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Affidavit

I, undersigned, Maya Williams, hereby declare that the work presented in this manuscript is my own work, carried out under the scientific supervision of Christelle Baunez and Mickaël Degoulet, in accordance with the principles of honesty, integrity and responsibility inherent to the research mission. The research work and the writing of this manuscript have been carried out in compliance with both the French national charter for Research Integrity and the Aix-Marseille University charter on the fight against plagiarism.

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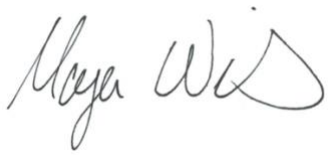

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Liste de publications et/ou brevets et participation aux conférences

1) Liste des publications et/ou brevet [a] réalisées dans le cadre du projet de thèse :

1. **Williams, M**., Vielle, C., Tiran-Cappello, A., Pelloux, Y., Baunez, C., Degoulet, M. (in review). Subthalamic Nucleus Deep Brain Stimulation as a Reward: Exploring Pleasure Through Electrical and Optogenetic self-stimulation and Neuronal Inhibition.

2. Vignal, L., Vielle, C., **Williams, M**., Maurice, N., Degoulet, M., & Baunez, C. (2024). Subthalamic high-frequency deep brain stimulation reduces addiction-like alcohol use and the possible negative influence of a peer presence. Psychopharmacology. https://doi.org/10.1007/s00213-024-06532-w

2) Participation aux conférences[b] et écoles d'été au cours de la période de thèse :

1. International Behavioral Neurosceince Society (IBNS) Aunnual Meeting, 2023- Oral and Poster presentation: *"The Neural Dynamics of the Subthalamic Nucleus hyperdirect pathway during cocaine use and 'natural' reward seeking behavior"*

2. Neurodays Conference by Doctoral Student, 2022- Poster presentation: *"Involvement of the subthalamic nucleus in electrical and optogenetic intracranial self-stimulation behavior"*

3. European Behavioral and Pharmacological Society, 2021- Poster Presentation: *"Involvement of the subthalamic nucleus in electrical and optogenetic intracranial self-stimulation behavior"*

4. GDR NeuralNet Mini School, 2021- Attendance

…

[a] Cette liste comprend les articles publiés, les articles soumis à publication et les articles en préparation ainsi que les livres, chapitres de livre et/ou toutes formes de valorisation des résultats des travaux propres à la discipline du projet de thèse. La référence aux publications doit suivre les règles standards de bibliographie et doit être conforme à la charte des publications d'AMU.

[b] Le terme « conférence » est générique. Il désigne à la fois « conférence », « congrès », « workshop », « colloques », « rencontres nationales et/ou internationales » … etc.

Indiquer si vous avez fait une présentation orale ou sous forme de poster.

Résumé

Le noyau subthalamique (NST), noyau des ganglions de la base, est la cible du traitement de la maladie de Parkinson par stimulation cérébrale profonde (SCP). Les travaux de notre laboratoire ont montré que l'inactivation du NST, par lésion ou SCP, réduit la motivation pour la cocaïne tout en augmentant celle pour le sucre. La modulation du NST peut empêcher les caractéristiques de l'addiction, telles que la perte de contrôle sur la consommation et la recherche compulsive de drogue. Ces résultats ont mis en évidence le rôle du NST dans les processus motivationnels et ont conforté notre suggestion de SCP du NST comme traitement chirurgical de l'addiction. **Le projet de cette thèse est de clarifier le rôle du NST et d'identifier lequel de ses réseaux neuronaux est impliqué dans les comportements motivés.**

L'inhibition du NST réduisant la prise de drogue et les réponses affectives, il est possible que le NST soit impliqué dans le « liking », le « wanting » ou les 2. Il a été rapporté que certains patients Parkinsoniens peuvent s'auto-stimuler par SCP, ce qui questionne le rôle du NST dans l'auto-stimulation intracrânienne (ICSS). **La première partie de cette thèse a donc étudié si la stimulation du NST pouvait générer de l'ICSS**. Pour tester cette hypothèse, nous avons utilisé la SCP électrique et l'optogénétique. Des rats implantés avec des électrodes dans le NST pouvaient s'auto-administrer une stimulation à trois fréquences différentes (8, 30, 130 Hz). Parallèlement, d'autres rats infectés par des opsines excitatrices, inhibitrices ou de contrôle dans le NST pouvaient s'auto-administrer des impulsions lumineuses. Les résultats ont montré que la SCP du NST à 130 Hz et l'inhibition optogénétique augmentaient l'ICSS, ce qui suggère que **le NST doit être inhibé pour générer l'ICSS** qui peut être liée au plaisir mais aussi à l'aspect renforçant des récompenses. Ces effets liés à la récompense ne sont pas limités au NST. **La dernière partie de cette thèse visait donc à identifier le réseau cérébral impliqué**.

Le NST reçoit des projections corticales directes (voie hyperdirecte), dont il faut comprendre le rôle dans les effets motivationnels des manipulations du NST. Nous avons utilisé l'imagerie calcique (photométrie par fibre) pour observer la dynamique d'activité de cette voie pendant un test de motivation pour le sucrose. Un protocole de Ratio

Progressif (PR) a été utilisé pour mesurer la motivation à produire un effort pour obtenir le sucrose. Les cortex infralimbique (IL), prélimbique (PL) et cingulaire antérieur (ACg) ont été ciblés par un virus GECI (Genetically Encoded Calcium Indicator) dépendant de la Cre, tandis que Cav2-Cre a été injecté dans le NST pour un marquage rétrograde. Des fibres optiques ont été implantées au-dessus du NST, enregistrant l'activité calcique dans les terminaisons cortico-NST pendant le comportement. Les résultats montrent une activité différentielle entre les voies hyperdirectes. Les voies PL-NST et ACg-NST montrent une diminution d'activité à l'obtention de la récompense dans le PR. Par contre, l'activité des neurones du NST montre une augmentation des signaux calciques pendant la consommation de la récompense. Ces résultats suggèrent que **les voies hyperdirectes issues des cortex PL et ACg sont impliquées dans le comportement de recherche de récompense, tandis que le NST est plus engagé dans la consommation de la récompense et l'évaluation de sa valeur incitative**.

Dans une dernière expérience, les voies IL-NST, ACg-NST et PL-NST ont été sélectivement inhibées à l'aide de l'optogénétique pendant la tâche de PR. **L'inhibition de chaque voie hyperdirecte a diminué la motivation pour le sucre.**

Dans l'ensemble, ces résultats mettent en évidence les rôles critiques et distincts du NST et de la voie hyperdirecte dans la motivation et la consommation de récompense. Ils apportent des preuves supplémentaires que la manipulation du NST peut être une stratégie prometteuse pour traiter l'addiction.

Mots clés : ganglions de la base, motivation, saccharose, optogénétique, activité calcique, comportement

Abstract

The subthalamic nucleus (STN), a small brain nucleus of the basal ganglia, is the current target of the treatment of Parkinson's Disease with Deep Brain Stimulation (DBS). Our lab's work has shown that inactivation of the STN, either through lesion or DBS, reduce motivation for cocaine while increasing motivation for sweet foods. STN modulation can prevent key features of addiction, such as escalation (loss of control over drug intake) and compulsive drug-seeking behavior. All these results have highlighted a role for STN in motivational processes and strengthened the suggestion of STN DBS as a promising surgical treatment for addiction. **The project of this PhD work was to further clarify the specific role of the STN and identify which of its neural networks is involved in motivational behaviors.**

Since STN inhibition can reduce drug-taking behavior, but also affective responses, raising the question whether these effects could be related to an involvement of STN in "wanting" or "liking" or both. Previous reports have shown that some PD patients can use their DBS devices for self-stimulation, raising the question of whether the STN can support intracranial self-administration (ICSS). The first study in this thesis thus investigated whether the STN could support ICSS behavior. To test this hypothesis, we employed both electrical DBS and optogenetic approaches. Rats implanted with STN electrodes could self-administer stimulation at three different frequencies (8, 30, 130 Hz). In parallel, other rats infected with excitatory, inhibitory, or control opsins in the STN could self-administer light pulses through optic fibers. The results showed that STN **130 Hz DBS and optogenetic inhibition significantly increased ICSS responding, suggesting that the STN has to be inhibited to generate ICSS behavior that can be pleasure-related but also reward-reinforcing**. These effects on reward related processes are not limited to STN. **The last part of this thesis aimed thus at identifying which cerebral network was mostly involved**.

Since the STN receives direct cortical projections via the hyperdirect pathway, understanding the role of this pathway in the observed motivational effects of STN manipulation is critical. We utilized calcium imaging (fiber photometry) to observe neural

dynamics within the hyperdirect pathway during behavioral assessments of motivation for sucrose in rats. A progressive ratio (PR) schedule of reinforcement was used to assess the motivation to produce an effort to obtain sucrose pellets. The infralimbic (IL), prelimbic (PL), and anterior cingulate cortex (ACg) regions were targeted with a Cre-dependent Genetically Encoded Calcium Indicator (GECI) virus, while Cav2-Cre was injected into the STN for retrograde labeling. Optic fibers were implanted above the STN to record calcium activity in the cortico-STN terminals during fixed and PR tasks for sucrose. The results revealed differential activity across the hyperdirect pathways. Specifically, the PL-STN and ACg-STN pathways showed decreased activity during reward delivery in the PR task. Additionally, recordings of STN neuron activity showed decreased calcium signals during the retrieval and consumption of the sweet reward. These findings suggest that **the hyperdirect pathway, particularly the PL and ACg components, is actively involved in reward-seeking behavior, while the STN is more engaged in reward consumption and the assessment of incentive value**.

In a last experiment, these various hyperdirect pathways (IL-STN, ACg-STN and PL-STN) were selectively inhibited using optogenetics during PR. **The results showed that inhibition of each mPFC hyperdirect pathway decreased motivation for sucrose.**

Altogether, these results highlight critical and distinct roles of the STN and the hyperdirect pathway in motivation and reward consumption. These findings provide further evidence that STN manipulation may be a promising strategy to treat substance use disorders.

Keywords : Basal Ganglia, motivation, sucrose, optogenetics, calcium activity, behavior

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List of Abbreviations

µl	microliter
µm	micrometer
cm	centimeter
ACg	Anterior cingular cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BLA	Basolateral Amygdala
CP	Cerebellar peduncle
CPA	Conditioned place aversion
CPP	Conditioned place preference
CeA	Central amygdala
CRSTT	choice serial reaction time task
CUD	cocaine use disorder
DA	dopamine
DAT	dopamine transporter
DBS	Deep Brain Stimulation
DDS	dopaminergic dysregulation syndrome
DSM-V	Diagnostic and Statistical Manual Fith Edition
EP	entopeduncular nucleus
fMRI	functional magnetic resonance imaging
FR	fixed ratio
G	gram
GABA	gamma-aminobutyric acid
GECI	genetically encoded calcium indicator
GP	globus pallidus
GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
h	hour
HFS	high-frequency stimulation
HF-DBS	high-frequency deep brain stimulation
Hz	hertz
ITI	intertrial interval
IL	Infralimbic cortex
i.m	intramuscular
i.p	intraperitoneal
LH	lateral hypothalamus
MFB	medial forebrain bundle
min	minute
mg	milligram
ml	milliliter
mm	millimeter
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin
mRNA	messenger ribonucleic acid
NAc	nucleus accumbens
NMDA	N-Methyl-D-aspartic acid
Nmol	nanomol
OCD	obsessive-compulsive disorders
OFC	orbital frontal cortex

PBN	parabrachial nucleus
PBS	phosphate buffered saline
PD	Parkinson's disease
PFA	paraformaldehyde
(m)PFC	(medial) prefrontal cortex
PL	Prelimbic cortex
PN	pontine nucleus
PPN	pedunculopontine nucleus
PPTg	pedunculopontine tegmental nucleus
PR	progressive ratio
s.c.	subcutaneous
SC	superior colliculus
SMA	supplementary motor area
SN	substantia nigra
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
SSRT	stop-signal reaction time
SUD	substance use disorders
USV	ultrasonic vocalizations
VTA	ventral tegmental area
VP	ventral pallidum
ZI	zona incerta

Introduction

Classically, the subthalamic nucleus (STN) has been viewed as a small, homogeneous glutamatergic structure that functions primarily as a relay within the indirect pathway of the basal ganglia, particularly in the context of motor functions and Parkinson's disease (PD). In non-human primate models of PD, the STN displays an increase in firing rate and abnormal burst discharges (Bergman et al., 1994). Modulating this abnormal activity through either STN lesions (Bergman et al., 1990) or high-frequency deep brain stimulation (HF-DBS) effectively alleviates motor symptoms in PD models and patients (Benazzouz et al., 1993; Limousin et al., 1995).

However, the network and functional role of the STN are far more complex than previously thought. The STN receives projections from various cortical areas (Auer, 1956; Canteras et al., 1990; Nambu et al., 2002), constituting what is known as the "hyperdirect" pathway to the basal ganglia. Furthermore, preclinical studies indicate that the STN plays a key role in cognitive and motivational processes in rats (Baunez & Lardeux, 2011), and similar effects have been reported in PD patients subjected to STN HF-DBS (Witjas et al., 2005; Ballanger et al., 2009). Specifically, STN lesions have been shown to alter attentional functioning and inhibition control (Baunez et al., 1995; Baunez & Robbins, 1997), while HF-DBS and STN lesions increase motivation for sweet food while decreasing motivation for cocaine (Baunez et al., 2005; Rouaud et al., 2010). This dualistic role of the STN in motivation positions STN HF-DBS as a promising treatment for substance use disorders (SUD), for which no effective pharmacological treatments currently exist.

The increasing burden of drug addiction in society has prompted a concerted effort within the field of neuroscience to explore new treatment strategies to aid public health initiatives. In recent years, DBS has been employed for various psychiatric disorders, including obsessive-compulsive disorder, treatment-resistant depression, and cocaine use disorder, with some promising, albeit limited, success (Mallet et al., 2008; 2019; Mayberg et al., 2005; Vorspan et al., 2023). Our team's work on brain motivational processes has identified the STN as an intriguing target, as DBS can prevent certain criteria of addiction, such as escalation and loss of control over drug intake, as well as

modulating compulsive cocaine seeking (Pelloux & Baunez, 2013). These findings highlight the potential of STN manipulation to reduce addictive behaviors toward drugs. Additionally, the side effects of STN HF-DBS in PD patients, such as weight gain (Steinhardt et al., 2023) and impulsivity (Lim et al., 2008), as well as their underlying causes, remain elusive.

The brain mechanisms elicited by STN HF-DBS remain a subject of debate, and the exact contribution of the STN—embedded within a complex network—requires further elucidation. Therefore, a better characterization of the functional effects of STN modulation is critical to mitigate any deleterious side effects of HF-DBS in patients suffering from PD, OCD, and potential SUD. Precise optogenetic manipulations of the STN and its network are necessary to clarify its specific role in motivation since electrical DBS can have unintended effects on afferent and effect fibers. Thus, the objective of this research is to delineate the specific functions of the STN and its network in motivational processes, paving the way for potential translation into human patients.

In this thesis, I sought to better characterize the influence of the STN on reward processing, as well as the role of the hyperdirect pathway and its impact on motivation. To achieve this, I employed electrical DBS for intracranial self-stimulation and optogenetic approaches in rats, alongside fiber photometry to record the activity of the hyperdirect pathway and STN neurons.

In the first experiment, I utilized electrical DBS and optogenetic tools to assess the self-stimulating properties of the STN across various stimulation frequencies, as well as through inhibition and high-frequency optical stimulation. In the second experiment, I recorded activity from the hyperdirect pathways and the STN using fiber photometry during motivational tasks focused on sucrose reward. In the third study, I evaluated the effects of optogenetic inhibition of these hyperdirect pathways on the motivation for sweet food.

Overall, this thesis aims to deepen our understanding of the STN's influence on reward processing and incentive salience. My results emphasize the importance of the STN and hyperdirect pathway in the motivation for sucrose. Additionally, the thesis seeks to better characterize the role of the hyperdirect pathway and the effects of its

neuromodulation on motivation for sucrose. Ultimately, my findings illuminate the involvement of both the STN and the hyperdirect pathway in motivational processes.

1. Biology of the Subthalamic Nucleus

1.1. Anatomy and Organization of the Subthalamic Nucleus

The Subthalamic nucleus (STN) was first described in 1865 by French neurologist Jules Bernard Luys, as a nucleus important for its role in motor functions. Originally named Luys' body, he described it as "displaying a linear form, bulged on its median portion and slanted on each of its extremities" giving our first insights into the STN structure (Parent, 2002).

Located between the midbrain and the thalamus, the lens-shaped nucleus with its diagonal orientation, as described by Luys, is a highly conserved brain area in rats, nonhuman primates, and humans, despite subtle species differences (Hardman et al., 2002; Whittier & Mettler, 1949). The STN size varies significantly: 0.8 ±0.1 mm^2 in rats, 34 ±6 mm^2 in macaques, and 240 ±23 mm^2 in humans (Hardman et al., 2002). The greatest thickness and width of the STN in the coronal plane occur mid-rostrocaudally, where the highest number of neurons is found. The relationship between the STN volume, the total brain volume, and the distribution of neurons within the STN is proportionally similar across species (Hardman et al., 2002).

The bilateral nucleus shows no difference between hemispheres or decreases in volume with age, based on data from 7 Tesla MRI imaging in humans (Plantinga et al., 2016). However, there is a lateral shift in the STN's location in aging humans, which should be considered during electrode placement for Parkinson's disease patients.

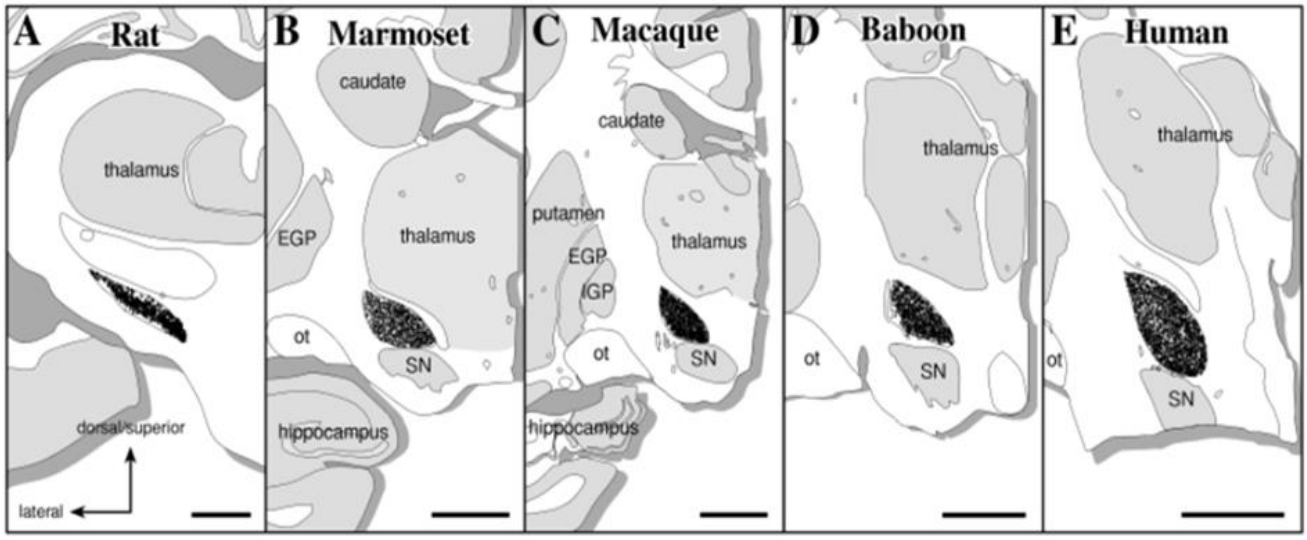

Figure 1. Drawing of the STN created from Nissl-stained coronal sections with immunohistochemically defined nuclear boundaries superimposed. EGP, external globus pallidus; IGP, internal globus pallidus; ot, optic tract; SN, substantia nigra; PV, parvalbumin. Scale bars: 1mm in A, 2mm in B, 4mm in C and D, 8mm in E. Adapted from Hardman et al., 2002

In all mammalian species, the STN is highly vascularized with thin and thick fibers and parvalbumin-containing cell bodies. Fibers of the fasciculus lenticularis originate from the medial globus pallidus internus (GPi) and form a bundle ventral to the zona incerta (ZI), separating the STN from the ventral thalamus. The lenticular fasciculus joins the ansa lenticularis and fibers from the superior cerebellar peduncle (CP) and brainstem, forming the thalamic fasciculus (H1 Field of Forel). Dorsal to the CP and the substantia nigra (SN), the lateral boundaries of the STN are surrounded by dense fibers of the internal capsule, which separate it laterally from the GPi (Hamani et al., 2004). Due to these major myelinated fiber bundles, the STN is considered a closed nucleus in primates (Yelnik & Percheron, 1979). In contrast, the rat STN lacks these boundaries and is considered an open nucleus. Instead of the dense fibers of the lenticular fasciculus, the ventral part of the rat STN is bordered by the CP and SN. Neurons on the lateral border of the STN contain dendrites crossing into the CP, while some centrally located dendrites extend into the ZI and lateral hypothalamic area. The STN is separated medially from the lateral hypothalamus by the perisubthalamic nucleus, and the entopeduncular nucleus (as opposed to the GPi in primates) borders the STN rostrally via the internal capsule (Afsharpour et al., 1985).

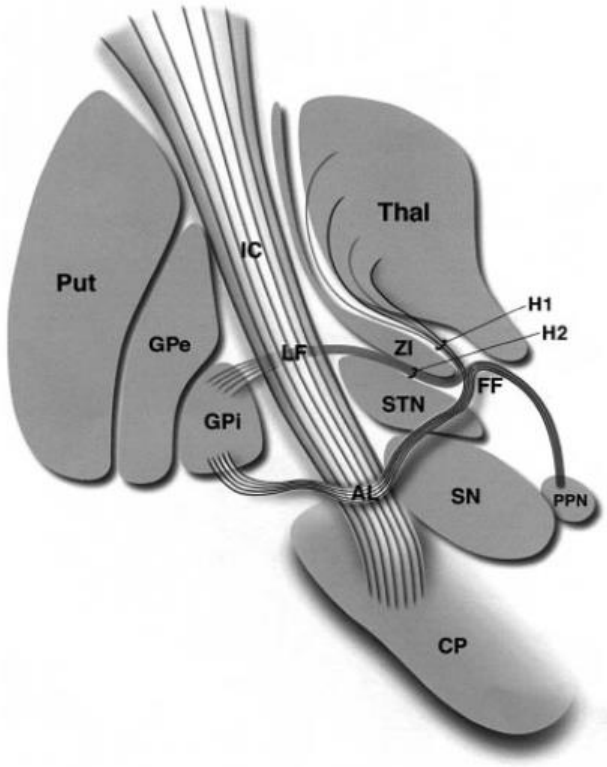

Figure 2. Representation of the major anatomical structures and fiber tracts associated with the STN. AL = ansa lenticularis; CP = cerebral peduncle; FF = Fields of Forel; GPe = globus pallidus externus; GPi = globus pallidus internus; H1 = H1 Field of Forel (thalamic fasciculus); IC = internal capsule; LF = lenticular fasciculus (H2); PPN = pedunculopontine nucleus; Put = putamen; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus; ZI = zona incerta. (Hamani et al. 2004)

The subthalamic nucleus is mainly composed of projection neurons, with an estimated 25,000 in rats, 155,000 in macaques, and 560,000 in humans (Hardman et al., 2002; Hamani et al., 2003). Their somata measure between 10-25um in rodents (Chang et al., 1983) and 35-40um in primates (Yelnik & Percheron et al., 1979), with each neuron having two to eight dentritic trunks (Rafols and Fox, 1976). STN axons, originating from the soma or proximal dendrite, bifurcate into multiple branches in the rodent and primate, forming diverse arborized collaterals that project to various output structures, allowing a single neuron to influence multiple areas (Deniau et al., 1978; Van Der Kooy & Hattori, 1980; Hammond & Yelnik, 1983; Sato et al., 2000).

Traditionally, STN were considered to be homogeneously composed of glutamatergic (excitatory) projection neurons, while the rest of the basal ganglia neurons are predominantly GABAergic (inhibitory) (Rafols & Fox, 1976; Chang et al., 1983; Smith & Parent et al., 1988). However, it has been established that a small population of GABAergic interneurons, accounting for 7.5% of the STN's total neuronal population, is present, with these GABAergic neurons being most significant in the medial STN (Lévesque & Parent, 2005). Additionally, the STN is anatomically and functionally organized based on cellular calcium-binding protein markers. It is the most intensely parvalbumin-immunoreactive component of the basal ganglia, particularly in its dorsolateral section, whereas calretinin is found in the ventromedial part of the STN (Parent et al., 1996; Lévesque & Parent, 2005). Recent single-nuclei RNA sequencing (snRNASeq) in mice revealed transcriptomic subregions within the STN defined by sets of promoter activities. Pitx2 mRNA encompasses the entire STN. Col24a1 is localized primarily in ventral STN, Pvalb primarily in dorsal STN. Col24a1/Pvalb2 co-localization was identified in the central aspect of the STN (Wallén-Mackenzie et al., 2020).

