Age-dependent changes in Ca2+ homeostasis in peripheral neurones: implications for changes in function." Aging Cell 6.3 (2007): 285-296.
- Budson, Andrew E., Kenneth A. Richman, and Elizabeth A. Kensinger. "Consciousness as a memory system." Cognitive and Behavioral Neurology 35.4 (2022): 263.
- Cabantchik, Zvi Ioav. "Labile iron in cells and body fluids: physiology, pathology, and pharmacology." Frontiers in pharmacology 5 (2014): 45.
- Chandler, R. E., et al. "Electron transport in quantum dot solids: Monte Carlo simulations of the effects of shell filling, Coulomb repulsions, and site disorder." Physical Review B 75.8 (2007):

085325.

- Chersi, Fabian, and Giovanni Pezzulo. "Using hippocampal-striatal loops for spatial navigation and goal-directed decision-making." Cognitive processing 13 (2012): 125-129.
- Cherepanov, Dmitry A., et al. "Mechanism of adiabatic primary electron transfer in photosystem I: Femtosecond spectroscopy upon excitation of reaction center in the far-red edge of the QY band." Biochimica et Biophysica Acta (BBA)-Bioenergetics 1858.11 (2017): 895-905.
- Choi, Sang H., et al. "Ferritin-templated quantum dots for quantum logic gates." Smart Structures and Materials 2005: Smart Electronics, MEMS, BioMEMS, and Nanotechnology. Vol. 5763. SPIE, 2005.
- Codol, Olivier, Paul L. Gribble, and Kevin N. Gurney. "Differential Dopamine Receptor-Dependent Sensitivity Improves the Switch Between Hard and Soft Selection in a Model of the Basal Ganglia." Neural Computation 34.7 (2022): 1588-1615.
- Courtney, Nicholas A., Aphroditi A. Mamaligas, and Christopher P. Ford. "Species differences in somatodendritic dopamine transmission determine D2-autoreceptor-mediated inhibition of ventral tegmental area neuron firing." Journal of Neuroscience 32.39 (2012): 13520-13528.
- Cui, Guohong, et al. "Concurrent activation of striatal direct and indirect pathways during action initiation." Nature 494.7436 (2013): 238-242.
- Da Silva, Joaquim Alves, et al. "Dopamine neuron activity before action initiation gates and invigorates future movements." Nature 554.7691 (2018): 244-248.
- Dugan LL, Sensi SL, Canzoniero LM, Handran SD, Rothman SM, Lin TS, Goldberg MP, Choi DW (1995) Mitochondrial production of reactive oxygen species in cortical neurons following exposure to N-methyl-Daspartate. J Neurosci 15:6377– 6388.
- Dulhunty, Angela F., Nicole A. Beard, and Marco G. Casarotto. "Recent advances in understanding the ryanodine receptor calcium release channels and their role in calcium signalling." F1000Research 7 (2018).
- Epsztejn, Silvina, et al. "H-ferritin subunit overexpression in erythroid cells reduces the oxidative stress response and induces multidrug resistance properties." Blood, The Journal of the American Society of Hematology 94.10 (1999): 3593-3603.
- Erdem, Derya, et al. "CoFe2O4 and CoFe2O4-SiO2 Nanoparticle Thin Films with Perpendicular Magnetic Anisotropy for Magnetic and Magneto-Optical Applications." Advanced Functional Materials 26.12 (2016): 1954-1963,

- Ermakova, A., et al. "Detection of a few metallo-protein molecules using color centers in nanodiamonds." Nano letters 13.7 (2013): 3305-3309.
- Everett, James, et al. "Illuminating the brain: revealing brain biochemistry with synchrotron x-ray spectromicroscopy." Journal of Electron Spectroscopy and Related Phenomena (2023): 147355.
- Fettes, Peter, Laura Schulze, and Jonathan Downar. "Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: promising therapeutic targets in psychiatric illness." Frontiers in systems neuroscience 11 (2017): 25.
- Fill, Michael, and Julio A. Copello. "Ryanodine receptor calcium release channels." Physiological reviews 82.4 (2002): 893-922.
- Floresco, Stan B., et al. "Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission." Nature neuroscience 6.9 (2003): 968-973.
- Fodstad, Harald. "The neuron theory." Stereotactic and functional neurosurgery 77.1-4 (2002): 20-24.
- Friedman, Alexander, et al. "Programmed acute electrical stimulation of ventral tegmental area alleviates depressive-like behavior." Neuropsychopharmacology 34.4 (2009): 1057-1066.
- Friedrich, I., et al. "Cell specific quantitative iron mapping on brain slices by immuno-μPIXE in healthy elderly and Parkinson's disease." Acta Neuropathologica Communications 9.1 (2021): 1-17.
- Frith, Chris, Richard Perry, and Erik Lumer. "The neural correlates of conscious experience: An experimental framework." Trends in cognitive sciences 3.3 (1999): 105-114.
- Gao, Guofen, et al. "Cellular iron metabolism and regulation." Brain Iron Metabolism and CNS Diseases (2019): 21-32.
- Gentet, L. J., & Williams, S. R. (2007). Dopamine gates action potential backpropagation in midbrain dopaminergic neurons. Journal of Neuroscience, 27(8), 1892-1901.
- Girard, Benoît, et al. "A biologically constrained spiking neural network model of the primate basal ganglia with overlapping pathways exhibits action selection." European Journal of Neuroscience 53.7 (2021): 2254-2277.
- Gleitze, Silvia, et al. "The calcium–iron connection in ferroptosis-mediated neuronal death." Free Radical Biology and Medicine 175 (2021): 28-41.
- Goldfarb, Adam N., et al. "Iron control of erythroid microtubule cytoskeleton as a potential target in treatment of iron-restricted anemia." Nature Communications 12.1 (2021): 1645.
- Gonçalves, L. C. P., C. Angelé-Martinez, S. Premi, M. A. Palmatier, F. M. Prado, P. Di Mascio, E. L. Bastos and D. E. Brash (2023) Chemiexcited neurotransmitters and hormones create DNA

- photoproducts in the dark. Biol, ACS Chem. in press.
- GraceAA (1990) Evidence for the functional compartmentalization of spike generating regions of rat midbrain dopamine neurons recorded in vitro. Brain Res 524:31– 41.
- Grace, Anthony A. "Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia." Neuroscience 41.1 (1991): 1-24.
- Gray, Harry B., and Jay R. Winkler. "Electron tunneling through proteins." Quarterly reviews of biophysics 36.3 (2003): 341-372.
- Gupta, Nipun Kumar, et al. "Temperature-Dependent Coherent Tunneling across Graphene–Ferritin Biomolecular Junctions." ACS applied materials & interfaces 14.39 (2022): 44665-44675.
- Gurney, Kevin, Tony J. Prescott, and Peter Redgrave. "A computational model of action selection in the basal ganglia. II. Analysis and simulation of behaviour." Biological cybernetics 84 (2001): 411-423.
- Gurney, K. N., et al. "Testing computational hypotheses of brain systems function: a case study with the basal ganglia." Network: Computation in neural systems 15.4 (2004): 263.
- Gurney, Kevin, Tony J. Prescott, and Peter Redgrave. "A computational model of action selection in the basal ganglia. I. A new functional anatomy." Biological cybernetics 84 (2001): 401-410.
- Hidalgo, Cecilia, and Marco T. Núñez. "Calcium, iron and neuronal function." IUBMB life 59.4-5 (2007): 280-285.
- Hidalgo, C., Carrasco, M.A., Munoz, P., andNunez, M.T. (2007).A role for reactive oxygen/nitrogen species and iron on neuronal synaptic plasticity. Antioxid. Redox Signal. 9, 245–255. doi:10.1089/ars.2007.9.ft-9
- Hoffer, B. J., et al. "Activation of the Pathway from Locus Coeruleus to Rat Cerebellar Purkinje Neurons: Pharmacological Evidence of Noradrenrtgic Central Inhibition." Journal of Pharmacology and Experimental Therapeutics 184.3 (1973): 553-569.
- Hoffman, Ralph E., et al. "Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia." Biological psychiatry 69.5 (2011): 407-414.
- Horsman, Dominic, et al. "Abstraction and representation in living organisms: when does a biological system compute?." Representation and reality in humans, other living organisms and intelligent machines (2017): 91-116.
- Horsman, Dominic, et al. "When does a physical system compute?." Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences 470.2169 (2014): 20140182.