Functionally, the STN is subdivided into three regions based on input organization: the dorsolateral sensory-motor territory receives projections from motor regions of the cortex, striatum, and GP; the ventromedial associative territory receives inputs from associative areas of the cortex, ventromedial striatum, and GP; and the medial limbic territory receives inputs from the prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral pallium (VP) (Parent & Hazrati, 1995). Diffusion-weighted imaging has confirmed these functional zones in humans based on brain connectivity (Lambert et al., 2012). These subdivisions are also present in rats and monkeys, although the borders limits are not well-defined and display a functional gradient (Afsharpour ,1985; Parent & Hazrati, 1995; Hamani, 2004; Kita et al., 2014; Karachi et al., 2005; Haynes & Haber 2013, Darbaky et al., 2005). Importantly, the internal organization of the STN is still under investigation. Studies challenging the tripartite model have presented zero to six subparts of the STN, indicating that more research on its organization from different aspect are likely to emerge (Prasad & Wallén-Mackenzie, 2024).

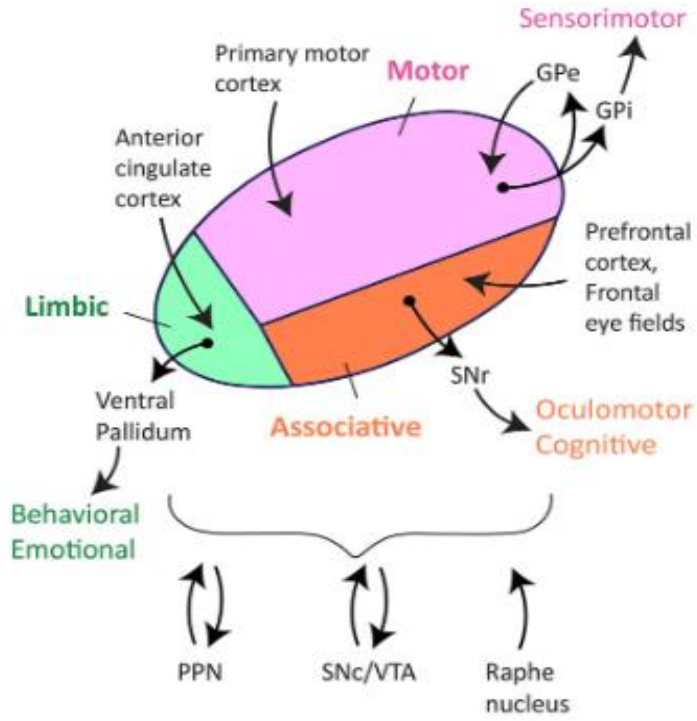

Figure 3. Tripartite model of primate STN; motor, associative and limbic territories based on multiple anatomical studies. Abbreviations: GPe, globus pallidus externa; GPi, globus pallidus interna; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; PPN, pedunculopontine nucleus; VTA, ventral tegmental area (Prasad, A. A., & Wallén-Mackenzie, Å. 2024).

1.1.1. Hodology of the Subthalamic Nucleus: afferents

1.1.1.1. Pallido-subthalamic afferents

The pallidosubthalamic afferents originate from the external segment of the Globus pallidum and constitute a major source of STN synaptic afferents composing the indirect pathway of the basal ganglia (cortico-striato-pallido-STN-SN). These GABAergic fibers (Smith et al., 1990; Vincent et al., 1982) were the first inputs described projecting to the entire STN via axon collaterals to the Entopenduncular nucleus (EP)/GPi and/or the substantia nigra pars reticulata (SNr) (Sato et al., 2000). The projections from the GP are organized with conserved functional topography (Parent & Hazrati, 1995). The most

robust contingent of these projections originates from neurons from the lateral motor part of the GP and project preferentially to the dorso-lateral two thirds of the STN (the sensorimotor region).

A larger population of terminals forming symmetrical synapses are also immunopositive for GABA, likely originating from the globus pallidus. These GABAergic terminals converge with cortical or thalamic terminals on the dendrites and spines of STN neurons, indicating that the "indirect pathways" of basal ganglia information processing converge at the level of individual STN neurons (Bevan, 1995). The VP, considered limbic, projects to the limbic (medial) STN forming synapses on the soma or proximal dendrites of the STN. (Carpenter et al., 1968; Smith et al., 1990; Bevan et al., 1997; Joel & Weiner, 1997). Likewise, a single GPe neuron can form multiple synapses with individual STN neurons (Baufreton et al., 2009).

1.1.1.2. Cortico-subthalamic afferents

The existence of the cortical projections to the Subthalamic Nucleus have been recognized as early as 1956 (Auer, 1956), but put into light by Nambu in 2002 (Nambu et al., 2002). The STN receives extensive projections from the cortex composing the hyperdirect pathway and constitutes a major source of activation for the STN (Kitai & Deniau, 1981; Haynes & Haber, 2013; Canteras et al., 1990).

The conserved topographical organization of these cortical neurons on the STN and their functional significance is more recently been discussed in the literature (Canteras et al., 1990, Nambu et al., 2002). Glutamatergic afferents originating from layer V of the cortex project to form collateral of the large pyramidal tract or cortical fibers on multiple ipsilateral brain regions including the striatum, associative thalamic nuclei, superior colliculus, zona incerta, pontine nucleus, brainstem areas, and the spinal cord (Kita & Kita, 2012) (Künzle & Akert, 1977; Monakow et al., 1978; Afsharpour, 1985; Canteras et al., 1988; Bevan et al., 1995; Kitai and Deniau, 1981).

In primate, the tripartite model of STN organization arises from somatosensory and motor cortical areas projections in the STN with somatic organization (Monakow et al., 1978; Nambu et al., 1996). Fibers from the primary motor cortex, the main source of

cortical innervation of the STN, innervate the dorsolateral area of the STN, while the premotor cortex and the supplementary motor area (SMA) project to the ventrolateral half of the STN (Haynes & Haber, 2013). The primary motor cortex fiber related to the legs, arms and face, respectively, represent from medial to lateral in the lateral portion of the STN. Inversely somatotopic distribution from the SMA, dorsal and ventral premotor fibers reach the medial portion of the STN (Nambu et al., 1996, 2002). Projections from anterior cingular cortex (ACg) and ventromedial prefrontal cortex terminate in the medial part of the STN. As previously mentioned, some functionally nonhomologous cortical projections overlap at the tripartite defined STN boundaries in primates, blurring the lines of the functionally defined terminal fields and creating potentially important interfaces (Haynes & Haber, 2013).

In rodents, the topographic organization of prefrontal cortex (PFC) afferents present less exclusive territories. However, molecularly distinct domains of the mouse STN reflect the anatomical territories defined by the cortico-subthalamic projections (Wallén-Mackenzie et al., 2020). Prelimbic-medial orbital areas of the prefrontal cortex project to the tip of the medial STN, adjacent to the H2 field, and lateral hypothalamus, and as part of the limbic loop (Groenewegen & Berendse, 1990). The STN has small somatosensory and parietal association cortex projecting zones at the dorsolateral-most part of STN (Kita & Kita, 2012 2014; Carpenter et al., 1981; Canteras et al., 1988; Cavdar et al., 2018). The dorsal part of ACg projects heavily to ventral-medial part of the caudal STN and ZI. In the rat, the dorsal part of the ACg includes the eye and nose areas of the primary motor cortex, suggesting that ACg may have dual functions, primarily motor and motor related cognitive. The Infralimbic (IL) Prelimbic (PL), dorsal peduncular cortex and lateral part of the lateral orbital cortex project densely to buttons in the medial part of caudal STN, adjacent to H2 (Kita & Kita 2014; Cavdar et al., 2018). The primary motor cortex (M1, area 4) projections occupy the large medial part of the STN, contrary to the topography of the primate cortico-thalamic projection which terminate in the lateral to medial STN (Afsharpour, 1985; Canteras et al., 1990; Nambu et al., 1996; Haynes and Haber, 2013.) The projection patterns and the morphological characteristics described above suggest that each neuron in the STN may receive inputs from wide areas of the cortex.

1.1.1.3. Thalamo-subthalamic afferents

The centromedian-parafascicular complex of the thalamus sends projections to the STN, which are less prominent compared to pallidal and cortical afferents. These projections, described in both rats (Groenewegen & Berendse, 1990; Féger et al., 1994) and monkeys (Sadikot et al., 1992), terminate on STN neurons, which in turn project to the GP (Sugimoto et al., 1983). Thalamo-subthalamic afferents are excitatory and utilize glutamate as a neurotransmitter (Féger et al., 1994).

Thalamo-STN projections show mediolateral topography. In rats, medial, central, and lateral STN territories are innervated by neurons from medial, ventrolateral, and dorsolateral thalamic parafascicular areas, respectively (Féger et al., 1994; Bevan et al., 1995; Lanciego et al., 2004). In primates, parafascicular neurons project to the medial tip of the STN, while centromedian nucleus neurons innervate the dorsolateral part of the STN (Sadikot et al., 1992). In both species, thalamo-STN afferents terminate on neurons projecting to the external and internal segments of the GP (Sugimoto et al., 1983; Lanciego et al., 2004).

1.1.1.4. Pedunculopontine-subthalamic afferents

Cholinergic afferents from the pedunculopontine nucleus (PPN), project bilaterally to the STN but with a preference for the ipsilateral side (Jackson et al., 1983; Canteras et al., 1990; Bevan & Bolam, 1995; Clarke et al., 1997; Kita & Kita, 2011). Cholinergic terminals from the PPN innervate both GABAergic and glutamatergic inputs in the STN, making contact primarily on dendrites (Bevan & Bolam, 1995). Although primarily cholinergic, they may also be GABAergic and glutamatergic, as indicated by the high levels of glutamate present at the terminals (Bevan & Bolam, 1995; Clarke et al., 1997).

1.1.1.5. Colliculo-subthalamic afferents

The lateral superior colliculus (SC) projects to the STN, linking the sensory network involving the brainstem to the STN (Tokuno et al., 1994; Coizet et al., 2009; Pautrat et al., 2018, Al Tannir et al. 2023). These projections relay information from the lower part of the visual field, the deep layers of the SC and its middle to caudal levels and terminate in

the rostral and dorsal sections of the STN. The neurotransmitters used by these connections are currently unknown, but this pathway is possibly predominantly excitatory (Coizet et al., 2009).

1.1.1.6. Parabrachio-subthalamic afferents

The parabrachial nucleus projections to the STN originate from lateral and medial parabrachial nucleus, terminating in the dorsal section and spread across the dorsal ventral area of the STN. Although mainly ipsilateral, a smaller third of these projections are also contralateral. The terminals form collaterals towards the SNc/SNr, and possibly the cortex creating a subcortical sensory- loop (Coizet et al 2010; Pautrat et al., 2018; Al Tannir et al. 2023). These afferences to STN are supposed to play a role in the transmission of pain-related information (Coizet et al., 2010)

1.1.1.7. Nigro-Subthalamic afferents

The STN receives ipsilateral dopaminergic (DA) projections from the substantia nigra pars compacta (SNc) (Kita & Kitai, 1987; Groenewegen & Berendse, 1990). These dopaminergic projections form contacts with somatodentritic compartments of STN neurons (Cragg et al. 2004). However, medio-lateral gradient in the density of these dopaminergic terminals can be observed (Hassani et al., 1997). Small dopaminergic terminal axons may modulate the activity of the STN, with particular regard to the non-motor regions (Hedreen et al., 1999). Parkinson's disease (PD) is caused by cell death of dopaminergic neurons (for review, Davie, 2008). The consequence of the dopaminergic deafferentation of the STN in PD is however poorly understood, but it could participate in the hyperactivity of the STN observed in animal models of PD (Emmi et al., 2023).

In rodents, dopaminergic receptor D_1 displayed variable immunoreactivity that ranged from absent to moderate across studies (Dawson et al., 1986; Dubois et al., 1986). Studies on humans reported conflicting results as far as D_2R is concerned, ranging from negative (Augood et al., 2000), to low (Hurd et al., 2001) or moderate (Wang et al., 2000), with little-to-no topographic information available. The expression of other dopaminergic

receptors, such as D_3R and D_4R, was documented in humans by Wang et al. 2000 and Matsumoto et al. 2002 respectively.

Additionally, a moderate GABAergic projection from the SNr has been described (Ichinohe et al., 2000). These projections into the associative regions of the STN reflect the complex neural integration underlying anticipation, motivation, and movement planning, exerting inhibitory control over a primarily excitatory structure (Emmi et al., 2023).

1.1.1.8. Ventral Tegmental Area afferents

The STN receives ipsilateral dopaminergic projections from the ventral tegmental area (VTA) (Hassani et al., 1997). Dopamine is produced in the VTA and SNc and a loss of dopamine (i.e. like PD) results in the loss of control of body movements (Latif et al., 2021). The VTA is degenerated in some PD models (Alberico et al., 2015). As indicated above for nigral-STN afferents, in the cases of DA depletion in PD, the STN is hyperactive (DeLong, 1990), suggesting an inhibitory effect on DA projections on the STN.

1.1.1.9. Dorsal Raphe Nucleus Afferents

The STN receives robust serotonergic inputs from the dorsal raphe nucleus (Canteras et al., 1990; Mori et al., 1985), which can either excite or inhibit STN neurons depending on the receptor types involved (Stanford et al., 2005; Xiang et al., 2005; Shen et al., 2007). STN neurons predominantly express the 5-HT2C receptor (Pompeiano et al., 1994), along with several other serotonin receptor subtypes, including 5-HT1A, 5-HT1B, and 5-HT4 (Bruinvels et al., 1993; Wright et al., 1995; Compan et al., 1996).

1.1.2. Hodology of the Subthalamic Nucleus: efferents

All projections from the STN are glutamatergic, and thus excitatory in nature, primarily targeting the pallidal complex (both external and internal segments) as well as the substantia nigra (including both the SNr and SNc) (Parent & Hazrati, 1995; Plantinga et al., 2016). These projections respect the functional topological organization of the STN: the medial part sends projections to limbic structures, the dorsolateral part to sensorimotor structures, and the ventral part to associative areas. STN axons are characterized by their branches, dividing at least once and creating multiple collaterals that innervate several nuclei, especially in rodents (Van Der Kooy & Hattori, 1980; Hammond & Yelnik, 1983; Kita et al., 1983; Koshimizu et al., 2013), and to a lesser extent in primates (Carpenter et al., 1981; Smith et al., 1990; Sato et al., 2000). Their terminals form synapses with the soma and dendrites of their target neurons (Kita & Kitai, 1987; Shink et al., 1996), where they act on AMPA and NMDA receptors (Tachibana et al., 2008; Ammari et al., 2010).

1.1.2.1. Subthalamo-pallidal efferents

The primary target of STN neurons is the external segment of the globus pallidus (GPe, or GP in rodents), with projections following the topographical and functional organization of the STN. The subthalamo-pallidal axons terminate in both pallidal segments in the form of dense elongated bands that lie parallel to the medullary laminae. Neurons in the limbic region of the STN project to the VP, while motor-related neurons target the GP (Groenewegen & Berendse, 1990; Parent & Hazrati, 1995; Joel & Weiner, 1997). Another significant target is the internal segment of the GP (GPi, or the entopeduncular nucleus (EP) in rats), with these projections also adhering to the STN's functional territories (Kita & Kitai, 1987). The STN's glutamate mediated excitatory projections converge with inhibitory GABAergic inputs from the striatum onto single pallidal neurons (Parent & Hazrati, 1995). The subthalamic fasciculus consists of fiber that interconnect the STN and globus pallidus.

Historically, the subthalamo-pallidal pathway was one of the first to be described (Whittier & Mettler, 1949a). Importantly, STN neurons are reciprocally connected with GPe cells creating a short feedback loop. The same group of neurons from both the STN

and GP, via axon collaterals, innervate functionally analogous regions within the GPi/EP (Shink et al., 1996).

1.1.2.2. Subthalamo-nigral efferents

The substantia nigra reticulata (SNr), along with the internal segment of the GPi or the EP, functions as a key output structure of the basal ganglia. A major focus of STN projections is the SNr, with these pathways organized topographically to align with the motor, associative, and limbic regions of the STN. Collateral projection from the STN targeting the GP branch out to arborize with the SNr (Hammond et al., 1978; Nauta & Cole, 1978; Koshimizu et al., 2013). Some of these projections also extend to the SNc, though to a lesser extent (Plantinga et al., 2016). The spatial organization of the connections change from one axis in the STN to a different axis in the SNr. Specifically, the mediolateral organization of the STN is mapped onto a dorsoventral organization in the SNr (Groenewegen et al., 1990; Parent & Hazrati, 1995b).

1.1.2.3. Subthalamo-striatal efferents

The projections from the STN to the striatum are less prominent and less topographically organized compared to the previously discussed pathways. These projections are characterized by long axons (Kita & Kitai, 1987; Parent & Hazrati, 1995). Neurons in the ventromedial region of the STN primarily target the rostral and caudal regions of the striatum, as well as the lateral part of the nucleus accumbens (NAc), while those in the lateral STN region project to the dorsal striatum (Groenewegen & Berendse, 1990; Takada et al., 1988). As previously mentioned, some STN axons that also project to the GP bifurcate to form arborizations that extend to the dorsolateral striatum (putamen in primates) and dorsomedial striatum (caudate nucleus) (Nauta & Cole, 1978; Beckstead, 1983; Kita & Kitai, 1987; Smith et al., 1990; Koshimizu et al., 2013;). Few studies have specifically detailed STN terminations in the striatum due to the diversity. Of cell types in the striatum. However recent research indicates that STN neurons in rodents predominantly form synapses with striatal GABAergic parvalbumin-expressing interneurons (Kondabolu et al., 2023).

1.1.2.4. Subthalamo-cortical efferents

In rats, STN neurons project ipsilaterally to the cortex creating a direct subthamo-cortical loop (Kita & Kitai, 1987; Degos et al., 2008). Glutamatergic projections innervate the layers I–IV of the sensory-motor and prefrontal areas, the densest projections terminating in the orofacial motor area. The topographic distribution of subthalamo-cortical neurons projections corresponds to the cortico-subthalamic, forming the basis of the cortical-STN loop. STN neurons projecting to a restricted given cortical area receive excitatory cortical inputs from this area. The STN neurons large dendritic fields allow convergent influence from wide cerebral territories, suggesting the loop is partially open (Degos et al., 2008). This cortico-subthalamic-cortical loop would allow interactions between different cortical territories. The existence of this STN-cortical projections has not been reported in humans or primates, however a probabilistic tractography study in humans also suggests its existence (Lambert et al., 2012).

1.1.2.5. Subthalamo-cerebellar efferents

A study using retrograde transneuronal transport of the rabies virus into regions of the cerebellar cortex in monkeys demonstrated a di-synaptic pathway from the STN to the cerebellar cortex (Bostan et al., 2010). Injections of the rabies virus into a motor region (lobule HVIIB) and a non-motor region (crus II) of the lateral cerebellar cortex labeled significant numbers of second-order neurons in motor and associative (non-motor) regions of the STN. These findings suggest a topographically organized pathway that influences both motor and non-motor functions of the cerebellum. In non-human primates, the STN sends projections to the pontine nuclei (PN), a major source of mossy fiber input to both the cerebellar cortex and nuclei (Giolli et al., 2001). In contrast, tracing studies in rats have indicated that the STN projects to the pedunculopontine tegmental nucleus (PPTg) (Takada et al., 1988). This suggests two potential routes through which the STN could influence the cerebellar cortex (Bostan & Strick, 2018).

1.1.2.6. Subthalamo-thalamic efferents

In cats and primates, STN neurons expressing VGlut2 sparsely project to the ventrolateral and rostroventral nuclei of the thalamus (Nauta & Cole, 1978; Rico et al., 2010). This projection is thought to originate from a distinct neuronal population separate from those that innervate the basal ganglia (Rico et al., 2010). In rats, there is evidence of a small population of STN neurons projecting simultaneously to both the contralateral GP and parafascicular thalamic nucleus, via axon collaterals (Castle et al., 2005).

1.1.2.7. Subthalamo-pedonculopontine efferents

In rodents, the STN cells send axon collaterals to both the GP, SN and PPN. However, independent output of the nucleus to the PPN originate in its thin lateral strip of the STN (Hammond et al., 1983; Takada et al., 1988).

1.1.2.8. Subthalamo-Pontine Nucleus efferents

The STN sends efferences to the pontine nucleus by forming a di-synaptic projection to the cerebellum and has been described in humans and rodents. These indirect projections from the STN to the cerebellar cortex are topographically organized (Bostan et al., 2010, Jwair et al., 2017; Wang et al., 2020). 78% and 62% of fibers from the right and left STN respectively, distributed to Crus I in the cerebellum, part of the remaining fibers projected to Crus II (Wang et al., 2020).

1.1.2.9. Subthalamo-Dorsal raphe efferents

A single study reports the existence of a projection from the STN to the dorsal raphe nucleus in rats (Kita & Kitai, 1987).

1.1.2.10. Subthalamo-Ventral tegmental area efferents

Finally, the STN sends projections to the ventral tegmental area (VTA) (Groenewegen and Berendse, 1990; Hassani et al., 1997).

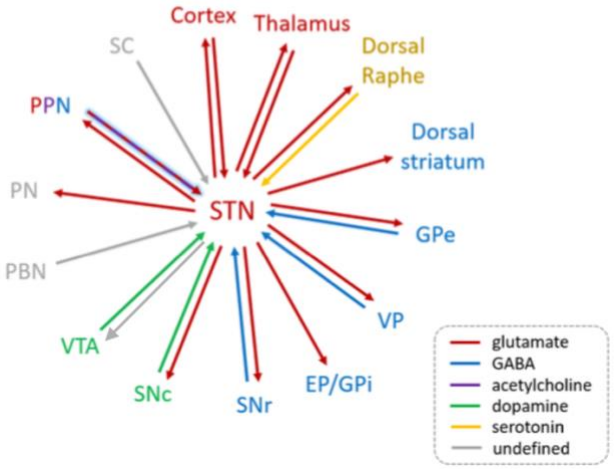

Figure 4. STN connectivity. The STN receives glutamatergic (red) inputs from the cortex, the thalamus, the superior colliculus (SC) and probably from the pedunculopontine nucleus (PPN). It also receives serotoninergic (yellow) afferents from the dorsal raphe, acetylcholinergic (purple) projections from the pedunculopontine nucleus (PPN), GABAergic (blue) inputs from the external segment of the globus pallidus (GPe) and ventral pallidum (VP), and substantia nigra pars reticula (SNr) and dopaminergic (green) inputs from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA). Finally, it receives inputs from the parabrachial nucleus. In return, the STN send glutamatergic efferences to the cortex, the thalamus, the dorsal raphe, the GPe, the VP, the entopeduncular nucleus/internal segment of the globus pallidus (EP/GPI), the SNr, the SNc, the pontine nucleus (PN) and the PPN. Adapted from Vielle 2018

1.2. Functional Involvement of the Subthalamic Nucleus

1.2.1. Motor

Historically, the STN was primarily recognized for its role in motor control, as evidenced by clinical and experimental observations. Early studies on primates demonstrated that surgical lesions in the STN resulted in involuntary movements, highlighting the STN's inhibitory influence on motor activity (Carpenter, 1955; Carpenter & Mettler, 1951). These findings suggested that dysfunction in the STN contributes to the emergence of hyperkinetic movements.

In Parkinson's disease (PD), a progressive neurological disorder characterized by both motor and non-motor symptoms due to the degeneration of dopamine neurons, mostly in the SNc, the STN plays a crucial role. The motor symptoms of PD include involuntary resting tremor, bradykinesia (slowness of movement), akinesia (difficulty initiating movement), muscular rigidity, and postural instability. Systemic MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) administration in primates induces parkinsonian symptoms, including rigidity, akinesia, and bradykinesia. Notably, these symptoms were linked to abnormal increases in tonic and bursting activity in the STN and GPi, alongside decreased activity in the GPe, implicating the STN and its efferent pathways in the pathology of PD (Miller & DeLong, 1987; Filion & Tremblay, 1991; Bergman et al., 1994). These findings led to the discovery that inactivating the STN in monkeys could improve motor symptoms in PD (Bergman et al., 1990; Aziz et al., 1991). High-frequency stimulation (HFS) of the STN was later applied in parkinsonian monkeys as an alternative to lesioning (Benazzouz et al., 1993), and it was subsequently successfully used in human patients with PD (Limousin et al., 1995).

Under normal conditions, dopamine in the direct pathway facilitates movement by promoting motor execution, while the indirect pathway inhibits competing movements, thereby fine-tuning motor activity (Gerfen & Surmeier, 2011). In PD, the degeneration of

SNc neurons leads to significant dopamine depletion in the striatum. This depletion suppresses the activity and responsiveness of striato-nigral (direct pathway) neurons to cortical inputs, while enhancing the activity of striato-pallidal (indirect pathway) neurons. Furthermore, the activity of fast-spiking interneurons in the striatum remains unaffected by dopaminergic depletion, potentially exacerbating the imbalance in striatal output by increasing feedforward inhibition of medium spiny neurons (MSNs) (Mallet et al., 2006). Abnormal activation of the indirect pathway leads to hyperactivity of the STN, a hallmark of PD pathology (DeLong, 1990).