- Howells, Fleur M., Dan J. Stein, and Vivienne A. Russell. "Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance." Metabolic brain disease 27 (2012): 267-274.
- Hulsmans, Maarten, et al. "Macrophages facilitate electrical conduction in the heart." Cell 169.3 (2017): 510-522
- Humphries, Mark D., and Kevin Gurney. "Making decisions in the dark basement of the brain: A look back at the GPR model of action selection and the basal ganglia." Biological Cybernetics 115.4 (2021): 323-329.
- Infante, Anthony A., et al. "Ferritin associates with marginal band microtubules." Experimental cell research 313.8 (2007): 1602-1614.
- Ishizaki, Akihito, and Graham R. Fleming. "Quantum coherence in photosynthetic light harvesting." Annu. Rev. Condens. Matter Phys. 3.1 (2012): 333-361.
- Janacsek, Karolina, et al. "Subcortical cognition: the fruit below the rind." Annual Review of Neuroscience 45 (2022): 361-386.
- Juárez Olguín, Hugo, et al. "The role of dopamine and its dysfunction as a consequence of oxidative stress." Oxidative medicine and cellular longevity (2016)
- Kadian, Monika, Garima Sharma, and Anil Kumar. "Iron-Calcium Crosstalk in Neurodegenerative Diseases." Brain-Iron Cross Talk. Singapore: Springer Nature Singapore, 2022. 109-137.
- Kane, Robert. The significance of free will. Oxford University Press, USA, 1998.
- Kaushik, Poorvi, Fredric Gorin, and Shireen Vali. "Dynamics of tyrosine hydroxylase mediated regulation of dopamine synthesis." Journal of computational neuroscience 22 (2007): 147-160.
- Kitchener, Peter D., and Colin G. Hales. "What neuroscientists think, and don't think, about consciousness." Frontiers in Human Neuroscience 16 (2022): 767612.
- Koch, Christof, et al. "Neural correlates of consciousness: progress and problems." Nature Reviews Neuroscience 17.5 (2016): 307-321.
- Koorts, A. M., and M. Viljoen. "Ferritin and ferritin isoforms II: protection against uncontrolled cellular proliferation, oxidative damage and inflammatory processes." Archives of physiology and biochemistry 113.2 (2007): 55-64
- Koplovitz, Guy, et al. "Single domain 10 nm ferromagnetism imprinted on superparamagnetic nanoparticles using chiral molecules." Small 15.1 (2019): 1804557.
- Koundouros, Nikos, and George Poulogiannis. "Phosphoinositide 3-kinase/Akt signaling and redox metabolism in cancer." Frontiers in oncology 8 (2018)