STN hyperactivity is also associated with increased beta (15–30 Hz) power within the dorsolateral STN and the motor cortex (Levy et al., 2000; Brown et al., 2001; Magill et al., 2001; Brown & Williams, 2005; Kühn et al., 2005; Weinberger et al., 2006; Hammond et al., 2007). In healthy individuals, beta power peaks during rest, desynchronizes during movement preparation and execution, and rebounds upon movement termination in both the STN and the primary sensorimotor cortex. However, in PD patients, beta power remains high at rest and shows reduced desynchronization during movement planning and execution compared to healthy individuals (Heinrichs-Graham et al., 2014; Canessa et al., 2016). STN High-frequency deep brain stimulation (HF-DBS) suppresses beta synchronization between the motor cortex and the STN, and clinical motor improvements are further associated with a decrease in STN beta power (Oswal et al., 2016). Stochastic antidromic spikes originating from the STN directly modify the firing probability of the corticofugal projection neurons, destroy the dominance of beta rhythm, and thus restore motor control to the subjects, be they patients or rodents (Li et al 2012).

Dopamine therapy (e.g., levodopa) restores dopaminergic transmission and alleviates PD motor symptoms (Barbeau, 1975, 1976). Dopaminergic medication also reduces pathological hyperactivity and beta power in the STN and basal ganglia (Filion et al., 1991; Brown et al., 2001; Levy et al., 2002; Yeh et al., 2020). However, long-term treatment with dopamine therapy can lead to a decline in efficacy and ultimately motor (e.g. dyskinesia) and non-motor (e.g. impulse control disorder) complications in the vast majority of patients (Bastide et al., 2015; Charvin et al., 2018). As an alternative, STN HF-DBS can alleviate the dyskinesia induced by dopaminergic treatment, with efficacy beyond 15 years from the intervention (Krack et al., 1997; Bove et al., 2021).

HF-DBS of the dorsolateral STN has been shown to effectively reduce bradykinesia, muscular rigidity, and tremor after a decline in levodopa efficacy (Benabid et al., 1994; Limousin et al., 1995). In healthy primates, unilateral stimulation of the STN induces hyperkinetic movements of the contralateral arm (Beurrier et al., 1997). In rats, the hyperkinetic movements observed during HFS are used to adjust the stimulation parameters in rat models of STN DBS (Darbaky et al., 2003; Baunez et al., 2007; Rouaud et al., 2010; Wade et al., 2017; Pelloux et al., 2018; Degoulet et al., 2021). The motor deficits induced by unilateral stimulation are thought to be mediated by glutamate, probably via the direct activation of STN axons to SNr (Boulet et al., 2006). The onset and severity of these deficits, including orofacial, axial, and forelimb dyskinesias, and contralateral rotations, depend on the intensity of the stimulation (Boulet et al., 2006). Unilateral stimulation also counteracts muscular rigidity assessed by catalepsy induced by dopaminergic antagonists such as haloperidol (Darbaky et al., 2003).

Electrophysiological studies have also shown that STN activity increases with movement, with neuronal selectivity in the dorsolateral STN, reflecting the topology of its afferent premotor cortex projections. The dorsolateral STN contains neurons that respond specifically to arm movements, while more lateral neurons are sensitive to leg movements (Wichmann et al., 1994; Nambu et al., 1996). Ventrally, STN neurons exhibit visuo-oculomotor-related activity (Matsumura et al., 1992). While STN activity increases during movement, its stimulation does not directly induce motor activity (Wichmann et al., 1994), yet STN lesions affect involuntary movements (dyskinesias) of the contralateral limb (Hamada & DeLong, 1992). Thus, the STN is proposed to inhibit competing movements to ensure the selection of an appropriate motor program (Matsumura et al., 1992; Mink & Thach, 1993; Wichmann et al., 1994) and to halt ongoing movements (Mink, 1996; Nambu et al., 2002). This "hold your horses" model of motor control then theorizes that an intended movement excites the cortex, which then sends excitatory inputs to both the striatum (modulating the direct and indirect pathways) and the STN (via the hyperdirect pathway). The rapid activation of the STN via the hyperdirect pathway activates the output structures of the basal ganglia (i.e., GPi and SNr). By modulating when a response is executed, the STN reduces premature responding and therefore has substantial effects on which response is ultimately selected, particularly when there are

multiple competing responses, facilitating adaptive frontal motor commands while suppressing others (Frank, 2006).

Supporting this role of the STN in motor suppression, optogenetic studies in mice demonstrated that inhibiting the STN enhances locomotion, while its activation reduces it (Guillaumin et al., 2020). Further confirming the STN's role in motor suppression, studies in rodents demonstrate that STN lesions induce anticipatory responses (Baunez et al 1995; Phillips et al., 1999) and that STN lesions or HF-DBS can restore movement initiation deficits caused by striatal dopamine depletion, as measured by reaction times (Baunez, 1995; Phillips & Brown, 1999; Darbaky et al., 2003; Temel et al., 2005). Although reaction time performance could be restored, abnormal anticipatory responses raised questions about the STN's involvement in cognitive processes, related to attention or inhibitory control.

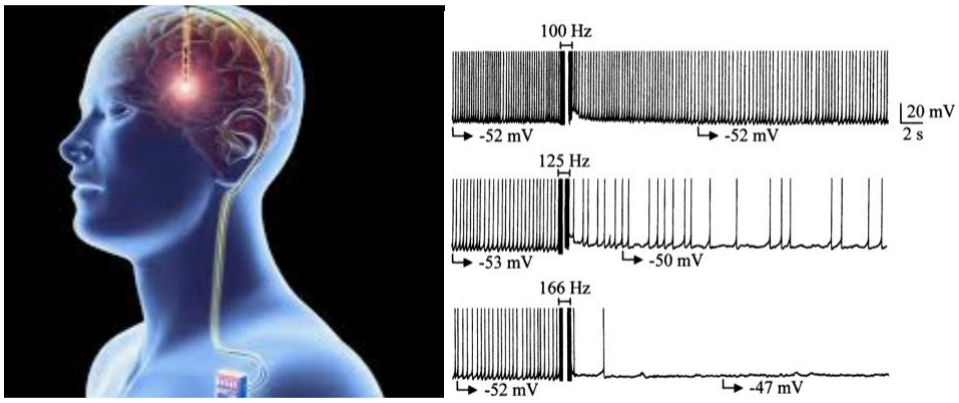

Figure 5. Bilateral HF-DBS of the subthalamic nucleus (STN) can alleviate both motor and non-motor symptoms induced by dopaminergic treatment, with long-lasting efficacy. DBS is achieved in patients by implanting a stimulating electrode into the STN, which is controlled by a pacemaker placed under the patient's skin. In patch-clamp recordings, HFS has been shown to silence or inhibit STN neurons, and it is believed that this inhibition contributes to the improvement in motor symptoms (Beurrier et al. 2001)

1.2.2. Associative

1.2.2.1. Behavioral inhibition

Behavioral inhibition can be viewed as a critical executive-control mechanism that regulates a wide range of cognitive and motor processes, in order to prevent or stop unwanted, inappropriate or maladaptive actions. Deficits in inhibition control due to deficits in cognitive processing results in impulsivity and compulsivity (Eagle & Baunez, 2010). Impulsivity is defined by the inability to prevent, slow down or stop an action or choice. Compulsivity is characterized by the urge to execute repetitive or ritual behaviors, despite a lack of reward or negative consequences. Pathological or maladaptive levels of inhibition failure are common in a number of neuropsychiatric conditions such as attention deficit and hyperactivity disorder (ADHD), Parkinson's disease, schizophrenia, obsessive-compulsive disorder (OCD), substance use disorders (SUD), and pathological gambling or shopping (Eagle & Baunez, 2010). A battery of tests have been used with great success to assess measures of inhibition (e.g., stop-signal, go/no-go and delay-discounting tasks) (for review Eagle & Baunez, 2010; Bari & Robbins, 2013).

In a reaction time (RT) task with rats, where animals are trained to release a lever after the onset of a visual stimulus within a time limit to obtain a food reward, bilateral lesion of the STN leads to an increase the number of premature responses and decrease in reaction time (Baunez et al., 1995). Phillips and colleagues also found an increase in premature responses in a similar test (Phillips and Brown, 1999). This consistent increase in premature responding suggests that STN lesions lead to cognitive impairment in attentional processes, behavioral disinhibition/impulsivity, or perhaps both.

An STN lesion also causes significant impairments in a stop-task test (Eagle et al., 2008). In this task, a subject is trained to rapidly execute a sequence of actions to obtain a reward. In a small proportion of trials, an auditory "stop signal" indicates to the subject to stop the sequence of actions to gain the reward. The test thus measures failure to stop, an index of impulsivity. The inhibition of STN increased stop signal reaction time (SSRT; the estimated time to stop the ongoing action) and increased the number of failed stop trials. In contrast, in PD patients, STN HF-DBS reduces the SSRT (van den Wildenberg et al., 2006). Functional magnetic resonance imaging (fMRI) studies in "healthy" human subjects revealed an increase in STN activity during the stop trials (Aron & Poldrack,

2006; Ray Li et al., 2008). At the single-neuron level, the STN contributes to both selecting and cancelling movements, with ventromedial STN neurons particularly involved in controlling fast, stop-related signals necessary for cognitive control (Mosher et al., 2021). More recently, phase synchronization analysis revealed a transient attenuation of synchronization between the orbital frontal cortex (OFC) and STN in the beta range during reactive stopping during stop-signal task (ter Horst et al, 2024).

Similarly, the go/no-go task assesses the ability to withhold a response to a "no-go" stimulus to gain a reward, with incorrect responses considered impulsive. In PD patients, STN HF-DBS was found to reduce the number of correct responses while increasing incorrect ones, suggesting that STN inhibition diminishes the ability to hold a response (Ballanger et al., 2009; Hershey et al., 2010). In line with this idea, in mice, optogenetic stimulation of the STN improves task performance by decreasing incorrect responses. Interestingly, optogenetic inactivation of STN-projecting PFC pyramidal neurons increases inappropriate responses, while activating the PFC-STN pathway reduces incorrect responses (Li et al., 2020). In humans, the degree of cortical area co-activation with the STN has been shown to predict stopping speed (Chen et al., 2020). These findings highlight the crucial role of the hyperdirect pathway in impulse control.

The STN also appears to play a significant role in compulsivity. A perseverative response refers to when a rat repeatedly performs an action that is associated with receiving a reward, even during a timeout period (signaled by a cue) when no reward is available. This behavior is viewed as compulsive because the animal continues the action despite the clear indication that the reward is temporarily unavailable. After STN lesions, pharmacological inactivation, or HF-DBS, the number of perseverative responses increases in a five-choice reaction time task (Baunez & Robbins, 1997, 1999; Baunez et al., 2007). "compulsive lever-pressing" behavior has also been observed in rats following STN lesions (Winter et al., 2008). This finding suggests not only a deficit in response control but also a heightened motivation for the reward.

Interestingly, the effects of STN modulation on compulsive behavior vary depending on the animal's pre-existing condition. In animals treated with quinpirole, a D2/D3 agonist that induces compulsive-like behaviors resembling the compulsive checking seen in OCD patients, STN pharmacological inactivation and HF-DBS can actually reduce these compulsive behaviors (Winter et al., 2008; Klavir et al., 2009). These findings suggest that

the STN has a dual role in compulsive behavior, which may depend on the animal's baseline level of obsessive-like behavior before STN neuromodulation.

STN theta oscillations (8 Hz) have recently been linked to compulsive behaviors. In rats exhibiting compulsive cocaine-seeking behavior, an increase in theta activity was observed. Notably, applying 8 Hz STN DBS to "non-compulsive" rats induced a shift in their behavior, making them "compulsive cocaine-seekers" (Degoulet et al., 2021). Similarly, increased theta activity has been observed in the STN of PD patients on long term levodopa treatment, which is often associated with impulse control disorders (Yeh et al., 2020; Lim et al., 2008). Theta-like oscillations in the ventral STN have also been recorded in patients with OCD, with the severity of these oscillations correlating with the intensity of OCD symptoms (Rappel et al., 2018). STN HF-DBS has been shown to significantly reduce compulsions and obsessions in PD patients who also suffer from OCD (Mallet et al., 2002; Fontaine et al., 2004). This has led to the use of STN HF-DBS as a treatment for OCD, with relatively successful outcomes (Mallet et al., 2008). At the end of the follow-up period (month 46) of this initial study, the compulsion, obsession, anxiety and depression scores, but also global functioning and social and family life scores were significantly improved (Mallet et al., 2019). These findings corroborate rodent studies, demonstrating a correlation between increased STN theta power and the emergence of compulsive-like behaviors, and underscore the potential of STN HF-DBS in treating compulsive disorders.

1.2.2.2. Attentional processing

The earliest studies suggesting a role of the STN in attentional processes showed cats with bilateral lesions to the STN become less responsive and inattentive to sensory stimuli (Lindsley et al., 1970). In rats, the use of the 5-choice serial reaction time task (5-CSRTT) allows to measure attentional and impulse control performances. During the task animals are trained to wait during an intertrial interval (ITI) before responding by nose poke to a short visual stimulus appearing randomly in one of five holes. Accuracy in the task is considered an index of attentional performance, while a premature response is considered an impulsive action. Bilateral lesion and pharmacological inactivation (via injection of the GABAergic agonist muscimol) of STN resulted in an attentional deficit,

characterized by a decrease in correct responses in the 5CSRTT (Baunez and Robbins, 1997, 1999). A transient decrease in accuracy was also observed following STN- HFS. Notably, the severity of the deficit was not to the extent produced by lesion, suggesting a slightly different mechanism, and not a full inactivation of the STN (Baunez et al.,2007). Furthermore, lesioning the medial prefrontal cortex (mPFC) on one side and the STN on the other leads to the same attentional deficits described after a bilateral STN lesion. These observations following mPFC-STN disconnection provided the first evidence that the hyperdirect pathway likely contributes to attentional processes (Chudasama et al., 2003).

Clinical studies assessing the cognitive functions of PD patients who underwent STN DBS showed contrasting results. Firstly, studies have shown that STN activity is modulated by visual distractors in an instrumental task (Bočková et al., 2011; Beck et al., 2018). However, when DBS in applied to the STN, some studies have documented attentional deficits in PD patients (Saint-Cyr et al., 2000; Mallet et al., 2007). Conversely, other research has reported no change (Brusa et al., 2001) or even improvement in attention (Fimm et al., 2009).

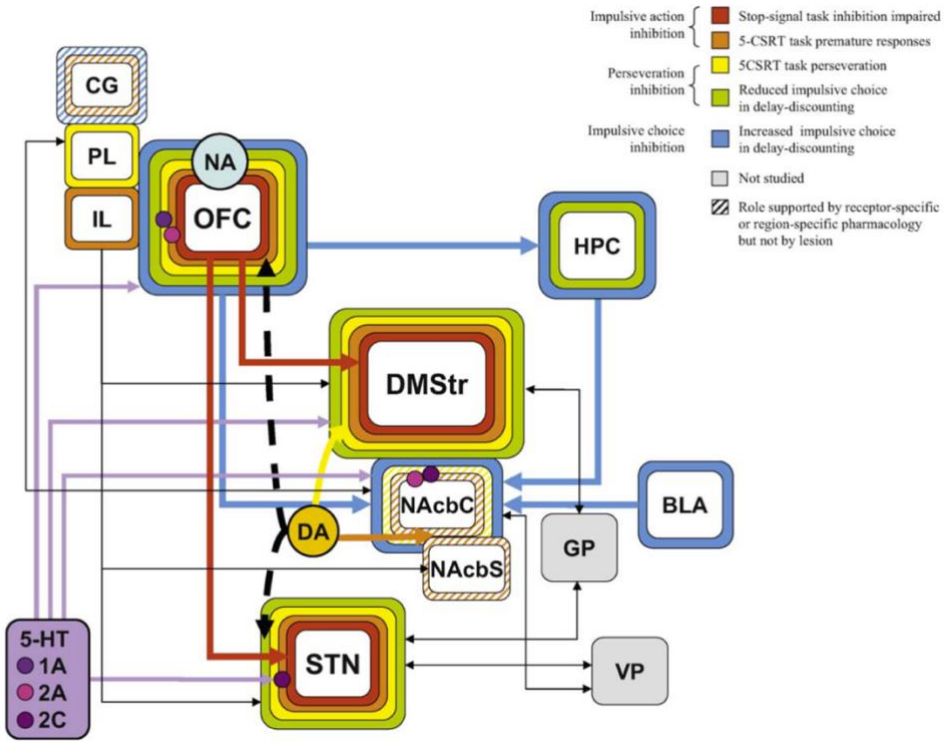

Figure 6. Schematic representation of the major inhibitory processes in the stop-signal, 5-CSRTT and delay-discounting tasks from lesion and pharmacological manipulations. Colored bands surrounding each structure highlight the roles of key structures in inhibitory processes. Hatched-shaded bands indicates no effect of excitotoxic lesions but an effect under other circumstances (e.g., dependent on previous behavior, or following pharmacological manipulations). Grey structures indicate that no information is available. Arrows highlight connections between regions that are of interest for response inhibition networks (Eagle & Baunez, 2010)

1.2.3. Limbic

1.2.3.1. Emotions

As described in the former chapter, the STN is connected to several structures involved in emotion processing, such as the ventral pallidum, amygdala, and insular cortex (Lambert et al., 2012; Berendse & Groenewegen, 1990). Among these, the ventral part of the STN is most prominently involved in emotional processes, as its HFS has been shown to increase positive emotions in PD patients (Greenhouse et al., 2011; Benedetti et al., 2004).

The involvement of the STN in emotions has been demonstrated multiple times, with early evidence emerging from case reports of mania following STN injury or damage (Trillet et al., 1995; Etemadifar et al., 2012). Similar manic symptoms, sometimes accompanied by major depressive episodes and anxiety, have also been observed following STN HF-DBS intervention in PD patients, particularly when applied in its ventromedial territory (Krack et al., 2001; Romito et al., 2002; Herzog et al., 2003; Funkiewiez et al., 2004; Mandat et al., 2006; Mallet et al., 2007).

Studies on PD patients undergoing STN HF-DBS have revealed that the STN is involved in all components of emotional processing, including cognitive evaluation, autonomic response, and emotional, motivational, and subjective experiences (for review

Péron et al., 2013). These patients often struggle with assessing vocal messages that convey emotional content and exhibit impaired recognition of facial emotions (Péron et al., 2010). The STN was shown to be functionally and structurally connected to the structures involved in emotional prosody decoding (i.e., orbitofrontal cortex, inferior frontal gyrus, auditory cortex, pallidum and amygdala) (Péron et al., 2016).

Apathy is frequently reported in PD and has been associated with deficits in reward sensitivity, modulated by decreased dopamine levels (Pluck & Brown, 2002; Dujardin et al., 2007; Brok et al., 2015; Muhammed et al., 2016). Additionally, dopaminergic therapy in PD patients has been shown to induce manic or hypomanic episodes. It has been suggested that apathy in PD may be linked to dopaminergic denervation, unmasked by the reduction in dopaminergic therapy following STN HF-DBS surgery (Lhommée et al., 2014, Eusebio et al 2013). However, recent studies indicate that the severity of apathy following STN HF-DBS does not correlate with the reduction in dopaminergic medication, suggesting a causal role of STN HF-DBS in worsening apathy (Boon et al., 2021).

These findings suggest that the integrity of the STN is essential for experiencing pleasure and preventing the general motivational deficiency associated with PD hypodopaminergic symptoms, such as apathy. In PD patients, local field potential recordings have revealed two spatially distinct populations of “affective” neurons responding to the emotional valence (pleasantness-unpleasantness) and arousal (intensity) that are encoded in the STN (Sieger et al., 2015). In patients with OCD, it has also been shown that the ventral part of the STN processes the emotional valence of stimuli (Buot et al., 2013). When a motor response is instructed, the presentation of pleasant and unpleasant stimuli elicits increased STN theta power in OCD patients, while only unpleasant stimuli seem to modulate STN theta activity. This suggests that STN theta power is a physiological marker of affective salience, which is differently affected in OCD and PD.

In line with the human data on apathy, the STN is involved in both positive and negative emotion processing. Animal studies have shown that STN lesions blunt positive and negative facial taste reactivity to sucrose and ethanol, respectively, (Pelloux et al., 2014; Pelloux & Baunez, 2017), prevent conditioned place aversion (CPA) elicited by interoceptive lithium chloride, and reduce negative ultrasonic vocalization (USV) emission following electrical foot shock (Pelloux et al., 2014). These results confirm the

involvement of the STN in emotional processes, regardless of the type of stimulus presented.

Emotion recognition, the ability to perceive others' emotions, is achieved in humans through facial expressions, whereas rats rely on vocalizations. Facial emotion recognition, particularly of negative emotions, has been shown to worsen in PD patients following STN HF-DBS (Biseul et al., 2005; Kalampokini et al., 2020).

To fully understand how emotions work, it is necessary to combine neuroimaging studies in humans, which provide insights into how subjective experiences are encoded, with animal studies that explore the deeper, objective aspects of emotions. Human studies are particularly important for measuring subjective pleasure because they allow direct emotional feedback from the subjects. Although objective measures of emotions can also be assessed in humans, animal models are more limited. Aspects of subjective experience is nearly impossible to capture in animals, where objective measures such as behavior and physiological responses are used instead. Neuroimaging techniques such as fMRI and PET scans help in mapping the brain regions involved in the emotional experience in humans, while animal models provide more granular insights into neural mechanisms underlying these processes. This combined approach is essential for developing a comprehensive understanding of how emotions are generated and regulated in the brain.

1.2.3.2. Social

The social context is fundamental to most behaviors and is crucial for the survival of many species. The "social brain" is described in the literature as the interconnected brain networks responsible for different social functions, collectively enabling social life. For instance, behaviors like maternal care and social play transmit vital social codes and skills necessary for survival. Social recognition, the ability to collect, store, and recall information about another individual's identity, is essential for appropriate social behavior. The STN is believed to play a role in emotion processing, and thus likely influences social behavior as well.

While STN HF-DBS effectively alleviates motor symptoms in PD patients and improves their quality of life, case studies report negative social outcomes, such as social

maladjustment, relationship deterioration, and aggression (Perozzo et al., 2001; Houeto et al., 2002; Drapier et al., 2005; Schüpbach et al., 2006; Jergas et al., 2021). A recent case report also reported changes in social personality following a unilateral STN damage (Seubert-Ravelo et al., 2020). Evaluations before and after STN HF-DBS have shown an exacerbation of apathy and a reduced ability to recognize facial expressions of fear and sadness (Drapier et al., 2008; Funkiewiez et al., 2004; Barone et al., 2009; Higuchi et al., 2015 ; Vicente et al., 2009). Imaging studies have also revealed that difficulties in recognizing social emotions after STN HF-DBS correlate with metabolic changes in neural networks involved in theory of mind (Peron et al., 2010), which is the ability to represent one's own mental state as well as that of others (Premack & Woodruff, 1978).

Like humans, rats live in a complex social environment requiring a wide range of social abilities. Due to these social skills, rodents serve as suitable models for studying the neural basis of social behavior (for review, see Schweinfurth, 2020)

In rats, ultrasonic vocalizations (USVs) serve as socio-affective signals (Nyby & Whitney, 1978; Brudzynski, 2005, 2013; Burgdorf et al., 2008). Adult rats' USVs are classified into two major types based on their acoustic features and emotional content: positive and negative USVs (Brudzynski, 2005). The negative 22-kHz USVs, characterized by a stable sound frequency and long duration, are typically emitted in anxiogenic or aversive situations, such as predator exposure, and serve as fear signals, eliciting anxiety behaviors like freezing in the receiver (Brudzynski, 2019; Kim et al., 2010; Wöhr & Schwarting, 2013; Jourdan et al., 2002). In contrast, the positive 50-kHz USV calls, characterized by highly variable frequency modulations and short durations, are emitted in appetitive situations, such as tickling by a human experimenter or social play. These calls are pro-social, inducing approach behavior by the receiver (Panksepp & Burgdorf, 2000; Brudzynski, 2013; Wöhr & Schwarting, 2007, 2009, 2012).

Recent studies have explored the role of the STN in rodent social recognition with intriguing results. Consistent with human case reports, these studies suggest that the STN is involved in social behavior, potentially through its role in social recognition. Individual rats even appear to have unique vocal signatures. They can recognize the identity of the USV emitter and will preferentially self-administer the playback of a stranger's 50-kHz USV over that of a cagemate. Lesioning the STN significantly reduced lever pressing for playback, abolishing the modulatory effect of familiarity on the rewarding value of social

stimuli, and suggesting that the STN is key to social recognition (Vielle et al., 2021). Additionally, STN optogenetic inhibition—but not HF DBS or lesions—leads to altered cagemate recognition. Overall, these findings demonstrate that normal STN activity is necessary for proper social recognition in rats (Vielle et al., 2023).

Interestingly, social isolation is known to increase drug intake in animals (Burke et al., 2014; Nader et al., 2012; Stairs & Bardo, 2009). The presence of a peer was found to reduce cocaine intake after drug escalation, similar to the effects of optogenetic inhibition and HF stimulation of the STN, suggesting that the STN plays a role in how peer presence influences drug consumption (Vielle et al., 2023). Moreover, while the presence of a peer differentially modulates drug intake in a sham-control rat depending on the peer's familiarity, STN lesions were found to abolish this familiarity-related modulation (Giorla et al., 2022). These findings indicate that the STN may play a crucial role in social recognition and that disrupting its function could impair this ability.