- Kramer, Paul F., et al. "Synaptic-like axo-axonal transmission from striatal cholinergic interneurons onto dopaminergic fibers." Neuron 110.18 (2022): 2949-2960.
- Kraus, Jacob G., and Peter Koulen. "Resveratrol directly controls the activity of neuronal ryanodine receptors at the single-channel level." Molecular neurobiology 57 (2020): 422-434.
- Kumar, Karuppannan Senthil, et al. "Long-Range Tunneling Processes across Ferritin-Based Junctions." Advanced materials 28.9 (2016): 1824-1830.
- Labra-Muñoz, Jacqueline A., et al. "Ferritin-Based Single-Electron Devices." Biomolecules 12.5 (2022): 705.
- Loughlin, S. E., S. L. Foote, and R. Grzanna. "Efferent projections of nucleus locus coeruleus: morphologic subpopulations have different efferent targets." Neuroscience 18.2 (1986): 307-319.
- Liu, Changliang, et al. "Dopamine secretion is mediated by sparse active zone-like release sites." Cell 172.4 (2018): 706-718.
- Liu, Changliang, Pragya Goel, and Pascal S. Kaeser. "Spatial and temporal scales of dopamine transmission." Nature Reviews Neuroscience 22.6 (2021): 345-358.
- Liu, Changliang, et al. "An action potential initiation mechanism in distal axons for the control of dopamine release." Science 375.6587 (2022): 1378-1385.
- Liu Y, Fiskum G, Schubert D (2002) Generation of reactive oxygen species by the mitochondrial electron transport chain. J Neurochem 80:780 –787.
- Llinás, Rodolfo, and M. Sugimori. "Electrophysiological properties of in vitro Purkinje cell somata in mammalian cerebellar slices." The Journal of physiology 305.1 (1980): 171-195.
- Ljubojevic, Nina, J. Michael Henderson, and Chiara Zurzolo. "The ways of actin: why tunneling nanotubes are unique cell protrusions." Trends in Cell Biology 31.2 (2021): 130-142.
- Ljungberg, Tomas, Paul Apicella, and Wolfram Schultz. "Responses of monkey dopamine neurons during learning of behavioral reactions." Journal of neurophysiology 67.1 (1992): 145-163.
- Macpherson, Tom, Makiko Morita, and Takatoshi Hikida. "Striatal direct and indirect pathways control decision-making behavior." Frontiers in psychology 5 (2014): 1301.
- Martinez-Banaclocha, Marcos. "Ephaptic coupling of cortical neurons: possible contribution of astroglial magnetic fields?." Neuroscience 370 (2018): 37-45.
- Mashour, George A., et al. "Conscious processing and the global neuronal workspace hypothesis." Neuron 105.5 (2020): 776-798.
- Matchett, Billie J., et al. "The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease." Acta neuropathologica 141.5 (2021): 631-

650.

- McCutcheon, Robert, et al. "Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis." Schizophrenia bulletin 44.6 (2018): 1301-1311.
- McFadden, Johnjoe. "Integrating information in the brain's EM field: the cemi field theory of consciousness." Neuroscience of Consciousness 2020.1 (2020): niaa016.
- McHaffie, John G., et al. "Subcortical loops through the basal ganglia." Trends in neurosciences 28.8 (2005): 401-407.
- Metzinger, Thomas, ed. Neural correlates of consciousness: Empirical and conceptual questions. MIT press, 2000.
- Mohseni, Masoud, et al. "Environment-assisted quantum walks in photosynthetic energy transfer." The Journal of chemical physics 129.17 (2008).
- Moreno, Sandra, Enrico Mugnaini, and M. Paolo Cerù. "Immunocytochemical localization of catalase in the central nervous system of the rat." Journal of Histochemistry & Cytochemistry 43.12 (1995): 1253-1267.
- Mumbauer, Simone, et al. "Ferritin heavy chain protects the developing wing from reactive oxygen species and ferroptosis." PLoS Genetics 15.9 (2019): e1008396.
- Muñoz, Pablo, et al. "Effect of iron on the activation of the MAPK/ERK pathway in PC12 neuroblastoma cells." Biological research 39.1 (2006): 189-190.
- Munoz, Pablo, et al. "Iron mediates N-methyl-D-aspartate receptor-dependent stimulation of calcium-induced pathways and hippocampal synaptic plasticity." Journal of Biological Chemistry 286.15 (2011): 13382-13392.
- Murchison, David, and William H. Griffith. "Calcium buffering systems and calcium signaling in aged rat basal forebrain neurons." Aging cell 6.3 (2007): 297-305.
- Murray, C. B., C. R. Kagan, and M. G. Bawendi. "Self-organization of CdSe nanocrystallites into three-dimensional quantum dot superlattices." Science 270.5240 (1995): 1335-1338.
- Murray, Christopher B., et al. "Colloidal synthesis of nanocrystals and nanocrystal superlattices." IBM Journal of Research and Development 45.1 (2001): 47-56.
- Mykhaylyk, Olga, et al. "On the magnetic ordering of the iron storage proteins in tissues." Journal of magnetism and magnetic materials 272 (2004): 2422-2423.
- Nie, Linyan, et al. "Quantum sensing of free radicals in primary human dendritic cells." Nano letters 22.4 (2021): 1818-1825.