In summary, animal studies support the role of the STN in social behavior, suggesting its involvement in social recognition and possibly emotion reading.

1.2.3.3. Motivation

The limbic STN, associated with motivation is the focus of this thesis work, and will thus be detailed at length in the following chapters.

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2. The Subthalamic Nucleus and Motivation

2.1. Theories of Motivation

Motivation is defined as the set of processes that drive the actions and behaviors of an individual or animal to achieve a goal or ensure survival. Motivational stimuli, which elicit motivated behaviors, are characterized by their "motivational valence," determining whether a response involves approach or avoidance. Positive stimuli, with positive motivational valence, encourage approach behaviors and promote actions that increase their presentation (positive reinforcement). Conversely, negative stimuli, with negative motivational valence, provoke avoidance behaviors to reduce their likelihood (negative reinforcement) (Di Chiara, 1995).

The classical homeostatic drive theory of motivation is rooted in the concept of homeostasis essential for survival, where the central nervous system, responding to physiological changes (i.e a drop in blood sugar), triggers a state of arousal (i.e hunger) (Cannon, 1932). Behavior motivated by natural stimuli is divided into three phases. The first phase, 'appetitive' (or arousal), prompts corrective actions—a second 'consummatory' phase (ie. eating), leading to the final phase of restored homeostasis 'post-consummatory' (Woodworth, 1938; Konorski, 1967). Once equilibrium is reestablished, a negative feedback signal, such as satiety, ends the motivational drive (Cannon, 1932). Thus, according to this theory, motivation ceases when the need is satisfied. However, it is well understood through experience that motivation for certain rewards can extend beyond merely satisfying a basic need.

Indeed, while the theory of homeostasis is essential, it leaves some questions about the functioning of motivation unanswered, particularly how the brain manages motivation beyond merely detecting internal imbalances. This limitation highlights the need to explore other aspects of motivation, as defining it solely by internal parameters is somewhat restrictive. The consumptive phase of motivated behavior alone is insufficient

to fully capture the complexity of motivation, indicating that a broader perspective is necessary.

To address this complexity, motivation can be divided into two phases: Motivational valence can be either unconditioned (primary motivation) or conditioned (secondary motivation) as a result of learning its association with a primary motivational stimulus or with the outcome of a motivated response (Craig, 1918; Di Chiara, 1995). This distinction allows for a more comprehensive understanding, where primary motivation is typically assessed by measuring the actual consumption of the reward, while secondary motivation is evaluated through instrumental behaviors aimed at obtaining the reward.

More recently, research has identified three components of reward: "liking", "wanting", and "learning" (Berridge & Robinson, 2009). "Liking" can be defined as the hedonic process that forms the emotional response to a reward, determining how much a stimulus is liked or disliked. A stimulus is considered more rewarding the more it elicits a pleasant reaction. In addition to liking a stimulus, it must also be “wanted” to be considered a reward in theory. "Wanting," or incentive salience, refers to the motivational value of a stimulus, independent of pleasure or the expectation of pleasure (Robinson & Berridge, 1993; Berridge & Robinson, 1998). Although "wanting" and "liking" often occur together, they are governed by different brain mechanisms and can exist without subjective awareness.

Beyond the emotional aspect, motivation also involves a cognitive, or “learning”, component. This process allows a neutral conditioned stimulus (CS) to become associated with an inherently rewarding or aversive unconditioned stimulus (US). Through repeated pairings, the CS acquires hedonic expectancy, meaning it predicts the US and triggers anticipatory motivation, as seen in Pavlov's classical dog experiments, where the CS (bell) elicited salivation that was initially induced by meat presentation (US) (Pavlov, 1927). Over time, the CS itself can become wanted and liked due to its association with the US. This leads to the incentive motivation theory, how a stimulus can trigger incentive motivation just like the original reward (Bolles, 1972; Bindra, 1974).

In affective neuroscience, the aim is to understand how pleasure and emotions are generated and the underlying brain mechanisms. "Wanting" is controlled by a wide range of brain regions including the mesocorticolimbic dopamine systems (Berridge, 1996)

(Figure 7). "Liking" is regulated by more selective structures, known as "hedonic hotspots." Key regions involved include the OFC, ACg, insula, as well as subcortical structures like the NAc, amygdala, LH, and medial forebrain bundle (MFB) (Leknes et al., 2008). Animal studies have demonstrated that the NAc and VP play important roles in detecting changes in hedonic states (Krause et al., 2010; Tindell et al., 2006).

The discovery of pleasure centers in the brain originated with the work of Olds and Milner in 1954. Their accidental electrode implantation in the MFB led to the observation that rats would repeatedly self-administer intracranial self-stimulation (ICSS) to this region. This pivotal finding opened the field of affective neuroscience and established a focus on identifying brain regions responsible for the subjective and objective experience of pleasure.

One key question in the field is how the brain produces positive affective reactions to sensory pleasure. Interestingly, pharmacological blockade of the dopaminergic system does not eliminate facial expressions of pleasure, as shown in studies by Peciña et al. (1997). This suggests that dopamine, typically linked to motivation, is not necessary for experiencing pleasure. The idea of a distributed "pleasure circuit" has emerged, proposing that hedonic hotspots in different brain areas may be interconnected in a larger, integrated system. This concept drives much of modern affective neuroscience research. The STN, with its glutamatergic connections to regions such as the PFC and GABAergic connections with the NAc and VP, may be implicated in the broader pleasure circuit.

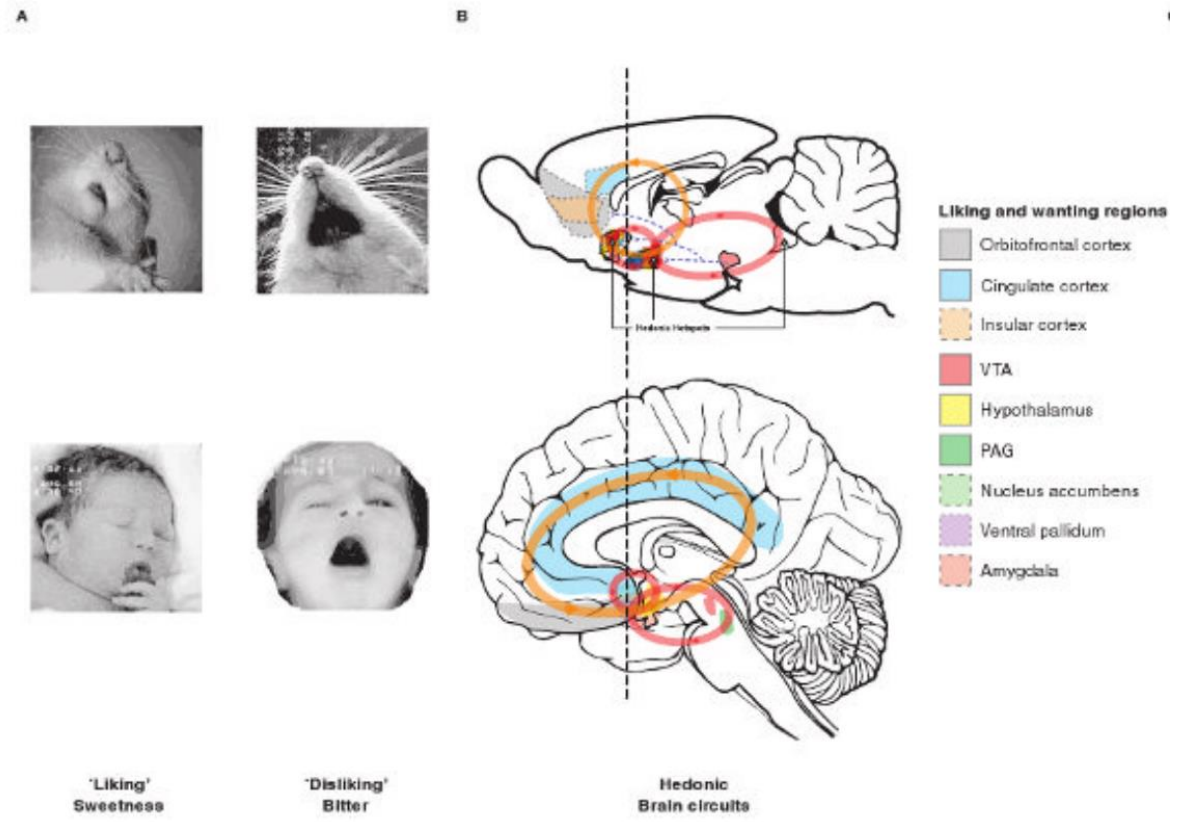

Figure 7. The schematic figure shows the brain regions for causing and coding fundamental pleasure in rodents and humans. (a) Facial 'liking' and 'disliking' expressions elicited by sweet and bitter taste are similar in rodents and human infants. (b, d) Pleasure causation has been identified in rodents as arising from interlinked subcortical hedonic hotspots, such as in nucleus accumbens and ventral 'pallidum, where neural activation may increase 'liking' expressions to sweetness. Similar pleasure coding and incentive salience networks have also been identified in humans. Adapted from Kringelbach & Berridge, 2009

The physiological state can also modulate incentive motivation. Toates (1986) integrated physiological changes into his theory, proposing that physiological deficits can enhance the incentive value of a stimulus. While these deficits do not directly dictate motivated behavior, they increase the hedonic impact and incentive value of both the conditioned stimulus and the reward. For example, an animal deprived of food will exhibit

greater motivation to work for food compared to a sated one. This phenomenon illustrates the concept of alliesthesia (Cabanac, 1979), where the perception of pleasure fluctuates with physiological states.

In more recent literature, the concept of allostasis has emerged as an alternative to homeostasis. Allostasis addresses the regulation of state changes within a system that continuously adapts while maintaining homeostatic balance, a stability that is not within the normal homeostatic range (e.g., reset the system parameters at a new set point) (Sterling & Eyer, 1981). When chronic arousal, repeated stress and negative affective states impose prolonged regulations far from normality, there is no margin left for responding to additional challenges, no opportunity for relaxation, and no capacity for more responsiveness. This stabilized new level of activity far from homeostatic equilibrium forms an allostatic state. A practical example of allostasis is observed in individuals with addiction, who consume drugs to prevent the onset of negative withdrawal symptoms. Authors have thus interpreted this so that "wanting" can occur without "liking," as addicted individuals may use drugs without deriving pleasure, solely to avoid withdrawal effects (Koob & Le Moal, 2001). This phenomenon has been recently names hyperkatifeia (Shurman et al., 2010). Hyperkatifeia provides an additional source of motivation for compulsive drug seeking via negative reinforcement. Negative reinforcement reflects an increase in the probability of a response to remove an aversive stimulus or drug seeking to remove hyperkatifeia (for review Koob, 2021).

2.1.1. Hijacking the reward circuit

A critical factor in maintaining homeostatic energy balance is the body's capacity to acquire and consume enough food to meet its metabolic needs. When the neural circuits that regulate feeding behavior become disrupted, conditions such as hypophagia (e.g., anorexia nervosa) and hyperphagia (e.g., binge eating, obesity) can arise. In recent decades, the increased availability of highly palatable, energy-dense foods has highlighted the impact of reward-related signals on eating behavior. These signals can override the body's natural homeostatic mechanisms, leading to overeating and subsequent weight gain (Begg et al., 2013).

Globally, obesity is a growing concern with more than 1 billion people affected as of 2024, and projections suggest this will rise to 1.53 billion by 2035 (World Health Organization, 2024; Phelps et al., 2024). Obesity brings significant health risks, including cardiovascular diseases, diabetes, and cancer. Recent research has explored the possibility that obesity could be considered a form of "food addiction," driven by similar neural mechanisms seen in SUD (for review Volkow et al., 2013). Both highly palatable foods and addictive substances trigger powerful reinforcing effects, primarily by increasing dopamine release in the brain's reward system. This has led scientists to investigate the parallels between food overconsumption and substance addiction, hoping to develop more effective treatments for obesity.

In this context, the overlap between the brain circuits governing feeding behavior and reward processing becomes evident. Just as drugs of abuse hijack the brain's reward pathways, highly palatable foods can engage similar mechanisms, further blurring the lines between overeating and addiction (Volkow et al., 2013).

In 2022, 292 million people worldwide were estimated to have used drugs at least once in the previous year, while consumption rates continue to increase, 20 % increase over the past 10 years. In 2022 its was estimated over 64 million people were diagnosed as suffering from SUD. Cocaine is one of the most used recreational drugs with an estimated 23.5 million cocaine users worldwide (UNODC, 2024).

SUD is defined by the Diagnostic and Statistical Mental Disorders V (DSM-5) as the persistent use of drugs (including alcohol) despite substantial harm and adverse consequences (American Psychiatric Association et al., 2017). SUD can be characterized by an array of emotional, physical, and behavioral problems, specifically the inability to reduce or stop consuming the substance(s) despite repeated attempts and physiological withdrawal symptoms.

SUD are thus characterized by abnormal **motivation** for the substance and a loss of control over consumption, both in terms of quantity and the context in which drugs are used. This loss of control manifests in the high amounts of drugs consumed, compulsive drug-seeking behavior despite negative consequences, and the inability to abstain even after periods of withdrawal.

Because of this irrepressible drug seeking/taking, SUD can be considered an impulse control disorder. A failure in behavioral inhibition, stemming from deficits in cognitive processes, leads to impulse control disorders, which manifest as both impulsivity and compulsivity. Impulsivity is characterized by the inability to delay, prevent, or stop an action, resulting in premature or hasty behavior. Compulsivity, on the other hand, is the urge for repetitive performance of behaviors or rituals, despite an awareness of their potential risks or lack of purpose. Both tendencies contribute to the maladaptive behaviors seen in SUD, where individuals struggle to resist urges and maintain control, even when they understand the negative consequences. These characteristics have allowed researchers to develop translational procedures to effectively model SUD in rodent studies, which help in understanding the neurobiological mechanisms underlying addiction.

For people using cocaine who face a high risk of relapse, no pharmacological treatment with proven efficacy has been developed. Current evidence from randomized controlled trials does not support the use of dopamine agonists for treating cocaine dependence (Minozzi et al., 2015). Given the significant toll cocaine addiction takes on society, particularly in terms of crime and public health, researchers are urgently investigating the pathological mechanisms underlying cocaine use disorder to develop more effective treatments.

2.1.2. Translational Neuroscience for Substance Use Disorder in animals

Various animal models have been designed to study the neurobiological mechanisms involved in drug dependence, including models that explore drug consumption, withdrawal, and relapse. One such model, intravenous drug self-administration, closely mimics how drugs are used by humans with a potential for abuse. In this procedure, animals are surgically implanted with a catheter in the jugular vein, connected to a port on their back. This allows for the direct injection of dissolved substances into the bloodstream. This setup enables precise control and measurement of

drug intake, making it a powerful tool for studying the reinforcing effects of substances and predicting potential drug abuse in humans.

In both humans and animals, the development of SUD can be imagined as a cascade of behaviors that lead to a cycle of addiction, which becomes increasingly difficult to escape once inside. This process begins with initial exposure to a substance and its recreational use. Over time, the motivation to consume the substance increases, which leads to an escalated increase in consumption and a loss of control of intake. Individuals will then continue to take the substance despite negative consequences. When attempts to quit fail, the individual relapses and re-enters the cycle, consuming large quantities of the substance.

This sequence of stages (Figure 8), from initial exposure to compulsive drug-seeking and relapse, provides a comprehensive model for understanding SUD in both humans and animals. The following section describes the translational animal models used to study these steps in the cycle of addiction.

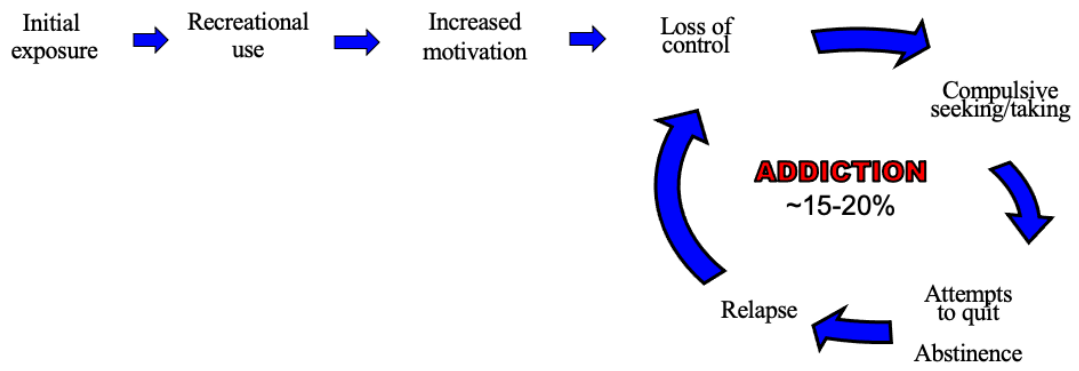

Figure 8. The cycle of addiction. From the initial exposure to a substance of abuse and its recreational use, increased motivation and loss of control over drug consumption lead ~15-20% of the drug users to substance use disorders, associated with compulsive seeking of substance, attempts to quit and relapse. All these behavioral features of drug consumption can be modelled in laboratory animals, using operant tasks.

2.1.2.1. Animals models for Pleasure and Primary motivation

The experimental approaches to study pleasure are diverse, including both subjective self-reports in humans and objective measures such as facial affective expressions and behavior in animals. In rodents and primates, taste reactivity tests and the associated facial or auditory expressions—such as the 55 kHz USVs in rats—serve as indicators of positive affect (Kringelbach & Berridge, 2009). ICSS, a technique dating back to Olds' original experiments, remains a key method in identifying pleasure regions in the brain.

Primary (unconditioned) motivation in animals is often quantitatively assessed by the amount of substance consumed. In fixed-ratio 1 (FR1) procedures, animals perform a single action, such as pressing a lever, to receive a dose of a reward, whether it's food or a drug injection (Figure 9). Access in the procedure is limited to 30 min – 1 to 2 hour per day. This continuous reinforcement setup allows animals to regulate their drug intake based on its potency, helping them develop consumption patterns. The FR1 test is commonly used to measure an animal's primary motivation for a reward, as minimal effort is required to obtain it, making the reward almost freely accessible. As a result, the amount of reward consumed can be accurately measured in FR1 experiments. Primary motivation can also be gauged by measuring food or substance consumption directly in the animal's home cage.

2.1.2.2. Animals models of Secondary and increased motivation

Reinforcement protocols, such as progressive ratio (PR) tests, help assess the level of effort animals are willing to exert to obtain a reward. These protocols are valuable for studying both natural rewards and drugs of abuse in self-administration models. The PR test specifically measures an animal's incentive motivation by progressively increasing the number of actions (e.g., lever presses) required to receive the same amount of reward. In its original application, the ratios used in these experiments increased by an increment

of two, so that the rats were required to emit two responses for the first reward, four for the second, six for the third, eight for the fourth, and so on (Figure 9). Each run of responses in this increasing schedule is called a ratio run. A timer in the circuit was set so that if at any time during the experiment the animal failed to respond for a period of 15 minutes, the session was automatically terminated (these measures can be adjusted by researchers for optimal experimental design). The point at which the animal stops working is known as the break point, which serves as a reliable measure of its motivation (Hodos, 1961).

Several tests exist to measure secondary (conditioned) motivation in experimental settings. Notable examples include the conditioned anticipatory locomotor activity test, which gauges increased movement in anticipation of a reward, conditioned reinforcement and autoshaping protocols, which track approach behaviors toward stimuli associated with rewards. Additionally, conditioned place preference (CPP) is widely used to assess motivation, where an animal's preference for an environment paired with a reward is measured. After conditioning, the animal's preference between a reward-associated environment and a neutral one, without the actual reward present, reflects its incentive motivation. These tests help assess the positive or negative properties of a reward through learned associations.

The development of increased motivation for cocaine is influenced by factors such as access conditions (e.g., dose or price) and the time frame of drug use. These factors correspond to two key mechanisms often seen in SUD: reward sensitization, where the drug's reinforcing effects become heightened, and tolerance, where increasing amounts are needed to achieve the same effect. Over time, animals continue to self-administer cocaine not to experience its rewarding effects but to avoid the discomfort of sub-satiety levels, representing negative reinforcement aimed at escaping withdrawal symptoms.

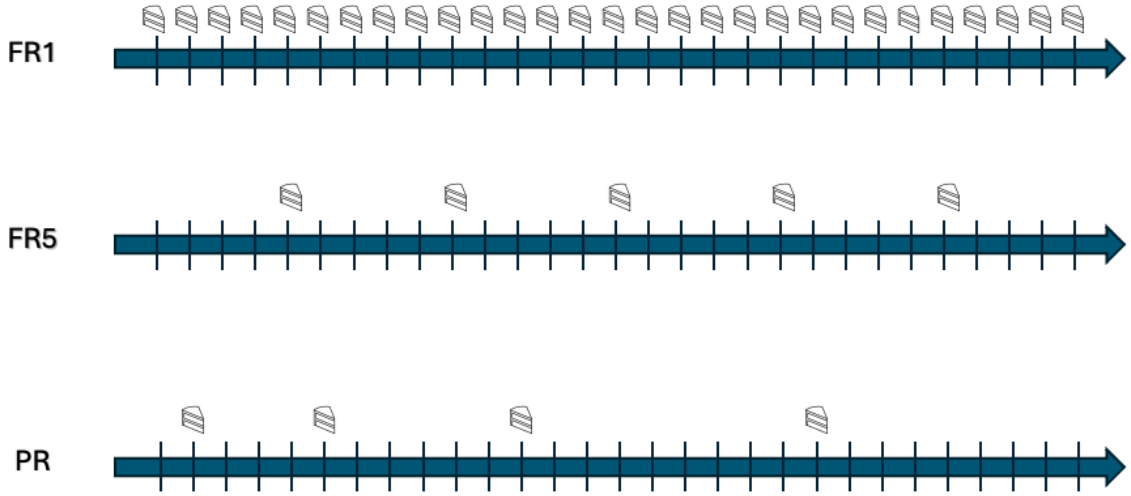

Figure 9. Representation of Fixed (FR1, FR5) and Progressive Ratio (PR) reinforcement schedules. Black tick marks indicate the correct response (lever press/nosepoke), and the piece of cake represents the delivery of a reward. In the FR1 schedule, a reward is delivered after every correct response. In the FR5 schedule, a reward is delivered after five correct responses. In the PR schedule, the reward is delivered after progressively increasing ratios (e.g., 2, 4, 6, 8 etc.).

2.1.2.3. Modeling the cycle of addiction

For decades, the neurobiology of addiction using animal models only used the former tasks and only addressed motivation dysregulation. In the early 2000s, the strategy of modeling the various criteria of the DSM4-5 emerged with the escalation model by Ahmed and Koob (1998) and the 3-criteria strategy developed by Deroche-Gamonet et al (2004).

As consumption increases, a loss of control emerges linked to the development of tolerance or withdrawal symptoms (Ahmed, 2012). In animals, this is typically modeled by providing prolonged access (6+ hours) to the substance, leading to escalation of the drug intake (Ahmed & Koob, 1998).

According to the DSM-5, a core feature of addiction is the compulsive seeking and use of drugs despite their negative consequences—such as using substances in hazardous situations or continuing despite health risks (American Psychiatric Association et al., 2017). While most rats learn to stop responding for the drug when its intake is associated with a mild electric foot shock, about 20% persist, reflecting compulsive drug use (Deroche-Gamonet et al., 2004). Another model applies the electric foot shock during the seeking of the drug, so that there is no drug delivery on the punished trials (Pelloux et al., 2007).

In humans, repeated failures to quit are a hallmark of addiction. Relapse in SUD can occur even after long periods of abstinence, often triggered by drug-associated cues, small doses of the drug, or stressful events (Koob & Moal, 2001). In animals, this is studied using models like the extinction/reinstatement paradigm, which tests the animal's drug-seeking behavior post-abstinence, mirroring relapse behavior in humans. Studies also examine how punishments or alternative rewards can suppress drug self-administration and serve as models for voluntary abstinence (Venniro et al., 2016).

The model underlying this thesis examines the role of motivation. In this manuscript, we will emphasize the use of FR and PR tasks in rats to explore these motivational processes.

2.2. The Neurobiology of Motivation: The Classic reward circuit

The neurobiological substrate of motivation is commonly called “the reward circuit”. It is composed of the ventral tegmental area (VTA), the nucleus accumbens (NAc), the prefrontal cortex (PFC), the amygdala (BLA and CeA), the ventral hippocampus, the ventral pallidum (VP), the lateral hypothalamus (LH) and the lateral septum (Figure 10). This system, which is crucial for positive reinforcement and processing pleasure and incentive salience of stimuli (i.e. food, social interactions, and drugs) operates mainly through dopaminergic and opioid pathways (Wise, 1980), with the mesocorticolimbic

pathway at its core. Broadly, the pathway originating from the VTA projects dopaminergic neurons to the NAc, the orbito-frontal and anterior cingulate cortices, as well as to the amygdala and lateral hypothalamus. This system plays a crucial role in motivation, reinforcement learning, and the regulation of behaviors.

As drug use progresses from occasional to compulsive, neuroadaptations occur in the meso-cortico-limbic pathway, shifting behavior toward uncontrolled drug-seeking. A central concept in this transition is "incentive sensitization," which explains the escalating craving for drugs over time. Over time, chronic drug use can lead to enduring neuroadaptations, making the brain hypersensitive to drugs and related stimuli. This heightened sensitivity turns normal "wanting" into powerful cravings. Additionally, the brain's reward circuit assigns "incentive salience" to environmental cues linked to drug use. Repeated exposure to addictive substances amplifies dopamine transmission, which induces synaptic changes, such as AMPA receptor redistribution, underlying drug-induced neural plasticity (Robinson & Berridge, 1993; Brown et al., 2010). In response, counter-adaptive mechanisms develop, reducing dopamine receptor availability during withdrawal, which raises the threshold for experiencing reward. These mechanisms contribute to enhancing motivation for the substance and ongoing drug-seeking and heightened relapse risk (Koob & Le Moal, 2001). In this process, each nucleus plays a distinct role which make them an interesting target for neuroscientific interventions.

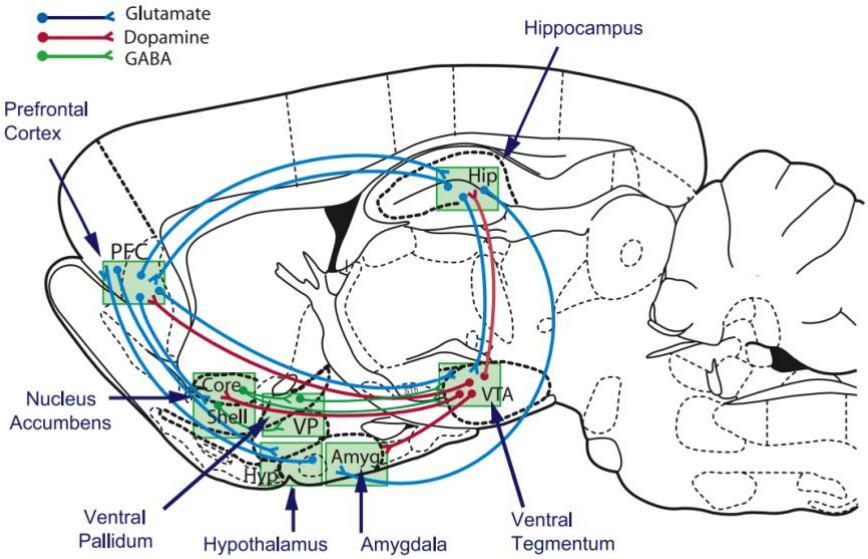

Figure 10. Neuroanatomical connections of the classic reward circuit. Berridge, 2004

2.2.1. The Ventral Tegmental Area

VTA, located in the midbrain, is a critical component of the brain's reward system. The VTA is primarily composed of dopaminergic neurons (60-65%), with GABAergic neurons making up about 30-35%, and a small portion of glutamatergic neurons (2-3%) (Swanson, 1982; Nair-Roberts, 2008). These dopaminergic neurons produce and release dopamine, a neurotransmitter closely associated with pleasure and reward in food and drugs of abuse, primarily targeting the NAc (Di Chiara, 1995). Together, the VTA and NAc form the core of the brain's reward circuitry.

Evidence supporting the VTA's role in the reward system comes from studies involving electrical intracranial self-stimulation and optogenetic stimulation of VTA dopaminergic neurons, which have demonstrated rewarding effects (Corbett & Wise, 1980; Tsai et al., 2009). Moreover, optogenetic activation of VTA dopaminergic neurons has been shown to enhance Pavlovian learning, further illustrating the VTA's role in reinforcement and motivation (Steinberg et al., 2013). This reward effect is mediated through the activation of D1 or D2 receptors in the NAc (Steinberg et al., 2014).

The most extensively studied projections from the VTA in relation to the reward system are those to the NAc (forming the mesolimbic pathway) and to the PFC (forming the mesocortical pathway). VTA neurons, including dopaminergic, glutamatergic, and GABAergic types, establish synaptic connections with medium spiny neurons and cholinergic interneurons in the NAc, as well as with the mPFC, the lateral habenula, and the STN. Other significant projections include those to the BLA and hippocampus.

The VTA receives glutamatergic and GABAergic inputs from a variety of regions, including the NAc, the VP, the mPFC, the lateral hypothalamus, the pedunculopontine tegmentum (PPT), the lateral habenula, the dorsal raphe nucleus, the latero-dorsal tegmentum, the periaqueductal grey, and the bed nucleus of the stria terminalis (for review Morales & Margolis, 2017).

Rodent studies have demonstrated that upon initial exposure to food rewards, DA neuron activity in the VTA significantly increases, leading to heighten DA release in the NAc (Norgren et al., 2006). Dopamine neurons are activated by rewarding events that exceed expectations, remain unchanged by events that meet expectations, and are inhibited by events that fall short of expectations. By signaling rewards based on prediction error, dopamine responses exhibit the defining features of a teaching signal (Shultz et al., 1997). Additionally, peripheral signals that regulate food intake influence this dopaminergic activity through both hypothalamic signaling to the VTA and direct effects on the VTA DA pathways, particularly the meso-accumbens and meso-limbic circuits. There is also extensive evidence that peripheral signals that modulate food intake exert their actions in part by hypothalamic signaling to VTA but also by their direct effects on the VTA DA meso-limbic pathways. Imaging studies have also shown that, consistent with the findings in laboratory animals, anorexigenic peptides (e.g. insulin, leptin, PYY) decrease the sensitivity of the brain reward system to food reward, whereas orexigenic ones (e.g. ghrelin) increase it (for review Volkow et al, 2011). Orexigenic peptides and hormones boost VTA DA cell activity, increasing DA release in the NAc in response to food stimuli, while anorexigenic hormones inhibit DA firing, reducing DA levels (Opland et al., 2010). In humans, studies have reported an inverse correlation between body mass index (BMI) and illicit drug use, as well as a lower risk for substance use disorders in individuals with obesity (Blüml et al., 2012). These findings suggest a potential competition between food and drugs for similar reward pathways.

The VTA is not only central to reward processing but has also been implicated in aversion. Synapses on DA neurons projecting to NAc medial shell were selectively modified by the rewarding stimulus while synapses on DA neurons projecting to mPFC were modified only by the aversive stimulus (Lammel et al., 2011).

A prevailing theory regarding cocaine abuse suggests that the natural reward circuit is reprogrammed following repeated exposure. Early evidence for this comes from studies showing that blocking opioid transmission in the VTA reduces initial cocaine consumption in rats (Ramsey et al., 1999). VTA neurons exhibit heterogeneous responses to cocaine, with some dopamine neurons being inhibited while others are excited (Mejias-Aponte et al., 2015). Early synaptic plasticity can be observed within hours following the first cocaine exposure, marked by a shift in the composition and ratio of AMPA/NMDA

receptor subunits in certain VTA dopaminergic neurons (Ungless et al., 2001; Bellone & Lüscher, 2005, 2006; Mameli et al., 2007, 2011; Yuan, 2013). This initial modification in the AMPA/NMDA ratio is sufficient to increase dopamine transmission from VTA neurons to the NAc (Lammel et al., 2011). Optogenetic self-stimulation of VTA dopamine neurons projecting to the NAc has been shown to mimic relapse after withdrawal and induce reinstatement with compulsive drug-seeking behavior (Pascoli et al., 2015). Moreover, repeated exposure to cocaine causes synaptic potentiation in VTA dopaminergic neurons, a change that persists even after more than a month of abstinence (Lu et al., 2003). Food or sucrose self-administration induced only a transient potentiation of VTA glutamatergic signaling. Thus, synaptic function in VTA DA neurons is readily but reversibly enhanced by natural reward-seeking behavior while voluntary cocaine self-administration induced a persistent synaptic enhancement that is resistant to behavioral extinction (Chen et al., 2008).

These findings suggest that the plasticity in the VTA following cocaine exposure facilitates later adaptive mechanisms induced by subsequent drug use, thereby remodeling the reward circuit. The VTA's central role in this circuit highlights that while dopaminergic neurons are crucial, the functioning of the reward system also relies on the interplay with other types of neurons and pathways.

2.2.2. The Nucleus Accumbens

The NAc, a major target of the VTA within the reward circuit, plays a pivotal role in mediating the reinforcing effects of both natural rewards and addictive substances. The NAc, also known as the ventral striatum, is primarily composed of GABAergic medium spiny neurons and is subdivided into two distinct regions: the core and the shell (for review Groenewegen et al., 1990; Di Chiara 2002). In addition to receiving dopaminergic input from the VTA, the NAc also receives substantial glutamatergic inputs from several brain regions, including the PFC, the ventral hippocampus, and the BLA.

The NAc has long been associated with motivational processes. In the early 20th century, Herrick (1926) proposed that the NAc played a role in locomotion and feeding.

Mogenson later introduced the concept of the NAc, as a "limbic-motor interface," suggesting it as a critical point where motivational and emotional processing interfaces with motor systems (Mogenson et al., 1980) (Figure 11). This idea was further developed when Mogenson and Wu (1982) demonstrated that manipulating DA levels in the NAc could influence feeding and drinking behaviors.

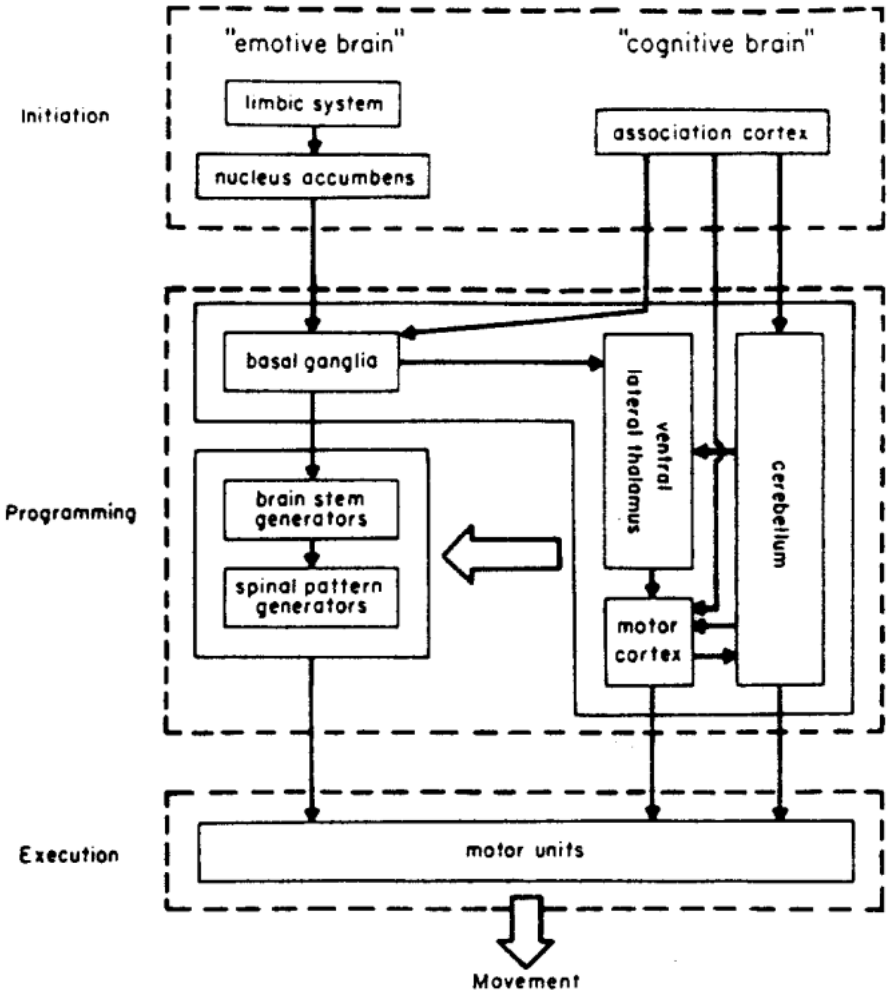

Figure 11. A schematic representation of the organization of the neural mechanisms that translate emotive and cognitive processes into behavioral motor responses. Mogenson et al., 1980

The two subregions of the NAc, the core and the shell, have distinct functions in reward processing (Zaborszky et al., 1985). Neurons in the NAc core are crucial for assigning motivational value to reward-associated stimuli and for updating these values

in response to changes in the environment. This allows for adaptive behavior based on the shifting relevance of rewards. On the other hand, neurons in the NAc shell are more involved in controlling behavioral responses following repeated exposure to rewards, such as those seen in chronic drug administration (Meredith et al., 2008).

Initial studies indicated that glutamate transmission in the nucleus accumbens core plays a significant role in goal-directed exploratory behavior (for review, Scofield et al., 2016). This suggests the NAc core is more involved in linking motor responses to motivationally relevant stimuli or contexts. Further research has supported this idea, showing that lesions in the NAc core impair several behaviors: Pavlovian conditioned responses to food-predictive stimuli (Parkinson et al., 2000), operant lever-pressing in response to drug-related cues (Ito et al., 2004), and adaptive behavior following changes in stimulus value (Corbit et al., 2001). In contrast, the NAc shell, particularly its medial part, appears to govern unconditioned motor responses associated with natural stimuli (Di Chiara et al., 1995).

The reinforcing properties of the NAc are further supported by findings that photo-stimulation of PFC and BLA glutamatergic terminals in the NAc, as well as direct stimulation of medium spiny neurons within the NAc, is rewarding (Britt et al., 2012). Additionally, the injection of dopaminergic antagonists into the NAc increases cocaine intake, likely due to the diminished reinforcing effects of the drug, which forces higher cocaine doses to achieve a similar effect due to already elevated extracellular dopamine levels (Phillips et al., 1994). Dopamine's action on the NAc is essential for the reinforcing effects of rewards, which is evident from studies showing that receiving a cocaine reward increases extracellular dopamine levels in the NAc (Wise et al., 1995; Cooper et al., 2017). This highlights the crucial role of the NAc in maintaining the balance of reward and reinforcement, and how disruptions in this balance can lead to compulsive behavior, as seen in addiction.

In the broader context of the mesolimbic pathway, drugs of abuse, including cocaine, significantly increase dopamine transmission, a critical factor in the brain's reward system (Di Chiara & Imperato, 1988). Cocaine has a profound impact on synaptic plasticity in the NAc, particularly on medium spiny neurons (MSNs) that express different dopamine receptors. These MSNs are primarily categorized based on their expression of

either D1 or D2 dopamine receptors, and cocaine affects these neurons in opposing ways. Specifically, cocaine induces synaptic potentiation in MSNs that express D1 receptors, a change closely associated with cocaine sensitization and cue-induced drug-seeking behavior. Conversely, cocaine weakens synaptic transmission in MSNs expressing D2 receptors, a phenomenon linked to aversive states and negative emotions (Lobo & Nestler, 2011).

Cocaine sensitization has also been shown to differentially affect glutamatergic inputs to the NAc. It strengthens the terminals originating from the ventral hippocampus while weakening inputs from the PFC, indicating a shift in the balance of excitatory signals within the NAc. This alteration may contribute to the heightened response to drug-associated cues and the reduced influence of cognitive control exerted by the PFC (Pascoli et al., 2014).

These findings suggest that the reward mechanisms in the NAc are modulated by a variety of processes, many of which are disrupted by exposure to drugs like cocaine. The resulting alterations in synaptic plasticity, shifts in glutamatergic input balance, and changes in cholinergic interneuron activity all contribute to the complex and maladaptive changes within the brain's reward circuitry that underlie addiction.

2.2.3. The Prefrontal Cortex

In rats, the PFC is a heterogeneous region encompassing several subregions, including the prelimbic, infralimbic, anterior cingulate, insular, and orbitofrontal areas (Heidbreder & Groenewegen, 2003). The PFC forms complex neurofunctional loops with the NAc and the VTA, contributing to various cognitive and emotional processes. The dorsal PFC is primarily involved in top-down control and metacognitive functions, while the ventromedial PFC is associated with emotion regulation and memory. The ventrolateral PFC and lateral OFC play crucial roles in automatic response tendencies and impulsivity (for review Goldstein & Volkow, 2011).

Neuroimaging studies have revealed an emerging pattern of generalized PFC dysfunction in drug-addicted individuals that is associated with more drug use, worse

PFC-related task performance and greater likelihood of relapse (Goldstein & Volkow, 2011). fMRI studies showed that when non-obese male subjects were asked to inhibit their craving for food while being exposed to food cues, they decreased metabolic activity in amygdala and OFC. The decreases in OFC were associated with reductions in food craving (Wang et al., 2009). The ability to inhibit the urges to eat desirable food varies among individuals and might be one of the factors that contribute to their vulnerability for overeating.

The connections between the PFC and the NAc are particularly important for executive control and goal-directed behaviors, including drug-seeking and other reward-related actions (Kalivas & Volkow, 2005). Activation of medial PFC projections to the VTA and NAc is well known to reduce reward-seeking behavior (Ferenczi et al., 2016). Additionally, chemogenetic inhibition of orbitofrontal projections or their striatal target cells has been shown to reduce compulsive seeking behaviors. Interestingly, while similar neuroplasticity, such as the maturation of silent synapses, occurs at the terminals of NAc afferents from both the prelimbic and infralimbic cortices, their roles in cocaine craving appear to be opposite. Optogenetic reversal of plasticity in prelimbic-NAc projections inhibits cocaine craving following prolonged withdrawal, whereas reversal in infralimbic-NAc projections potentiates it (Ma et al., 2014).

Further research has highlighted the role of the ACg in learning from reinforcement. In rats, lesions in the ACg impair the learning of stimulus-reward associations in tasks involving auto-shaping (Bussey et al., 1997). Functional MRI studies in humans also underline the PFC's involvement in motivational processes. Medial and lateral PFC have a parallel hierarchical organization from posterior to anterior regions for motivating and selecting behaviors (Kouneiher et al., 2009). Overall, the PFC is extensively involved in motivated behaviors, ranging from simple Pavlovian conditioning to more complex instrumental conditioning.

2.2.4. The Amygdala

The amygdala plays a crucial role in emotional learning, fear processing and motivational processes, with its various nuclei contributing differently to these functions

(for review, Sun et al., 2020). The basolateral amygdala (BLA), for instance, sends glutamatergic inputs to the NAc, where the effects are thought to be mediated by dopaminergic receptor activation on these terminals (Stuber et al., 2011a, 2011b). These connections are critical for assigning incentive value to rewards (Cardinal et al., 2002). Activation of this pathway has been shown to induce optogenetic intracranial self-stimulation (Stuber et al., 2011a), supporting cue-triggered motivated behaviors (Cador et al., 1989), reward-seeking behaviors (Ambroggi et al., 2008), and cocaine-seeking (Di Ciano & Everitt, 2004). Moreover, research by Kim et al. (2017) has identified two distinct neuronal populations within the amygdala that regulate appetitive behaviors differently, with opposing circuits controlling either positive or negative motivational responses. This intricate interplay between different amygdala nuclei underscores its complex role in both reinforcing and aversive aspects of behavior.

Indeed, the involvement of the amygdala in SUD extends beyond the BLA. Other areas, such as the central amygdala (CeA), are also implicated. For example, patients with cocaine use disorder typically show a general decrease in the entire amygdala volume (Makris et al., 2004). During withdrawal from cocaine self-administration, molecular changes have been observed in the amygdala, particularly in the CeA (Grimm et al., 2001; Lu et al., 2003). Optogenetic studies further reveal that activation of the CeA, but not the BLA, increases motivation for cocaine and associated cues (Warlow et al., 2017). CeA is also involved in the hyperkatifeia described by Koob as playing a critical role in addiction (Koob, 2022).

2.2.5. The Hypothalamus

The hypothalamus, through neuropeptides like leptin, cholecystokinin (CCK), ghrelin, orexin, insulin, and neuropeptide Y (NPY), as well as the sensing of nutrients such as glucose, amino acids, and fatty acids, is a central region for regulating food intake based on caloric and nutritional needs (Dietrich et al., 2009). Manipulating activity in the lateral hypothalamus has a significant impact on feeding behavior across species. Lesions to the lateral hypothalamus led to a cessation of feeding, often resulting in starvation. Conversely, stimulation of the lateral hypothalamus triggers intense feeding, even in

animals that are already sated, with the behavior occurring in synchronization with the stimulation (for review Sharpe, 2024).

The LH has been conceptualized as a "drive center" due to its involvement in motivated behaviors, but it is also seen as a pleasure center because of its role in ICSS behaviors (Hoebel & Teitelbaum, 1962; Roberts & Carey, 1965). Berridge and Valenstein argued the role of the lateral hypothalamus is to assign food cues with incentive salience (Berridge & Valenstein, 1991). Its role in food regulation is intertwined with the brain's reward and motivational systems, which influence eating behaviors (Farooqi et al., 2007). Food intake regulation involves the interaction between reward-related and homeostatic neurocircuits. Imaging studies have proposed that obesity results from an imbalance between neural circuits driving behavior (through reward and conditioning) and those responsible for inhibiting impulsive responses. This model identifies four key neural circuits: (i) reward–salience; (ii) motivation–drive; (iii) learning–conditioning; and (iv) inhibitory control–emotional regulation–executive function. Interestingly, this framework parallels models of drug addiction, highlighting overlapping mechanisms between overeating and substance abuse (Volkow et al., 2008).

Interestingly, afferent inputs from the NAc to the LH have been shown to be critical in cocaine-related sensitization, motivation, and drug-seeking behaviors (Larson et al., 2015). For instance, LH activity is known to trigger seeking behavior not only for natural rewards but also for drugs such as cocaine (Hamlin et al., 2008), and its inhibition can abolish drug-seeking behaviors (Marchant et al., 2010). Within the LH, orexin (hypocretin)-producing neurons exhibit significant plasticity in response to both physiological needs and cocaine exposure (Yeoh et al., 2012). These neurons are specifically involved in cocaine-seeking behavior but not food-seeking, which highlights their unique role in substance use disorders (Martin-Fardon et al., 2018).

Additionally, the number and activity of these orexin neurons in the LH have been found to correlate with the motivation to seek cocaine and may even predict vulnerability to relapse (James et al., 2019; Pantazis et al., 2020). This suggests that orexin cells in the LH could serve as a potential biomarker for susceptibility to SUD.

2.2.6. Other

There are several other brain regions that have been implicated in motivated behavior due to their connections to the mesolimbic system and their effects on behavior. These structures include the ventral hippocampus, ventral pallidum, lateral septum, and substantia nigra.

The ventral hippocampus sends glutamatergic projections to the NAc converging with inputs from the basolateral amygdala to support motivational behaviors (French & Totterdell, 2003). The substantia nigra (SN), influenced by the prefrontal cortex and the VTA, is considered an entry point in the reward circuit, akin to the NAc (Groenewegen & Berendse, 1990). The DA neuronal activity recorded by Schultz was indeed originating in both SNc and VTA (Schultz 1983)

The VP receives major inputs from the NAc and is involved in reward expectation (Leung & Balleine, 2013), incentive salience attribution (Chang et al., 2018), and "liking" responses (Smith & Berridge, 2007).

Lastly, the lateral septum, a major GABAergic relay between the hippocampus and lateral hypothalamus, is connected with numerous other structures, including the amygdala, VTA, NAc, PFC, and thalamus. These connections make the lateral septum an essential node for integrating cognitive and limbic information, which allows for motivated behaviors (Luo et al., 2011). Early ICSS studies have also demonstrated the rewarding properties of the lateral septum (Olds & Milner, 1954).

2.3. The Subthalamic Nucleus' role in Motivation

The STN is traditionally not considered part of the reward circuit. In fact, in the traditional model, the STN is regarded as the motor output of the circuit. However, since the STN shares similar connections with the NAc, particularly with the PFC and the VTA,

as well as with the BLA, thalamus, and ventral pallidum, it could also be considered a candidate for transforming motivation into action (Figure 12).

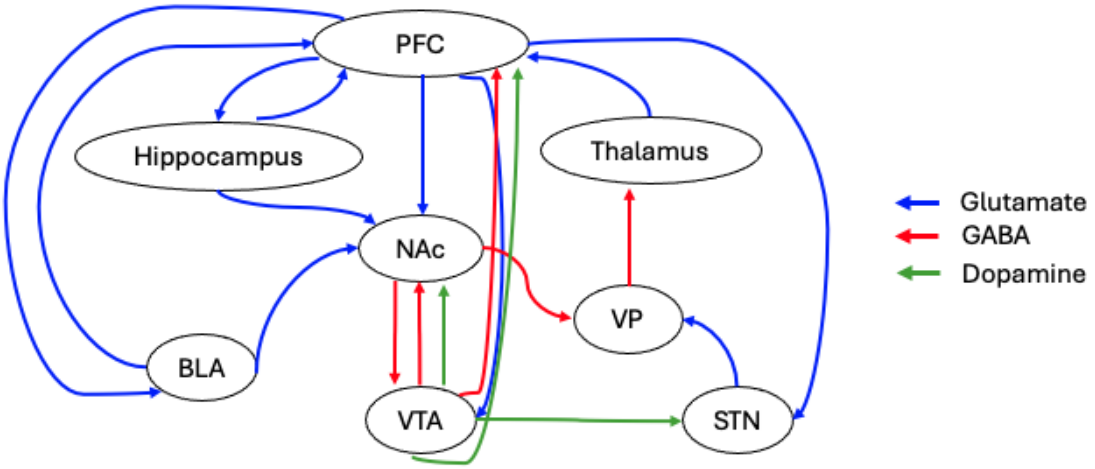

Figure 12. Schematic of the classical reward system adapted from by Mogenson et al. (1980), who first proposed the idea of a "limbic-motor interface" or “motivation to action” role of the NAc and later adapted by Wolf (2002). It is here implemented with the STN, which has been linked to the reward system due to its connections to both motor and limbic circuits. The inclusion of the STN reflects its role in mediating the inhibition of impulsive and reward-related behaviors through the hyperdirect pathway, which involves projections from the PFC directly to the STN. This connection emphasizes the STN's influence over decision-making and behavioral inhibition related to both natural rewards and addictive substances.