- Orino, Kouichi, et al. "Ferritin and the response to oxidative stress." Biochemical Journal 357.1 (2001): 241-247..
- Ozturk, S. Furkan, et al. "Chirality-Induced Magnetization of Magnetite by an RNA Precursor." arXiv preprint arXiv:2304.09095 (2023).
- Peles, Dana N., et al. "Human iridal stroma melanosomes of varying pheomelanin contents possess a common eumelanic outer surface." The Journal of Physical Chemistry B 113.32 (2009): 11346-11351.
- Perez, Ismael Diez, et al. "Electron tunneling in ferritin and associated biosystems." IEEE Transactions on Molecular, Biological and Multi-Scale Communications (2023).
- Peters, Sarah K., Katharine Dunlop, and Jonathan Downar. "Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment." Frontiers in systems neuroscience 10 (2016): 104.
- Philpott, Caroline C., et al. "Cytosolic iron chaperones: proteins delivering iron cofactors in the cytosol of mammalian cells." Journal of Biological Chemistry 292.31 (2017): 12764-12771.
- Piazza I - Piazza, Pier Vincenzo, et al. "The influence of dopaminergic A10 neurons on the motor pattern evoked by substantia nigra (pars compacta) stimulation." Behavioural brain research 31.3 (1989)
- Piazza II - Piazza, Pier Vincenzo, et al. "Circling behavior: ethological analysis and functional considerations." Behavioural brain research 31.3 (1989): 267-271.
- Pissadaki, Eleftheria K., and J. Paul Bolam. "The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease." Frontiers in computational neuroscience 7 (2013): 13.
- Plum, S., et al. "Combined enrichment of neuromelanin granules and synaptosomes from human substantia nigra pars compacta tissue for proteomic analysis." Journal of proteomics 94 (2013): 202-206.
- Pockett, Susan. "Difficulties with the electromagnetic field theory of consciousness." Journal of Consciousness Studies 9.4 (2002): 51-56.
- Prescott, Tony J., et al. "The evolution of action selection." Towards the Whole Iguana. MIT Press, Cambridge, MA, to appear (2001).
- Raman, Indira M., and Bruce P. Bean. "Ionic currents underlying spontaneous action potentials in isolated cerebellar Purkinje neurons." Journal of Neuroscience 19.5 (1999): 1663-1674.