The earliest evidence indicating the involvement of the STN in motivation came from electrophysiological recordings in monkeys during an operant oculomotor task. These studies revealed changes in STN activity when the monkeys were expecting a food reward (Matsumura et al., 1992). Specifically, certain STN neurons responded only when the target predicting the reward was fixated. Further research demonstrated that some STN neurons also respond to both the anticipation and delivery of rewards (Darbaky et al.,

2005; Espinosa-Parrilla et al., 2015). Subsequent studies in rats have provided a more detailed understanding of the STN's functional role in motivation and reward processing.

In the first part of this thesis, we will investigate how the STN contributes to the "liking" aspect of reward processing, focusing on tasks using ICSS with varied stimulation frequencies and optogenetic manipulation of STN neurons. This will help to understand the role of the STN within the broader pleasure network in the brain.

2.3.1. Does the STN contribute to "liking" and "wanting"

STN lesions affect the "wanting" and "liking" components of reward differently. STN lesions increase "wanting" for sweet food but decrease "liking," as evidenced by a blunted positive taste reaction to sucrose in rats (Pelloux et al., 2014). STN-lesioned rats also prefer glucose (more bland but caloric solution) over saccharin (a sweet but non-caloric solution), contrasting with sham-operated rats, suggesting internal states like energy balance influence decision-making (Figure 13). STN neuron activity correlates with feeding behaviors in mice based on homeostatic status and food type in mice and their modulation with optogenetics is sufficient to regulate food intake (Wu et al., 2020). Finally, the subjective hedonic value of the reward (its "liking" component), as well as its subjective cost, was positively correlated with an increase in theta activity in the STN (Zénon et al., 2016).

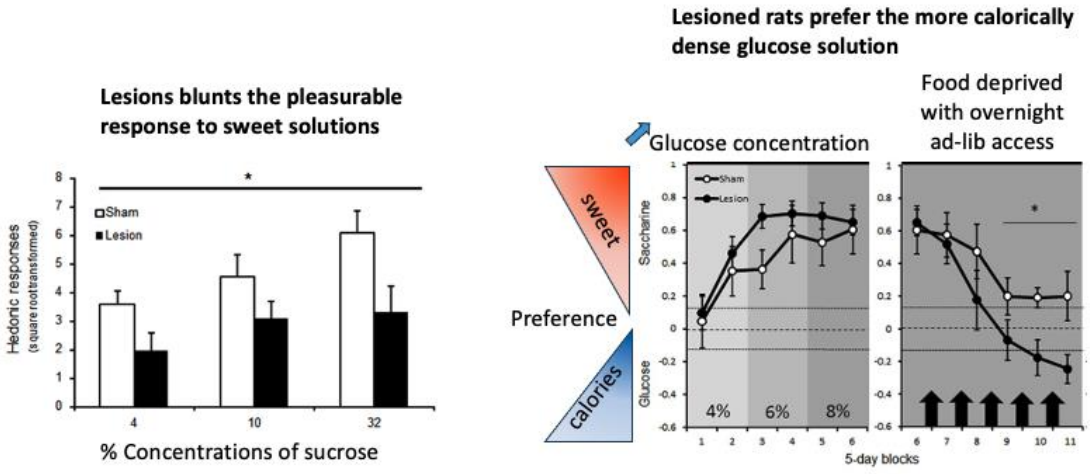

Figure 13. The role of the STN in affective processing. Adapted from Pelloux et al., 2014

2.3.2. STN and motivation for food and sex

The current findings suggest that the STN plays a critical role in regulating incentive motivation for food. In patients with PD, STN-DBS has been associated with weight gain, food cravings, and binge eating (Witjas et al., 2005; Ardouin et al., 2006; Lim et al., 2008; Zahodne et al., 2011; Kistner et al., 2014; Aiello et al., 2015). Indeed, following HFS of the STN, frequent and sometimes significant weight gain has been observed in these patients (Rieu et al., 2011). The observed weight gain seems to stem not from increased hunger or enhanced pleasure but from a modulation of homeostatic mechanisms that heighten the incentive salience of food. This indicates that the STN may influence how much effort is put into obtaining food, making it more desirable without necessarily affecting the subjective experience of pleasure. However, the mechanisms underlying these effects in PD patients are not fully understood, necessitating further investigation into how STN HF-DBS affects motivational processes.

Individual characteristics, such as impulsiveness, may make some patients more prone to weight gain following STN-DBS (Aiello et al., 2017). Terenzi et al. (2018) supported this, demonstrating that binge eating in PD is associated with cognitive abnormalities. However, they suggest binge eating in PD may not always result from increased incentive salience, implying complex cognitive and individual differences (Terenzi et al., 2018).

Interestingly, hypersexuality in PD patients after STN HF-DBS has also been linked to an increase in the incentive salience of erotic stimuli (Serranová et al., 2013), further demonstrating the complex influence of STN-DBS on motivational systems in the brain.

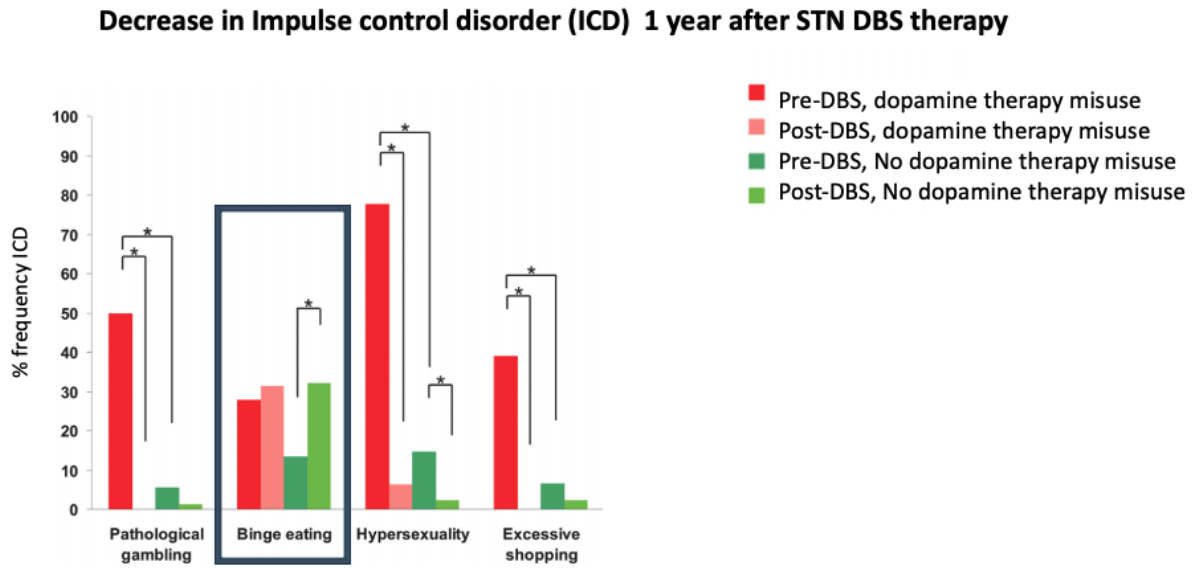

Figure 14. STN DBS relieves impulsive symptoms in Parkinson's Disease, expect in the case of binge eating disorder, where STN DBS increases the frequency of this ICD. Adapted from Eusebio et al., 2013.

In rats, studies have demonstrated that bilateral lesion of the STN enhances secondary motivation for food -related stimuli. Specifically, these lesions increase the animals' responsiveness to conditioned reinforcers associated with food, reflecting enhanced Pavlovian conditioning, and boost the effort exerted to obtain food (Baunez et al., 2002; Baunez et al., 2005). Importantly, bilateral lesions of the STN does not alter the hunger state of the animal. Whether the animals have ad libitum access to food or not, STN-lesioned animals do not consume more than control animal, although they ate it faster and their locomotor activity was increased when they anticipated the food reward delivery (Baunez et al., 2002). STN-lesioned rats also prefer glucose over saccharin suggesting caloric intake is modulated in part by the STN (Pelloux. et al., 2014).

Further evidence from PR tasks indicates that rats with bilateral lesions in the STN show an increased motivation to work for food rewards. In these tasks, animals are required to progressively increase their effort (e.g., more lever presses) to obtain the same reward, and their motivation is measured by the breaking point—the last effort the animal makes before ceasing to respond. STN-lesioned animals consistently

demonstrated a higher breaking point, indicating a greater willingness to work for food compared to sham controls (Baunez et al., 2002; Baunez et al., 2005). These findings were also replicated in experiments using HF-DBS of the STN (Rouaud et al., 2010).

Although bilateral excitotoxic lesions of the STN did not affect the animals' overall food consumption, they significantly increased their motivation for food, as evidenced by more perseverative (excessive) and premature responses, and a higher breaking point under PR schedules of reinforcement (Baunez & Robbins, 1997; Baunez et al., 2005). These results highlight the STN's role in modulating reward-seeking behaviors, especially under conditions that require increased effort for obtaining rewards.

In a study involving a five-choice attentional task, it was observed that rats with lesions in the STN demonstrated reduced perseverative seeking behaviors into the food magazine when provided with unlimited food prior to the task. However, even with the reduction, the lesioned rats still exhibited significantly higher perseverative responses compared to ad libitum-fed sham rats (Baunez & Robbins, 1997). This suggests that although the STN lesions diminish some aspects of excessive reward-seeking behavior, the lesioned animals retain an elevated response rate compared to controls, highlighting the STN's role in regulating motivational processes independent of hunger.

Studies using Pavlovian training have examined the impact of STN lesions on a specific aspect of food motivation: the attribution of incentive salience to reward-related cues. In these experiments, where a CS, like a lever, is paired with a food reward (US), lesions to the STN have been shown to increase the number of presses on the CS, indicating heightened motivation to obtain the reward (Baunez et al 2002; Uslaner et al., 2008). Similarly, in studies using the CPP paradigm, where an environment (CS) is associated with a rewarding stimulus (US), STN lesions lead to a stronger preference for the food-associated environment (Baunez et al., 2002).

This heightened attribution of incentive value is further supported by electrophysiological recordings in rats, showing that STN neurons respond to both reward delivery and CS incentive stimuli (Teagarden et al., 2007; Lardeux et al 2009; 2013). Additionally, in PD patients, the placebo effect—which influences reward expectancy—was found to modulate STN neuronal activity (Frisaldi et al., 2014). Furthermore, individuals who have experienced damage to the STN due to stroke or

tumors may exhibit hyperphagia and increased appetite, reinforcing the role of the STN in reward processing and appetite regulation (Barutca et al., 2003; Etemadifar et al., 2012). This evidence highlights the STN's involvement in both processing actual rewards and anticipating rewards based on subjective expectations.

Altogether, these results suggest a significant increase in the motivation to obtain the reward without altering the hunger state or the association between conditioned and unconditioned stimuli by the STN lesion.

2.3.3. The STN and motivation for Drugs of abuse

One fascinating property of the STN is its differential modulation of incentive motivation depending on the type of reward, particularly between natural rewards (such as food) and substances of abuse. Studies have shown that both HFS and lesions of the STN increase motivation for food rewards like sucrose, while simultaneously reducing motivation for drugs like cocaine (Baunez et al., 2005; Rouaud et al., 2010)(Figure 15). This differential encoding of reward types by STN neurons (Lardeux et al., 2013; Breysse et al., 2015; Espinosa-Parrilla et al., 2015) suggests a level of adaptability, making the STN a potential target for treating SUD (Pelloux & Baunez, 2017).

However, understanding the physiological effects of STN HF-DBS in both normal and pathological states remains critical to avoid unintended side effects in patients with PD and OCD, such as emotional blunting, mood disorders, or apathy. Future research should focus on these aspects to refine therapeutic interventions involving the STN.

2.3.3.1. Alcohol

The role of the STN in alcohol-related motivation is complex and varies based on the individual's predisposition to alcohol consumption. STN lesions do not seem to affect the primary motivation for alcohol, as they do not alter the amount of alcohol consumed, nor

the preference between alcohol and water in rats (Lardeux & Baunez, 2008). During prolonged access to alcohol, STN lesions exhibit a protective effect by reducing alcohol consumption compared to controls. Its lesions blunt both the animals' aversive orofacial reaction to a first exposure, and the positive one after repeated exposures. Even after the escalation of alcohol intake, STN lesions result in lower alcohol intake and reduced motivation to consume alcohol, suggesting a protective role of the STN in controlling excessive alcohol consumption (Pelloux & Baunez, 2017). This suggests that the STN is not involved in the direct desire for alcohol, similar to its role in food motivation.

However, when it comes to secondary motivation, which is the motivation influenced by cues and the subject's predisposition, the STN plays a more nuanced role. In rats with a high propensity to drink alcohol, STN lesions increase the incentive salience of alcohol-related cues and the motivation to work for alcohol, as demonstrated by higher breaking points in a PR task. On the contrary, in low-drinking rats, STN lesions reduce both the salience of alcohol-related cues and the motivation to obtain alcohol (Lardeux & Baunez, 2008).

Research highlights the significant role of social context in influencing alcohol consumption among humans (Bardo et al., 2013). Animal studies have shown similar effects, where the presence of peers can modulate drug use in rats (for review Pelloux et al, 2019). STN DBS which has demonstrated beneficial effects on addiction to cocaine or alcohol, also affects the social influence of peer presence on drug consumption (Giorla et al., 2022; Vielle et al., Vignal et al., 2024). Specifically, while neither STN DBS nor the presence of an alcohol-naive peer significantly altered recreational alcohol intake in rats, STN DBS did reduce ethanol consumption following escalation procedures. Interestingly, the presence of an alcohol-naive peer only increased alcohol consumption in low-drinking rats, but this effect was nullified by STN DBS (Vignal et al., 2024). These findings underscore the STN's role in addiction-like alcohol consumption and its interaction with social influences on drug use.

The influence of the STN on alcohol consumption and motivation also seems to be mediated by its projections to the VP, indicating that the STN-VP pathway may play a crucial role in regulating alcohol-seeking behavior, especially in cases of alcohol abuse (Prasad & McNally, 2016).

In summary, while the STN does not directly regulate primary alcohol consumption, it significantly influences secondary motivation for alcohol depending on the subject's baseline drinking behavior, and its modulation may offer protective effects against alcohol abuse.

2.3.3.2. Heroine and Methamphetamine

The STN plays a significant role in the motivation for various substances of abuse, including methamphetamine and heroin (Carson et al., 2010; Baracz et al., 2012; Wade et al., 2017). For methamphetamine, chronic intraperitoneal (i.p.) injections of oxytocin reduce methamphetamine-induced c-fos activity in both the STN and NAc (Carson et al., 2010). Moreover, a single administration of oxytocin in the STN can prevent methamphetamine-induced CPP and relapse, through the local activation of oxytocin receptors (Baracz et al., 2012, 2015). However, chronic methamphetamine exposure disrupts oxytocin plasma levels and alters the density of oxytocin receptor-immunoreactive fibers in both the STN and NAc (Baracz et al., 2016). Since oxytocin plays a critical role in social behavior (Ferguson et al 2001), this disruption could highlight the STN's role in mediating the effects of social factors on drug consumption.

For heroin, HFS DBS of the STN reducing both heroin intake and the tendency for heroin consumption to escalate again after a period of abstinence (Wade et al., 2017). Additionally, human studies indicate that STN activity increases when former heroin users are exposed to drug-related cues, further suggesting the STN's involvement in heroin addiction (Zijlstra, et al., 2009).

2.3.3.3. Cocaine

There is considerable evidence demonstrating the role of the STN in regulating cocaine intake in rats. Notably, both STN lesions and HF-DBS do not significantly alter cocaine self-administration under a FR1 schedule of reinforcement. However, both interventions reduce the animals' willingness to work for cocaine under a PR task, suggesting a decrease in secondary motivation for the drug following STN lesion and HF-DBS (Baunez et al., 2005; Rouaud et al., 2010). This reduction in motivation appears to be

linked to a diminished incentive salience for cocaine, as STN lesions result in decreased CPP for cocaine-associated environments (Baunez et al., 2005).

Interestingly, STN lesions in rats with low baseline cocaine consumption seem to have the opposite effect, increasing the incentive salience of cocaine cues in sign-tracking experiments (Uslaner et al., 2008). This highlights the STN's role in modulating drug motivation based on baseline consumption levels, as seen previously with alcohol. Further studies demonstrated that inactivation of the STN via GABAergic agonists reduces cocaine demand for high doses but not for low ones, further supporting this context-dependent role (Bentzley & Aston-Jones, 2017).

In terms of escalation, recent findings from our group reveal that STN lesions and HF-DBS both prevent the initial escalation of cocaine intake. Additionally, HF-DBS reduces re-escalation following long periods of abstinence (Pelloux et al., 2018). The protective effects of STN inactivation appear to be linked to its ability to block abnormal theta oscillations, a neural biomarker associated with impulse control dysfunction. Low frequency (theta and beta bands) neuronal oscillations were also shown to increase in the STN, after repeated exposure to cocaine (Pelloux et al., 2018). These oscillations within the STN have been identified as potential predictors of compulsive drug-seeking behavior. Animals later identified as “resistant” to the punishment associated with cocaine seeking exhibited an increase in basal low frequency oscillations during escalation of cocaine intake. Confirming the link between these low oscillations and compulsion, STN 8-Hz DBS applied during a escalation phase in rats previously identified as “sensitive to punishment” could transform them into “resistant” animals (Degoulet et al., 2021). Furthermore, STN DBS at 30-Hz reduced compulsive cocaine seeking in rats.

In social contexts, the presence of a peer—especially a non-familiar, drug-naive one—has been shown to significantly reduce cocaine intake. This reduction in consumption was mirrored by STN lesions, suggesting that the STN is a critical mediator of the social influence on drug use (Giorla et al., 2022). Our lab also demonstrated that, after cocaine escalation, both optogenetic inhibition and HF-DBS of the STN reduced intake, in presence like in absence of a peer. This confirms the role of the STN in mediating social and motivational aspects of drug consumption (Vielle et al., 2023). In human studies of patient with cocaine use disorder (CUD), during inhibition tasks (Stop Correct vs. Stop Incorrect), activity in the right STN, right inferior frontal gyrus, and bilateral OFC was

modulated by the type of cue presented (cocaine related or neutral). Interestingly, when an observer was present during the task, this effect was reversed in most brain areas for individuals with CUD. These results underline the significant influence of social context and drug-related cues on inhibitory control mechanisms in CUD (Terenzi et al., 2024). The right STN and bilateral OFC appear to play a critical role in mediating these effects, highlighting the need to account for social context in addiction research.

2.3.3.4. STN-DBS as a strategy to treat Substance Use Disorder

While the STN is typically not classified as part of the traditional reward circuitry, throughout this manuscript we have described that it receives significant inputs from key regions such as the PFC, VTA, and VP. This unique connectivity positions the STN as a promising target for treating SUD. Unlike other regions, the STN exhibits a differential influence on various rewards, reducing drug consumption (e.g., cocaine) without diminishing motivation for natural rewards like food (Baunez et al., 2005; Rouaud et al., 2010).

STN lesions or HF-DBS consistently reduce motivation for drugs of abuse, while increasing the desire for natural rewards. This dual role highlights the STN's importance in modulating reward systems, especially given that SUD is characterized by both increased motivation for drugs and a decreased drive for alternative rewards (American Psychiatric Association, 2017). Additionally, the STN plays a role in impulse control (Eagle and Baunez, 2010), which is vital as individuals with SUD often exhibit a transition from impulsive to compulsive behaviors (Belin et al., 2009).

In preclinical studies, STN lesions or HF-DBS reduced alcohol and heroin consumption in rats, even after escalated drug intake and abstinence periods, highlighting the STN's protective effects against relapse (Pelloux & Baunez, 2017; Wade et al., 2017). Similar findings were observed with cocaine, where STN HF-DBS prevented escalation and reduced relapse following prolonged abstinence (Pelloux et al., 2018). Furthermore, alterations in STN neuronal oscillations (e.g., theta and beta bands) have been identified as biomarkers of impulse control dysfunction and vulnerability to SUD (Degoulet et al., 2021).

Clinical evidence supporting the STN's role in addiction comes from observations in PD patients, where STN HF-DBS has been shown to alleviate compulsive medication use, a condition known as dopaminergic dysregulation syndrome (DDS)(Witjas et al., 2005; Lhommée et al., 2012) and CUD (Mira et al., 2024). Neuroimaging studies also suggest that greater STN activation is linked to lower resilience and impulse control in early adolescence, predicting substance use in adulthood (Weiland et al., 2012). Decrease in STN activity following cognitive behavioral therapies for SUD further support its involvement in controlling compulsive drug-seeking behaviors (DeVito et al., 2012). Interestingly, a recent case of PD patient consuming cocaine confirmed the beneficial effects of STN DBS, since the patient stopped his cocaine intake after the surgery (Mira et al 2024).

Overall, these findings underscore the STN's significant role in SUD, identifying it as a key target for therapeutic interventions. STN DBS offers a promising approach to personalized treatment for SUD, particularly through the use of variable stimulation frequencies to address different aspects of the disorder effectively.

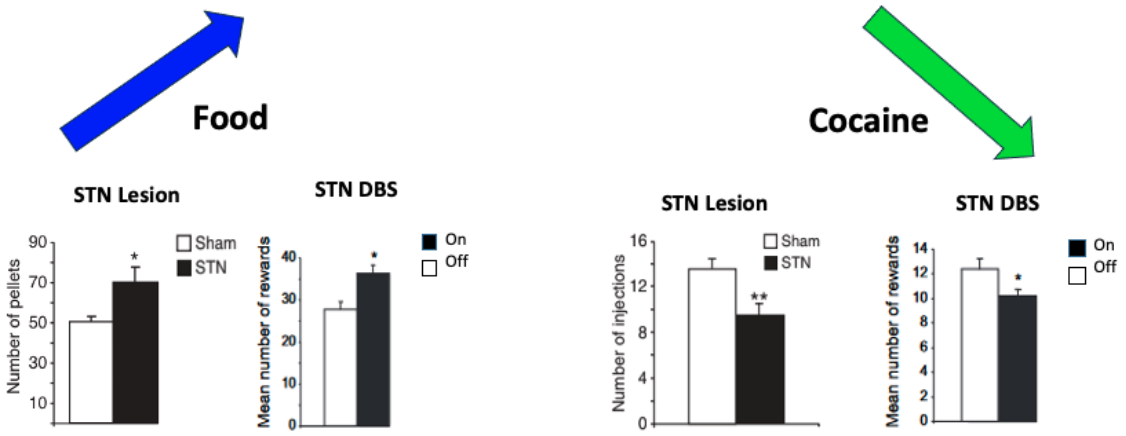

Figure 15. STN lesion and DBS has opposite motivational influence on natural vs drug rewards. Adapted from Baunez et al., 2005 and Rouaud et al., 2010.

3. Thesis Objectives

3.1. The STN in Motivation and Reward

HF-DBS of the STN has demonstrated promising therapeutic benefits by increasing motivation for sweet foods while simultaneously reducing motivation for cocaine use (Rouaud et al., 2010). It has also been effective in preventing and reversing the escalation of cocaine intake (Pelloux et al., 2018), positioning STN HF-DBS as a potential treatment for SUD, particularly given the current lack of highly effective pharmacological options (Pelloux & Baunez, 2013). However, its application in PD patients has raised concerns due to potential side effects, including heightened euphoria, significant weight gain, and impulse control disorders such as compulsive gambling (Witjas et al., 2005; Krack et al., 2010). These observations suggest that the STN is involved in regulating motivated behaviors, making it essential to further investigate the effects of STN-DBS in the context of treating CUD.

Additionally, STN-DBS may have unintended effects, potentially due to antidromic stimulation of STN afferent and efferent projections, as well as its impact on passing fibers (Maurice et al., 1998). A noteworthy clinical case described a PD patient who used their DBS device to self-stimulate, seeking morphine-like effects (Morgan et al., 2006). This raises the question of whether the STN could function as a "hedonic hotspot," capable of producing pleasurable sensations. We propose that, due to its connections with the PFC, NAc, and VP, the STN may indeed be part of the brain's hedonic circuitry. To test this theory, we use optogenetic and electrical ICSS paradigms.

This thesis also focuses on the hyperdirect pathway and its role in motivated behaviors, with the aim of better understanding the side effects of weight gain and impulse control disorders observed in STN-DBS for PD patients. We employ calcium imaging with fiber photometry to record activity at the terminals of the hyperdirect pathway, and use optogenetics to modulate its function, further exploring its involvement in motivative seeking behaviors.