- Rebentrost, Patrick, et al. "Environment-assisted quantum transport." New Journal of Physics 11.3 (2009): 033003.
- Reinert, Anja, et al. "Iron concentrations in neurons and glial cells with estimates on ferritin concentrations." BMC neuroscience 20.1 (2019): 1-14.
- Roest, Aarnoud L., et al. "Electron-conducting quantum-dot solids with ionic charge compensation." Faraday discussions 125 (2004): 55-62.
- Rourk, Christopher John. "Ferritin and neuromelanin “quantum dot” array structures in dopamine neurons of the substantia nigra pars compacta and norepinephrine neurons of the locus coeruleus." Biosystems 171 (2018): 48-58.
- Rourk, Christopher J. "Indication of quantum mechanical electron transport in human substantia nigra tissue from conductive atomic force microscopy analysis." Biosystems 179 (2019): 30-38.
- Rourk, Christopher J. "Functional neural electron transport." Advances in Quantum Chemistry. Vol. 82. Academic Press, 2020. 25-111.
- Rourk, Christopher, et al. "Indication of Strongly Correlated Electron Transport and Mott Insulator in Disordered Multilayer Ferritin Structures (DMFS)." Materials 14.16 (2021): 4527.
- Ruddell, Richard G., et al. "Ferritin functions as a proinflammatory cytokine via iron-independent protein kinase C zeta/nuclear factor kappaB–regulated signaling in rat hepatic stellate cells." Hepatology 49.3 (2009): 887-900.
- Rudow, Gay, et al. "Morphometry of the human substantia nigra in ageing and Parkinson’s disease." Acta neuropathologica 115 (2008): 461-470.
- Ruffini, Giulio, et al. "Realistic modeling of mesoscopic ephaptic coupling in the human brain." PLoS computational biology 16.6 (2020): e1007923.
- Rumble J (ed) (2020) CRC handbook of chemistry and physics, 102nd edn. CRC Press, Boca Raton
- Saenz, Natalie, et al. "Insights on the (auto) photocatalysis of ferritin." Inorganic Chemistry 55.12 (2016): 6047-6050.
- Sala, Davide, et al. "Investigation of the iron (II) release mechanism of human H-ferritin as a function of pH." Journal of Chemical Information and Modeling 57.9 (2017): 2112-2118.
- Salmi, Juha, et al. "Cognitive and motor loops of the human cerebro-cerebellar system." Journal of cognitive neuroscience 22.11 (2010): 2663-2676.
- SanMartín, Carol D., et al. "Ryanodine receptor-mediated Ca2+ release underlies iron-induced mitochondrial fission and stimulates mitochondrial Ca2+ uptake in primary hippocampal neurons." Frontiers in molecular neuroscience 7 (2014).

- Schipke, Carola G., et al. "Astrocyte Ca2+ waves trigger responses in microglial cells in brain slices." The FASEB Journal 16.2 (2002): 1-16
- Schultz, Wolfram. "Predictive reward signal of dopamine neurons." *Journal of neurophysiology* 80.1 (1998): 1-27.
- Schultz, Wolfram. "Reward functions of the basal ganglia." Journal of neural transmission 123.7 (2016): 679-693.
- Seehra, M. S., et al. "Neutron scattering and magnetic studies of ferrihydrite nanoparticles." Physical Review B 61.5 (2000)
- Seger, Carol A. "The involvement of corticostriatal loops in learning across tasks, species, and methodologies." The basal ganglia IX. Springer New York, 2009.
- Sharmin, Rokshana, et al. "Fluorescent nanodiamonds for detecting free-radical generation in real time during shear stress in human umbilical vein endothelial cells." ACS sensors 6.12 (2021): 4349-4359.
- Shesh, Bhavyata Pandya, and James R. Connor. "A novel view of ferritin in cancer." Biochimica et Biophysica Acta (BBA)-Reviews on Cancer (2023): 188917.
- Smith, Y., et al. "Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey." Journal of Comparative Neurology 344.1 (1994)
- Stuhrmann, H. B., et al. "Low angle neutron scattering of ferritin studied by contrast variation." Journal of Molecular Biology 100.3 (1976): 399-413.
- Sulzer, David, et al. "Neuromelanin detection by magnetic resonance imaging (MRI) and its promise as a biomarker for Parkinson's disease." NPJ Parkinson's disease 4.1 (2018): 11.
- Tai, Jung-Shen B., and Ivan I. Smalyukh. "Static Hopf solitons and knotted emergent fields in solid-state noncentrosymmetric magnetic nanostructures." Physical Review Letters 121.18 (2018): 187201
- Tepper JM, Sun BC, Martin LP, Creese I (1997) Functional roles of Dopamine D2 and D3 autoreceptors on nigrostriatal neurons analyzed by antisense knockdown in vivo. J Neurosci 17:2519 –2530.
- Tribl, Florian, et al. "Identification of L-ferritin in neuromelanin granules of the human substantia nigra: a targeted proteomics approach." Molecular & Cellular Proteomics 8.8 (2009): 1832-1838.
- Usachev YM, Thayer SA (1999b) Ca2+ influx in resting rat sensory neurones that regulates and is regulated by ryanodine-sensitive Ca2+ stores. J. Physiol. 519 (Part 1), 115–130.