3.1.1. Exploring the Rewarding Properties of the STN: Intracranial Self-Stimulation

The first aim of this thesis was to investigate whether rats would self-stimulate the STN, which might suggest its role in reward processing. Using electrical DBS, we employed a FR1 reinforcement schedule to measure primary motivation, allowing rats to self-stimulate the STN at various frequencies (8 Hz, 30 Hz, and 130 Hz). Given that the mechanisms underlying STN HF-DBS effects are not fully understood, we also utilized optogenetic tools to selectively activate or inhibit STN neurons, enabling more precise assessment of the STN's role in ICSS. This combined approach aimed to elucidate the extent to which the STN is involved in the rewarding effects and possible side effects observed with HF-DBS in PD patients.

3.1.2. Investigating the Hyperdirect Pathway in STN-Related Motivation

While STN HFS has shown promise, it can inadvertently activate afferent, efferent, or passing fibers, which may lead to unintended effects. For example, antidromic activity in the PFC has been observed following STN DBS (Maurice et al., 1998). Given the critical role of the PFC in behavioral inhibition and impulse control, it became imperative to explore the hyperdirect pathway's contribution to addiction-like behaviors and its modulation of motivation.

3.1.2.1. Recording Hyperdirect Pathway Activity Using Fiber Photometry

The second aim of this thesis was to utilize fiber photometry to selectively target the hyperdirect pathway and better characterize its influence on motivated behaviors. Specifically, we recorded activity from the infralimbic, prelimbic, and anterior cingulate regions of the PFC projecting to the STN during FR1, FR5, and PR reinforcement schedules in both sucrose and cocaine self-administration tasks. This approach enabled us to observe real-time neural dynamics within the hyperdirect pathway during reward-seeking behaviors.

3.1.2.2. Modulating the Hyperdirect Pathway with Optogenetics

In the final phase of the study, optogenetics was employed to inhibit the hyperdirect pathway, allowing us to assess the impact on motivation for natural rewards, such as sucrose. This experiment aimed to provide further insights into the broader role of the STN in motivation and to clarify the contribution of the hyperdirect pathway to both adaptive and maladaptive reward-seeking behaviors.

This research provides a comprehensive examination of how the STN influences motivation, highlighting the crucial role of the hyperdirect pathway in mediating reward-seeking behaviors. The findings demonstrate the effects of STN HF-DBS on food motivation and suggest that a deeper understanding of STN circuitry may pave the way for novel clinical interventions targeting SUD and other conditions involving maladaptive reward processing.

4. Experimental contributions

4.1. STN electrical and optogenetic intracranial self-stimulation behavior

Aims:

The STN has been well-established as a key target for DBS in the treatment of motor symptoms in PD. Over recent years, DBS has been increasingly explored for its potential in addressing non-motor conditions such as depression and obsessive-compulsive disorder, though the precise mechanisms behind its therapeutic effects remain unclear. While the STN's role in motivational processes has been investigated (Baunez & Lardeux, 2011), fewer studies have focused on its role in hedonic experiences. Research by Pelloux et al. (2014) demonstrated a reduction in hedonic responses following bilateral STN lesions, despite evidence showing that STN-lesioned rats exhibit increased motivation for food rewards.

The primary aim of this study was to explore whether rats could become motivated to self-stimulate the STN. Classical studies, such as Olds and Milner (1954), revealed the lateral septum as a hedonic hotspot through the use of ICSS procedures. More recent reports have highlighted the potential for misuse of DBS in humans, such as a 2006 case study involving a PD patient using DBS for self-stimulation (Morgan et al., 2006). Given the growing interest in extending DBS to treat physiological and psychological disorders, including addiction, understanding its effects on motivated behavior is increasingly important.

This study examined the role of the STN in ICSS behavior using both DBS and optogenetics. Rats were trained to self-stimulate the STN at three different frequencies (130, 30, 8 Hz) via DBS, with each stimulation lasting three seconds following an active nose poke (FR1). Building on previous work by former PhD student Cassandre Vielle, this

study also utilized optogenetic techniques to investigate different populations of neurons in the STN. In optogenetic experiments, rats were bilaterally infected with excitatory, inhibitory, or control opsins and trained to self-stimulate with laser activation following an active nose poke.

Main Results:

The findings indicated that high-frequency DBS (130 Hz) and optogenetic inhibition of the STN increased the animals' response for ICSS. These results suggest that STN DBS may activate the brain's motivational network, raising important considerations for its potential misuse in PD patients. Additionally, the findings highlight the need for further research into the possible utility of STN DBS in modulating reward processes, particularly in the context of drug addiction.

This experiment was part of a set of experiments that lead to the publication presented below (Williams et al. 2024).

Subthalamic Nucleus Deep Brain Stimulation as a Reward: Exploring Pleasure Through Electrical and Optogenetic Self-Stimulation and Neuronal Inhibition

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Abstract

Background: Subthalamic nucleus (STN) high-frequency (HF) Deep Brain Stimulation (DBS) is a treatment for Parkinson's Disease (PD), psychiatric disorders such as obsessive-compulsive disorder and has been suggested for addiction treatment. Patients with PD can divert the use of their DBS device for self-stimulation. We have previously shown the involvement of STN in reward-related processes, but whether or not the STN can support intracranial self-administration (ICSS) in a model remains to be determined.

Objective/Hypothesis: Since STN DBS reduces drug intake, we hypothesize that it is because of the rewarding effect it has by itself. This study seeks to determine if STN HF DBS could lead to ICSS behavior and be mimicked by selective inhibition of STN neurons.

Method: We used electrical DBS and optogenetic approach to target specifically STN neurons. Rats with bilateral electrodes in the STN could self-stimulate different frequencies (8, 30, 130Hz). In optogenetic experiments, rats infected with excitatory, inhibitory, or control opsins in the STN, could self-administer light pulses through optic fibers.

Results: DBS stimulation at 130Hz and optogenetic inhibition of the STN increased ICSS responding in rats.

Conclusion: The STN is a reward-related structure, in which inhibition can support ICSS behavior. STN HF-electric DBS mimics the effects seen in STN optogenetic inhibition, suggesting that the rewarding effect of HF DBS is mediated via the inactivation of STN neurons. This work supports the idea that STN DBS, by providing an alternative reward to the drug, could be beneficial at treating addiction.

Keywords: Subthalamic nucleus, Deep Brain Stimulation, addiction, reward

Introduction

Deep Brain Stimulation (DBS), historically established as an alternative strategy to dopaminergic treatments, and the standard of care for managing motor symptoms in advanced Parkinson's disease (PD)[1] has witnessed recent applications for psychiatric disorders. Notably, DBS has demonstrated promising outcomes for obsessive-compulsive disorder and treatment-resistant depression [2,3]. The subthalamic nucleus (STN), a small glutamatergic structure within the basal ganglia [4] is classically associated with motor functions. It stands as the most efficient target of DBS for both PD and obsessive-compulsive disorders[2]. Former studies have revealed the involvement of STN in the reward circuit, inhibition control, and motivation (for reviews [5–8]), leading to the proposal of STN DBS for the treatment of addiction[8]. Substantial evidences indicate that the modulation of the STN neuron activity, either through lesion or DBS, can diminish motivation for cocaine while simultaneously increasing motivation for sweet food[9,10] . Electrophysiological studies have also highlighted the role of STN neurons at encoding reward-related information[11–14].

In animal behavioral models of cocaine self-administration, it has been demonstrated that STN DBS exerts frequency-dependent effects on addiction-like behaviors. For instance, 130Hz STN DBS can prevent the loss of control over cocaine or alcohol intake, and further reduce the amplitude of relapse for cocaine, alcohol or heroin [15–17]. Additionally, low frequency stimulation at 8Hz and 30Hz bidirectionally induces and reduces compulsive-like cocaine seeking behavior, respectively[18]. Collectively, these findings underline the

potential of STN manipulation in mitigating addictive behaviors associated with substance of abuse intake, all the while preserving the natural reward-seeking behavior associated with sweet food consumption.

Interestingly, it has been reported that some PD patients subjected to STN DBS could exhibit a compulsive-like behavior by diverting the DBS parameters to feel a 'morphine like' effect[19]. Additionally, PD patients with dopamine dysregulation syndrome have been shown to reduce their abuse of the prescribed L-dopa medication following STN DBS surgery[20–23]. STN DBS significantly reduced various forms of impulse control disorders in patients, with the exception of binge eating, which in some cases was significantly increased[24]. The first STN DBS clinical trial for a patient with severe crack cocaine dependence was conducted in 2023[25] with mixed results. The patient viewed the trial as a success and remained abstinent 6 months after the end of the study, despite the lack of a significant decrease in cocaine craving from STN-DBS during the study.

It is plausible that these effects may result from a direct influence of STN DBS on the brain's reward circuitry. Given the beneficial effects of STN DBS on drug related behavior, it might be possible that STN DBS results in an alternative rewarding effect to the drug, in which case, STN DBS at high frequency should induce a reinforcing effect. To test this hypothesis, we have employed the intracranial self-stimulation (ICSS) paradigm. In this operant model, rodents can self-administer electrical stimulation through implanted electrodes. If the stimulation is reinforcing, it should elicit reward-related behaviors, and therefore increase lever pressing[26] , as it is the case for septal area. Here, we aimed to ascertain whether the STN DBS applied at various frequencies (8, 30, and 130Hz) could lead to ICSS behavior. Rats with a history of cocaine use and naïve rats were tested with electrical DBS experiments to discern any difference in ICSS behavior due to drug use. To further specify the mechanism involved in the ICSS behavior induced by STN DBS, we have tested whether specific optogenetic STN neuronal inhibition or activation could replicate this behavior.

Materials and Methods

Animals

60 Adult Lister Hooded male rats (~380g, Charles River) used in the experiments were housed in groups of two in Plexiglas cages and maintained on an inverted 12h light/dark cycle (light onset at 7pm) with food and water available ad libitum, in a temperature and humidity-controlled environment. All experiments were conducted during the dark cycle (8am-7pm). Animal care and use conformed to the French regulation (Decree 2010-118) and were approved by local ethic committee at the University of Aix-Marseille, under the French ministry of Agriculture authorization #03129.01.

Surgery

Animals were anesthetized with ketamine (Imalgen, Merial, 100mg/kg, i.p.) and medetomidine (Domitor, Janssen, 0.5mg/kg, i.p.), and mounted on a stereotaxic apparatus (Kopf instruments) for bilateral optogenetic viral injections, optic fibers or electrodes implants. Rats received an antibiotic treatment by injection of amoxicillin (Citramox, LA, Pfizer, 100mg/kg, s.c.) and an injection of meloxicam (Metacam, Boehringer Ingelheim, 0.5mg/kg, s.c.) for analgesia.

For electrical ICSS experiments, rats (naïve n=22, history of cocaine use n=8) were implanted with bilateral homemade electrodes (see supplementary for electrode design) at the same STN coordinates than those used for virus injections. Electrodes and fiber implants were secured with four anchoring screws and dental cement.

For optogenetic experiments (n=30), animals received a bilateral 0.45µl microinjection of a virus at a rate of 0.16ul/min. To transfect STN neurons, we used AAV5 with the recombinant protein expression under CamKIIa-promoter control (UNC Vector Core, Chapel Hill, USA). Excitatory AAV5-CaMKII-hChR2(E123T/T159C)-p2A-EYFP-WPRE ($4x10^{12}$ pp; n=11), inhibitory AAV5-CaMKII-ArchT3.0-p2A-EYFP-WPRE ($4x10^{12}$ pp; n=10) or control AAV5-CaMKIIa-EYFP ($7.1x10^{12}$pp; n=9) opsins were injected in the STN at the coordinates AP: −3.7/+5.3mm; L: ±2.4mm; DV: −8.35/+1.65mm, from bregma and interaural point respectively and then averaged, and incisor bar set at − 3.3mm. The injector was left idle at the injection site for 5min to allow efficient diffusion. Optic fibers were implanted 0.4mm above injection site. The virus was allowed to incubate three weeks before optogenetic manipulation began. Previous studies have confirmed the efficacy of these viruses in inhibiting and stimulating STN neurons through *in vivo* and *ex vivo* electrophysiology[27].

At the end of each surgery, animals were awakened with an injection of atipamezol (Antisedan, Janssen, 0.15mg/kg, i.m.), an antagonist of medetomidine, and were left to recover for 7 days before behavioral training.

Rats with a History of cocaine use

Rats (n=8) were surgically implanted with a chronic intravenous silicone catheter into the right jugular vein, as described previously[9]. Following recovery, they were subjected to a cocaine taking/seeking-chained procedure. They were then subjected to an escalation protocol (15 days of extended access to cocaine (daily 6h-sessions)), followed by a test of resistance to punishment[18] (see supplementary methods). Finally, animals had a 3-month withdrawal period before being subjected to the ICSS (Figure 1c). Of note, cocaine self-administration was performed with lever presses, while ICSS involves nose-pokes to prevent possible confusion in operant responses (see below). Moreover, the rewarded-side was switched between the two protocols, so that the ICSS nose-poke behavior could not be related to cocaine self-administration.

Electrical ICSS Task

The DBS current intensity (50–150µA) was adjusted for each rats' hemispheres to the lowest value to observe the hyperkinetic movement in the contralateral paw of the site of stimulation at 130Hz (according to former studies[10,15,18]). Once the minimal current for STN DBS was identified for each animal, it was lowered by 0.1uA and held constant for the remainder of the study. One week after surgery, or 3 months after the end of the cocaine self-administration protocol, animals were placed in operant conditioning chambers equipped with holes and infrared beams detecting nose-pokes, and trained on a fixed-ratio-1 schedule (FR1) of reinforcement. During the 30min behavioral session each nose poke in the active hole activated a 3s cue-light illuminated above the hole and delivery of the electric stimulation (unipolar pulse with 80us period) applied during 3s. The active hole, in which correct ICSS responses were performed, was counterbalanced - right or left - across all animals. Perseverative responses, i.e. nose-pokes in the active hole performed during the 3s timeout period, were recorded. Nose pokes in the inactive hole were recorded as error responses. During these sessios, electrodes were connected to homemade electric stimulation cables, themselves connected to a digital stimulator (DS8000, WPI) via a stimulus isolator (DLS100, WPI) and a rotating commutator (Plastic-

One). Three groups where counterbalanced in the order of frequency tested (three different frequencies: 8, 30, 130Hz) for 10 sessions per frequency.

Optogenetic Stimulation and Inhibition ICSS Task

Light stimulation was performed during experiments using 200mW 532nm DPSS laser controlled with a signal generator and connected with an optic coupler (Thorlabs, FCMM625-50A) through a rotary joint (Doric Lenses) to relieve torsion due to animal movements. Light output was assessed before each experiment with a power meter (Thorlabs, PM20A). In order to better compare with electrical DBS, optogenetic stimulation was chosen to be tested at 130 Hz. The other parameters were: for stimulation: 10mW, 2ms pulse, 130Hz; and for inhibition: 5mW, 3s continuous pulse. Animals were placed in the same operant conditioning chambers than those tested in the electric DBS experiments, and the same procedure was followed (FR1) to respond for photomodulation of the STN during a 30min session for 10 sessions.

Histology and Immunohistochemistry

At the end of the experiments, rats were deeply euthanized with pentobarbital (Dolethal; 200mg/kg i.p.), and perfused with 4% PFA. Brains were removed and frozen in liquid isopentane (−80 °C) to be cut in 40-µm-thick frontal slices with a cryostat. For electrical ICSS, histological controls for electrodes' placements were performed after staining with cresyl violet (Figure 1a). Rat brain slices from optogenetic experiments were processed with immunohistochemistry (supplementary methods). Slides were observed under Apotome.2 Microscope (Zeiss) (Figure 1b). In case of missed electrode, virus, or fiber optic implant placement, the subjects were excluded from final analysis.

17 animals in total were discarded from the study after histology. Due to misplacement of the stimulating electrodes, 11 rats in the naïve group were excluded from analysis, while no rats from the history of cocaine group were excluded for misplaced electrodes. Figure 1a illustrates the trace of an electrode placement that was considered acceptable.

A lack of correct expression of GFP was found in 6 rats in the optogenetic groups, which were excluded from the analysis (n=3 in the ArchT3.0 group and n=3 in the hChR2 group). GFP expression in the STN is illustrated in Figure 1b.

Statistical Analysis

Statistical analysis was performed for the number of ICSS responses (active nose-pokes), perseverative and error responses, using R software (R Core Team, 2012). Linear mixed models (LMM) were run using the "lmer" function in the "lm4" package (version 1.1.28)[28]. P-values were obtained from the analysis of variance type 3 Wald chi-square tests (ANOVA) using the "car" package (version 3.0.12)[29]. Post-hoc comparisons were performed using the "emmeans" package" (version 1.7.2)[30]. Post-hoc analyses (Holm-Bonferroni correction) were applied to adjust for multiple pairwise comparisons and reduce Type I error rates. P-values <0.05 were considered significant. Optogenetic data were also analysed using two-way ANOVA with group (control, inhibition, or stimulation) as a between factor and sessions or blocks of sessions as repeated measures, followed by Bonferroni post hoc test.

Results

Can STN DBS be self-administered?

In naive rats (n=13), the LMM showed a main effect of the frequency of stimulation on the correct ICSS response ($\chi^2(2) = 19.00$, $p = 7.45e^{-5}$). Post hoc tests revealed that 130Hz stimulation significantly increased ICSS responding compared to 8Hz ($\beta = 6.16$, $p = 6.71e^{-9}$) and 30Hz ($\beta = 4.15$, $p = 1.50e^{-4}$), while no differences emerged between 8Hz and 30Hz stimulation ($\beta = 2.01$, $p = 0.0959$). ICSS responses were highest for 130Hz stimulation (Fig 1a). No other significant results emerged from the LMM (order of the frequency ($\chi^2(1) = 0.15$, $p = 0.70$), session ($\chi^2(2) = 0.26$, $p = 0.60$), interactions ($\chi^2(2) = 4.36$, $p = 0.11$).

When considering the perseverative responses (an indication of failure to inhibit responding when no reward is available) of naïve rats, the LMM showed a main effect of the frequency of stimulation on perseverative responses ($\chi^2(2) = 14.50$, $p = 7.09e^{-4}$). Indeed, as seen for correct ICSS, perseverative responses increased for the 130Hz frequency when compared to low frequencies 30Hz ($\beta = 3.48$, $p= 7.02e^{-3}$) and 8Hz ($\beta = 4.93$, $p= 4.90e^{-5}$) (Figure1b). There was no difference in the post-hoc test comparing 8Hz vs 30Hz ($\beta = 1.46$, $p= 3.58e^{-1}$). Neither the session ($\chi^2(1) = 0.69$, $p = 0.40$), order of the frequency ($\chi^2(1) = 0.05$, $p = 0.81$) or interactions ($\chi^2(2) = 3.16$, $p = 0.21$) had any effect on perseverative responses.

STN DBS had no effect on error responses, which level was low (Figure 1c) and no frequency effect in naïve rats ($\chi^2(2) = 0.56$, $p = 0.76$).

ICSS in rats with former exposure to cocaine

Cocaine-exposed rats (n=8) were tested in the ICSS paradigm in order to check whether a history of cocaine abuse would alter the effects of HFS on ICSS responding. As seen in naïve rats, the LMM revealed a significant main effect of the frequency of stimulation on the number of ICSS responses ($\chi^2(2) = 30.21$, $p = 2.76e^{-7}$). Specifically, HFS of 130Hz was the most rewarding frequency, eliciting significantly greater number of ICSS responses than lower frequencies 30Hz ($\beta = 7.23$, $p = 3.11e^{-12}$) and 8Hz ($\beta = 10.3$, $p < 0.0001$) (Figure 3a). The pairwise comparison confirmed the significant increase of ICSS responses during 130Hz to 8Hz and 30Hz, but also revealed a small but significant increase in responses at 30 Hz compared to 8Hz ($\beta = 3.08$, $p = 3.64e^{-3}$). The session ($\chi^2(1) = 0.22$, $p = 0.64$), order of the frequency ($\chi^2(1) = 0.43$, $p = 0.51$), and interaction ($\chi^2(2) = 1.92$, $p = 0.38$) had no effect on the number of ICSS responses.

Perseverative responses were also significantly greater with HFS, the LMM revealing a main effect of frequency of stimulation ($\chi^2(2) = 10.53$, $p = 0.005$). The mean number of perseverative responses significantly increased during 130Hz HFS compared to 8Hz ($\beta = 6.15$, $p= 8.75e^{-7}$), while 30Hz also increased responding when compared to 8Hz ($\beta = 3.85$, $p = 3.87e^{-3}$) (Figure 3b). There was no increase in responding when comparing 30Hz to 130Hz ($\beta = 2.30$, $p = 0.10$), indicating that 130Hz and 30Hz frequencies increase impulsive seeking behavior, as measured by perseverative responses. There was a small main effect of interaction (session x stimulation ($\chi^2(2) = 8.35$, $p = 0.01$), but neither the session ($\chi^2(1) = 0.03$, $p = 0.86$) or the order of frequency ($\chi^2(1) = 3.30$, $p = 0.07$), had an effect on perseverative responding.

The frequency of stimulation had no significant effect on the low level of error responses ($\chi^2(2) = 0.21$, $p = 0.90$) (Figure 3c right).

Overall, our results showed that electrical DBS of the STN is rewarding at the high frequency of 130Hz for both naïve and cocaine-exposed rats. To a lesser extent, 30Hz was also rewarding for rats with a history of cocaine use. Although the 2 groups seem different, there was no significant group effect in the global statistical analysis ($F(1, 19) = 0.01$, $p = 0.92$).

Can Optical inhibition or stimulation of STN neurons be self-administered?

In optogenetic experiments, we investigated the effect of inhibition (eArchT 3.0, n=7) and HF stimulation (hChR2, n=8) of infected neurons in the STN on self-stimulation responses over 10 sessions. Rats infected with the EYFP (n=9) virus were used as controls (Figure 4). The LMM revealed no significant main effect of stimulation/inhibition/control on the number of ICSS responses ($\chi^2(2) = 3.84$, $p = 0.14$). However, the session did have a significant main effect on the number of correct ICSS responses ($\chi^2(1) = 15.16$, $p = 9.84e^{-5}$). There was also a significant interaction between the opsin used (stimulation/control/inhibition) and the session ($\chi^2(2) = 22.62$, $p = 1.22e^{-5}$). The post hoc pairwise comparison revealed a significant increase in ICSS responses when comparing inhibition vs control ($\beta = 3.45$, $p = 0.047$) and inhibition vs stimulation ($\beta = 5.89$, $p = 9.26e^{-4}$), but no difference between stimulation and control ($\beta = 2.44$, $p = 0.11$) (Fig 4a).

The repeated measures two-way ANOVA analysis assessing the dynamic of the effects (first 5 vs last 5 sessions) revealed a significant main effect of photomodulation on ICSS responses, ($F(2,12) = 42.06$, $p < 0.0001$), indicating that the type of photomodulation significantly influenced the number of ICSS responses. However, there was no significant main effect of block ($F(1,12) = 2.40$, $p = 0.148$) or subjects ($F(12,12) = 0.65$, $p = 0.764$). Importantly there was a significant interaction between photomodulation and blocks ($F(2,12) = 11.09$, $p = 0.0019$) indicating that the effect of photomodulation on ICSS responses varied significantly across different blocks, in line with the LMM analysis.

In the inhibition group, post hoc pairwise comparison revealed that ICSS responses were significantly increased between the first and the last 5 sessions ($p = 0.0028$) (Figure 4b). In the stimulation or control groups, there was no difference in ICSS responding between blocks ($p = 0.1218$ and 0.999 respectively).

For perseverative responses, there was no significant effect of optogenetic manipulation ($F(2,12) = 1.776$, $p = 0.2110$), subject ($F(12,12) = 11.09$, $p = 0.0019$), or interaction($F(2,12) = 0.2843$, $p = 0.7574$) (Figure 4c), but a small main effect of block ($F(1,12) = 4.973$, $p = 0.0456$). The post hoc Bonferroni's test revealed however no significant difference in any of the pairwise comparisons of block 1 vs 2 (inhibition $p=0.3137$, stimulation $p=0.5611$, control $p= 0.999$).

There was no significant effect of optogenetic manipulation on error responses ($F(2,12) = 1.468$, $p = 0.2689$), block ($F(1,12) = 3.343$, $p = 0.924$), subject ($F(12,12) = 0.9501$, $p = 0.5346$), nor interaction ($F(2,12) = 0.5305$, $p = 0.6015$) (Figure 4d).

Together, these results suggest that optical inhibition of STN supports self-stimulation behavior and is therefore rewarding.

Discussion

In the present study, we have shown that STN DBS at 130Hz can be self-administered by both naïve rats and animals with a history of cocaine abuse. In order to elucidate the mechanism by which DBS may be acting on the STN to elicit ICSS, we employed optogenetic inhibition and HF-stimulation of STN neurons and showed that selective inhibition, but not HF-stimulation, of STN neurons also increased ICSS responding.