- Vanmaekelbergh, Daniel, and Peter Liljeroth. "Electron-conducting quantum dot solids: novel materials based on colloidal semiconductor nanocrystals." Chemical Society Reviews 34.4 (2005): 299-312.
- Velíšek, Libor, Jana Velíšková, and Solomon L. Moshé. "Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats." Experimental neurology 173.1 (2002): 145-152.
- Verkhratsky AJ, Shmigol A (1996) Calcium-induced calcium release in neurones. Cell Calcium 19, 1–14.
- Verkhratsky AJ, Petersen OH (1998) Neuronal calcium stores. Cell Calcium 24, 333–343.
- Vilas-Boas, Eloisa A., et al. "Goldilocks calcium concentrations and the regulation of oxidative phosphorylation: Too much, too little, or just right." Journal of Biological Chemistry 299.3 (2023).
- Wang, Yue-Qi, et al. "The protective role of mitochondrial ferritin on erastin-induced ferroptosis." Frontiers in aging neuroscience 8 (2016): 308.
- Watt, G. D., Richard B. Frankel, and G. C. Papaefthymiou. "Reduction of mammalian ferritin." Proceedings of the National Academy of Sciences 82.11 (1985): 3640-3643.
- Wilkinson, Nicole, and Kostas Pantopoulos. "The IRP/IRE system in vivo: insights from mouse models." Frontiers in pharmacology 5 (2014): 176.
- Wolszczak, Marian, and Joanna Gajda. "Iron release from ferritin induced by light and ionizing radiation." Research on chemical intermediates 36 (2010): 549-563.
- Wu, Kaiqi, et al. "Diamond relaxometry as a tool to investigate the free radical dialogue between macrophages and bacteria." Acs Nano 17.2 (2023): 1100-1111.
- Wu, Xianyong, Daniel P. Leonard, and Xiulei Ji. "Emerging non-aqueous potassium-ion batteries: challenges and opportunities." Chemistry of Materials 29.12 (2017): 5031-5042.
- Xiong, Nian, et al. "Stereotaxical infusion of rotenone: a reliable rodent model for Parkinson's disease." PloS one 4.11 (2009): e7878
- Yao, Wei-Dong, Roger D. Spealman, and Jingping Zhang. "Dopaminergic signaling in dendritic spines." Biochemical pharmacology 75.11 (2008): 2055-2069.
- Yuan, Zhen, et al. "Magnetic properties of self-assembled ferritin-core arrays." Journal of applied physics 99.8 (2006)
- Zampese, Enrico, et al. "Ca2+ channels couple spiking to mitochondrial metabolism in substantia nigra dopaminergic neurons." Science Advances 8.39 (2022): eabp8701.

- Zhang, Chenxi, Xiaorong Zhang, and Guanghua Zhao. "Ferritin nanocage: a versatile nanocarrier utilized in the field of food, nutrition, and medicine." Nanomaterials 10.9 (2020): 1894.
- Zheng, Fengshan, et al. "Hopfion rings in a cubic chiral magnet." Nature 623.7988 (2023): 718-723.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.