ICSS is a classic experimental paradigm used to study the neural substates of reward processing and motivated behavior by measure of brain-stimulation rewards[26,31]. When subjects make active responses to obtain the stimulation, it suggests the targeted region supports ICSS, indicating its involvement in positively reinforcing effects[32]. ICSS procedures have identified the medial forebrain bundle, but also the lateral hypothalamus and ventral tegmental area as reward processing centers due to their capacity to increase responding during electrical stimulation[26]. Several studies have shown that the STN is involved in reward processing and motivation[5–7,33,34] . The location of the STN within the cortico-basal-ganglia loop supports the theory that it plays a role in reward processing. Given that the STN receives direct inputs from the orbitofrontal cortex, anterior cingulate and insula and that it is interconnected with the DA system[4,35], it could partially explain the STN's involvement in cost benefit decision making and motivation-related processing. Additional anatomical evidence of the STN's role in reward processing comes from studies on the functional sub-territories of the STN. The medial ventral portion of the STN, regarded as the "limbic area" and receiving direct projections from the medial PFC, has been described in rodent, non-human primates and humans[4,36,37] and is the target of DBS for the treatment of OCD[2].

Moreover, the STN has been shown to encode reward value in rats and nonhuman primates[11,13,38]. Interestingly, STN lesions have been shown to increase the "wanting" component of sweet food rewards while decreasing the "liking" component[39]. STN lesions

reduced rats' positive taste reactions to a sweet solution. Additionally, when given a choice between saccharin (a sweet but non-caloric solution) and glucose (a more bland but caloric solution), STN-lesioned rats preferred glucose, unlike sham animals that preferred saccharin. This suggests that the STN plays a role in the diminished hedonic "liking" for sweet rewards and that STN lesions may interfere with affective processes[39]. This raises the possibility that the increased ICSS behaviors we are observing after STN HFS does not result from increased affective experience of rewards in general, but rather to an increase in the incentive salience associated with HFS. A recent study investigating the reward representation of ICSS in the VTA, whether general or specific, supports the idea that specific frequencies of stimulation function to create a sensory event that acts as reward, in its own right. By using the Pavlovian-to-instrumental transfer effect, they showed that 50Hz, but not 20Hz, stimulation of dopamine neurons produced strong ICSS behavior, acting as a distinct reward to motivate behavior [40]. Multiple studies show that STN inactivation, whether by lesion or high-frequency stimulation (HFS), increases motivation for sweet foods[9,10]. The current study uses the ICSS procedure during an FR1 schedule, demonstrating that rats self-administer HFS (130Hz) due to the pleasurable impact of the reward consumption[41] and implies a reward enhancing effect of HFS on sweet food. In the naïve rats, only 130Hz was shown to be rewarding, providing further evidence that only specific high frequencies of stimulation will produce the rewarding effects in the targeted brain regions.

An intriguing aspect of the STN is its ability to modulate incentive motivation differently depending on the type of reward, such as "natural rewards" versus substances of abuse. Indeed, STN HFS or inactivation through lesions can have varying effects based on the type of reward (alcohol, cocaine, and food) and the subject' preferences. STN lesions increase motivation for alcohol in rats with a high alcohol preference, while decreasing it in those with a low preference[42]. Conversely, STN DBS at 130Hz can reduce alcohol intake over time after loss of control (escalation)[43]. Additionally, STN DBS, lesions, and inactivation with the GABA-antagonist muscimol increase motivation for sucrose, while decreasing motivation for cocaine[9,10]. These pioneering studies highlight the STN's dissociative role in modulating motivation for food versus cocaine, suggesting its potential as a target for addiction treatment[8]. However, the precise mechanism behind the dissociation of motivation remains unclear and has yet to be fully understood.

There has been much work to uncover the mechanism of HFS on the STN since its efficacy as a treatment for the tremor of PD was established[44]. Despite progress in the field in understanding the neural mechanisms underlying the behavioral changes caused by HFS, there are still many possible hypotheses under debate, one of which is that 130Hz DBS stimulation improves motor symptoms through inhibition of the STN neurons. Previous studies have proposed short term depression as a mechanism of DBS action in the STN[45–48]. Our current study gives further credence to this theory: electric high frequency stimulation and optogenetic inhibition produced an increased ICSS behavior in contrast to low frequency electric stimulation and high frequency optogenetic simulation. The fact that optogenetic inhibition of STN neurons replicated the effect of electric 130Hz stimulation in these experiments argues in favour of an inhibitory effect. However, the differences observed in the perseverative responses and the late emergence of the ICSS behavior in optogenetic inhibition suggests additional factors involved in electrical deep brain stimulation, not present in the optogenetic experiments. One factor that may account for the different effects seen in optogenetic vs electrical results may be the lack of precision in the applied electrical stimulation, since the application of electrical frequencies to the STN can have direct effect on STN neurons, but can also activate passing fibers as well as afferent and efferent connections[35], producing unintended antidromic effects in connection and stimulation of the passing fibers. The connection between the limbic cortex and the medial STN[37] may explain the increase in ICSS responses during HFS in rats observed in this study, as these regions are involved in reward processing and the PFC has been demonstrated to be antidromically activated following STN DBS[35]. Since selective STN neuronal inhibition induces the same ICSS effect, it is unlikely that it results from an antidromic direct effect on cortical activity. On the other hand, it is unlikely that ICSS observed here could result from a cortically-related mechanism since PFC-STN is an excitatory glutamatergic projection, but it is HFS of STN, that is supposedly inactivating the structure, or its neuronal inhibition, that induce a rewarding effect. Overall, the results indicate that the inhibition of STN neurons is necessary to significantly increases ICSS responses, and this effect grows stronger over time.

In animals previously exposed to cocaine self-administration, the rewarding effect of STN DBS was facilitated, since it started with 30Hz only in those animals. STN manipulation has been shown to affect cocaine self-administration. Indeed, while neither lesions nor HF-DBS modify cocaine self-administration in rats under FR1 schedule, both reduce

animals' willingness to work to self-administer the drug in a PR task [9,10]. There is also evidence that different DBS frequencies have varying effects on behaviors depending on the stage of addiction. For example, 130Hz reduces cocaine relapse in rats[15], while 30Hz reduces compulsive cocaine seeking[18]. During addiction, reward sensitivity can be dysregulated. We thus determined if the STN ICSS effect was shifted in rat with cocaine history. We showed that rats with a history of cocaine use increased ICSS responding when 30 and 130Hz was applied, suggesting a shift in reward sensitivity following drug use. These results demonstrate that, unlike for naïve rats, after a period of withdrawal from cocaine, 30Hz STN stimulation appears rewarding and pleasurable. Withdrawal from cocaine and nicotine is associated with deficits in brain reward function and a decrease in electrical ICSS, interpreted as reward attenuation following withdrawal[49,50]. Acting as a possible alternative reward to cocaine, it could explain why this frequency has been shown to reduce compulsive drug-seeking in pathologically addicted individuals[18]. To note, this significant increase in rats with cocaine history might be due to a lower, but not significant, level of ICSS responding at 8Hz when compared with the naïve rats. Similar interpretation could be used to explain the beneficial effect of 130Hz at preventing relapse after a period of abstinence following escalation of cocaine intake[15]. If we consider that STN DBS applied at 130Hz, like in PD patients, is rewarding and therefore affects reward sensitization, it could also explain why L-dopa addiction was reduced by STN DBS in PD patients suffering from severe Dopamine dysregulation syndrome [1,21,51].

These latter observations highlight how STN manipulation interferes with DA dysregulation, when DA is lacking (in PD patients), but also when DA is stimulated (with L-DOPA or cocaine). In line with this evidence, some studies have indicated that there is an enhanced perception of the rewarding nature of food stimuli in Parkinson's disease patients following STN-DBS, which has been linked to increased food consumption and weight gain, a common non-motor consequence of the treatment[38,52,53]. Interestingly, a recent study combining functional magnetic resonance imaging (fMRI) with a novel version of the Stop Signal Task (which incorporated images of cocaine versus neutral pictures) showed the involvement of the right STN in the control of inhibition among individuals with cocaine use disorder (CUD). Additionally, it was found that the craving for cocaine in CUD participants positively correlated with the STN activity during inhibition in the presence of cocaine cues[54]. Due to conflicting results in the literature, neurologists are unable to predict the deleterious psychiatric side effects that may occur

in PD patients after STN DBS, such as increase in impulsive behavior, a rise in depression and apathy, mania, and aggressive behaviors[55], highlighting the complex and multifaceted results the treatment can have. This may be due in part to the placement of the electrode and the management of medications and stimulation parameters post-operatively.

The STN is indeed a reward processing center within the basal ganglia, processing both wanting and liking in a complex system based on the incentive salience of the reward. 130Hz electrical DBS and optogenetic inhibition of STN neurons increased ICSS responding. The similar effect of electrical DBS and optogenetic inhibition of STN confirms that inhibition of STN neurons is necessary for ICSS and that the rewarding effect of ICSS observed with STN HFS is mostly STN specific and only mildly related to nonspecific electric diffusion in other brain areas.

Conclusion

The findings that the STN supports ICSS behavior highlight the potential of targeting the STN for addiction-related behaviors. STN DBS has proven effective in reducing compulsive behaviors in PD and OCD patients without diminishing the desire for natural rewards, suggesting its promise in addressing drug addiction. Thus, stimulating the STN at high frequency could provide an alternative reward to drugs of abuse. The STN is the most frequent target of DBS in clinical trials around the world [56], thus this study is essential to understanding the effect of DBS in a non-disease model.

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Author’s roles

YP, ATC, CV, MD & CB designed the experiments

MW, ATC and YP performed the electrical DBS experiments

CV, ATC and MD performed the optogenetic experiments

MW, YP, MD and CB wrote the manuscript

Declaration of competing interest

The authors declare no competing interest

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Figures

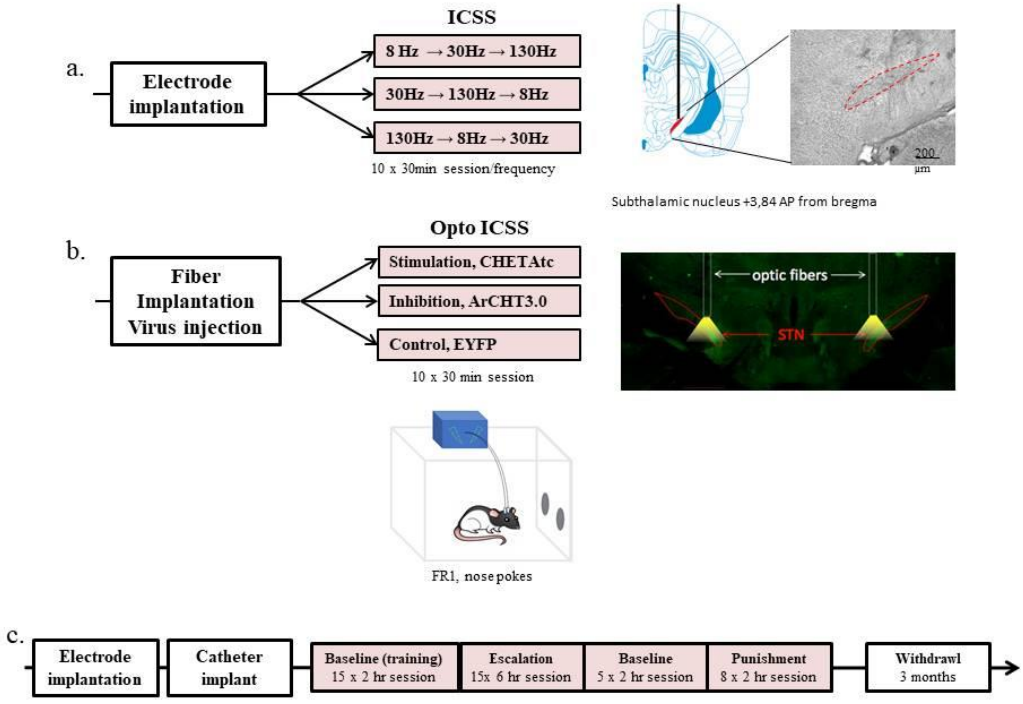

Figure 1: Timeline of behavioral experiments.

(a) Timeline of electrical STN DBS ICSS experiments (left) and example of an electrode implant in the STN (right).

(b) Timeline of optogenetic ICSS experiments (left) and an example of GFP expression within the STN (right)

(c) Timeline of cocaine self-administration experiments of rats with a history of cocaine use.

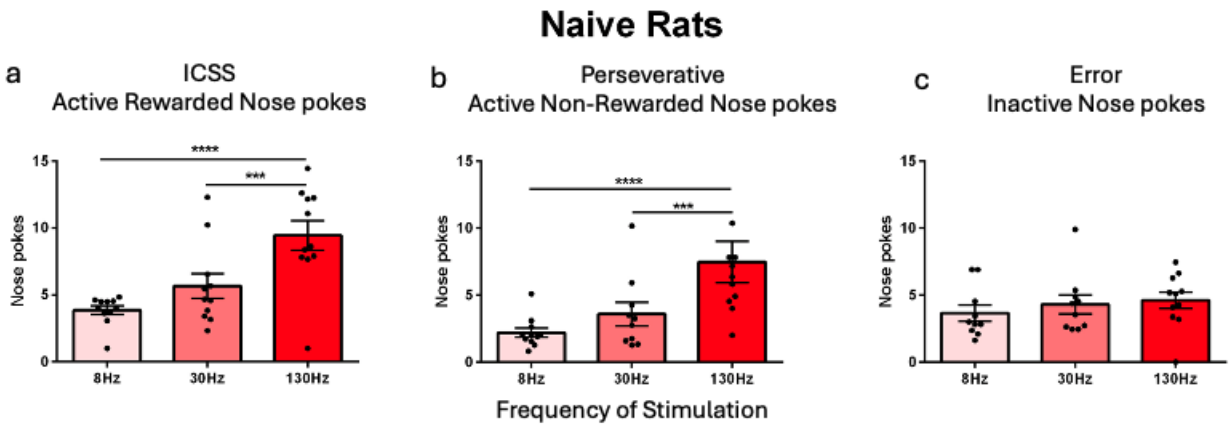

Figure 2: High frequency stimulation of 130Hz increases ICSS responding in naïve rats (n=13).

(a) LMM showed a main effect of the frequency of stimulation on the correct ICSS response ($\chi^2(2) = 19.00$, $p = 7.45e^{-5}$). ICSS responses were highest for 130Hz stimulation (mean = 10.30 ± 2.98), compared to 30Hz (mean = 5.99 ± 2.12) and 8Hz (mean = 4.14 ± 1.04).

(b) The LMM showed a main effect of the frequency of stimulation on perseverative responses ($\chi^2(2) = 14.50$, $p = 7.09e^{-4}$). There was increased perseverative responses for 130HZ HFS (mean = 8.01 ± 3.13) when compared to low frequency stimulation 30Hz (mean = 3.58 ± 1.64) and 8Hz (mean =2.22 ± 0.90).

(c) The frequency of stimulation had no main effect on error responses in naïve rats ($\chi^2(2) = 0.56$, $p = 0.76$). They exhibited a low level of responding in the inactive nose hole (130Hz (mean = 5.08 ± 1.40)); 30Hz (mean = 4.29 ± 1.60); 8Hz (mean =3.65± 1.28). Data in the graph are expressed as mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

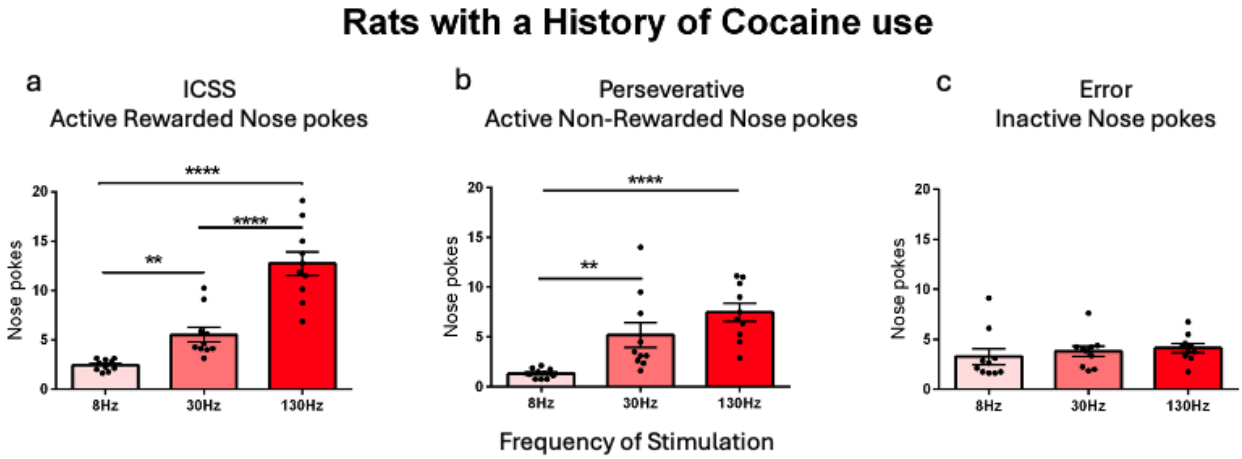

Figure 3: Rats with a history of cocaine use increased ICSS responding for 130Hz and 30Hz stimulation (n=8).

(a) LMM showed frequency of simulation had a significant effect of on the correct ICSS responses ($\chi^2(2) = 30.21$, $p = 2.76e^{-7}$). Mean ICSS responses were greater during 130Hz (mean = 12.74 ± 2.93) and 30Hz (mean = 5.51 ± 1.44) stimulation than 8Hz (mean = 2.44 ± 0.54).

(b) Perseverative responses were also significantly greater with HFS, the LMM revealing a main effect of frequency of stimulation ($\chi^2(2) = 10.53$, $p = 0.005$). Mean responses were higher during 130Hz (mean = 7.48 ± 3.04) and 30Hz (mean = 5.18 ± 2.04) but lower during 8Hz (mean = 1.33 ± 0.62).

(c) The frequency of stimulation had no significant effect on error responses ($\chi^2(2) = 0.21$, $p = 0.90$). There was no significant difference in error responses across stimulations 130Hz (mean = 4.13 ± 1.22), 30Hz(mean = 3.80 ± 1.11), and 8Hz (mean = 3.28 ± 1.57). Data in the graph are expressed as mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

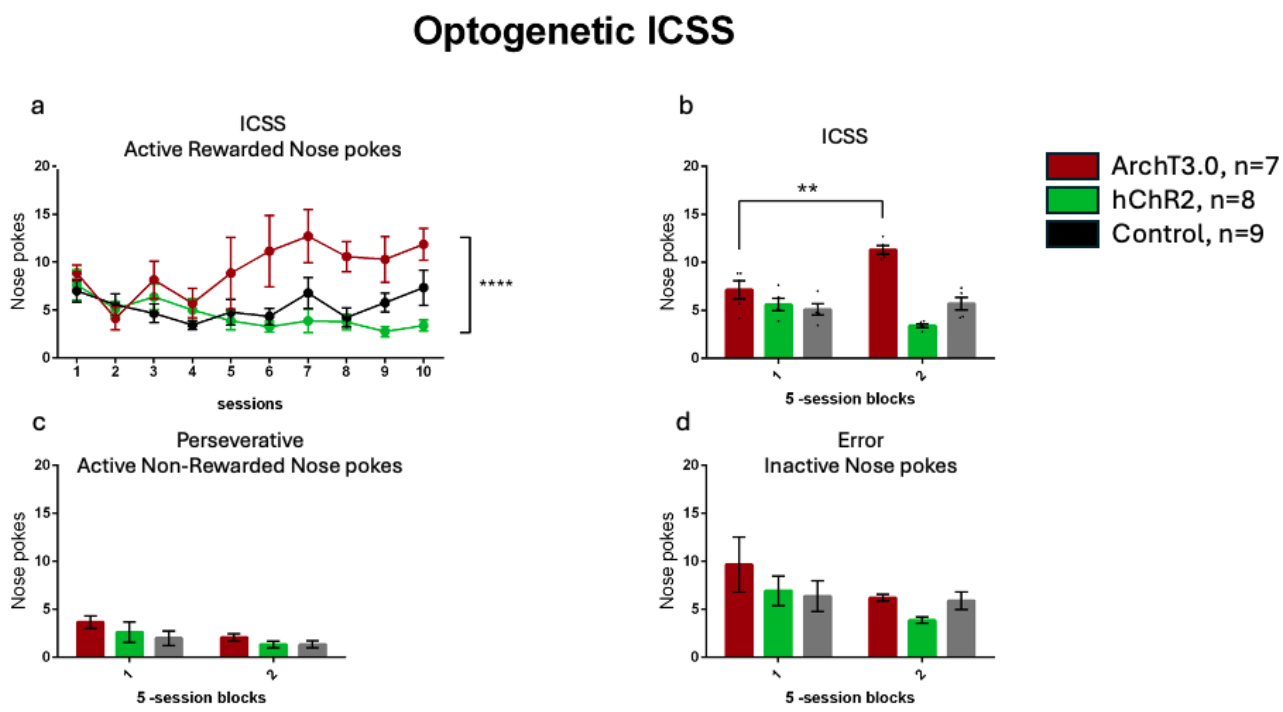

Figure 4: Inhibition of STN neurons increases ICSS responses

(a) Inhibition (red line and bars, ArchT3.0, n=7) of STN neurons increased ICSS responses over time. Stimulation (green line and bars, hChR2, n=8) and control (grey line and bars, EYFP, n=9) groups remained stable in ICSS responding. Repeated measures two-way ANOVA on the effect of photomodulation and blocked (first 5 vs last 5) sessions on ICSS responses. The analysis revealed a significant main effect of photomodulation on ICSS responses, ($F(2,12)= 42.06$, $p<0.0001$).

(b) Post hoc pairwise comparison using Bonferroni's test revealed for the inhibition group, ICSS responses during the first 5 session (mean =7.143 ± 1.856) were significantly different ($p=0.0028$) from the second sessions (mean=11.314 ± 2.42), indicating a significant increase over time. There was no difference in ICSS responding in the stimulation group (first block (mean =5.6 ± 1.153) vs second (mean =3.4 ± 0.735) $p=0.1218$) nor in the control group (first block (mean =5.089 ± 1.01) vs second (mean =5.689 ± 1.259) $p=0.999$)

(c) There was no significant effect of optogenetic manipulation ($F(2,12)= 1.776$, $p=0.2110$), on perseverative responses. There was no difference in perseverative responses in the inhibition (first block (mean = 3.66 ± 1.36) vs second (mean = 2.06 ±

1.09) p=0.3137) stimulation group (first block (mean =2.6 ± 1.01) vs second (mean =1.325 ± 0.757) p=0.5611) nor in the control group (first block (mean =1.98 ± 0.69) vs second (mean =1.33 ± 0.517) p=0.9999)

(d) There was no significant effect of optogenetic manipulation on error responses ($F(2,12)= 1.468$, p=0.2689). There was no difference in perseverative responses in the inhibition (first block (mean = 9.657 ± 3.42) vs second (mean = 6.20 ± 1.479) p=0.4346) stimulation group (first block (mean =6.925 ± 1.89) vs second (mean =3.85 ± 0.949) p=0.5720) nor in the control group (first block (mean =6.11 ± 1.24) vs second (mean =5.86 ± 1.24) p=0.9999). Data in the graph are expressed as mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Supplementary

Electrode and Fiber optic implant design

Electrodes were made of Platinum-Iridium wires coated with Teflon (75µm). Coating was removed over 0.5mm at the tips and two wires were inserted into a 16mm long 29G stainless steel tubing to form an electrode. Two of these electrodes, separated by 4.8mm (twice the STN laterally), were soldered to an electric connector, allowing connection with a stimulator. Electrodes were tested with an isolated battery to avoid electrical short circuits. Electrodes (impedance = 20kΩ ± 2.25) and connector were subsequently deeply bound, using a custom mold and dental cement.

Fiber optic implants were built with 230µm optic fibers (NA 0.22, Thorlabs) glued to 2.5mm ceramic ferrules (Thorlabs) using epoxy. Ferrules were slightly grinded with a Dremel to improve the contact with the dental cement.

Rats with a history of cocaine use

Intravenous cocaine self-administration behavioral testing commenced week post-operation (0.25 mg/90 µl per injection). Rats were trained in a 2 h session to press the seeking lever, when successfully pressed released a taking lever on the adjacent side of the operant chamber. After 15 days of training, with 3 consecutive days of stable cocaine intake, rats advanced to the escalation protocol for 15 days. During 6hr escalation session,

rats were allowed to press a taking lever every 20s. After escalation, 5 baseline sessions were run, in which the rats were presented with a seeking lever, when pressed initiated waiting period of between 72-240 ms. After the waiting period, the taking lever was presented and rats were allowed to press for a cocaine injection. After 5 days of baseline training, rats were placed in Punishment protocol for 8 days. The punishment protocol allows us to differentiate compulsive rats (resistant to the foot-electric chock, that continue to look for cocaine and overlooked the possible negative consequence) from non-compulsive rats (sensible to the shock). During the 2 h punished seeking session, rats were allowed to press to receive a cocaine injection or 50% chance of a mild foot shock (0.5 mA and 0.5 s). There was a 3-month period of withdrawal, with no behavioral testing, passed before these rats were used for ICSS experiments.

Histology and Immunohistochemistry

Brain slices were mounted directly on Superfrost Plus, Adhesion slides (VWR, 631-0108). Histological controls, for ICSS position of the electrodes were performed after staining with cresyl violet (Figure 1a) and coated with Eukitt mounting medium (Sigma, 03989) and glass cover slides (VWR, 631-1575) and allowed to dry. Rat brain slices from optogenetic experiments were processed with immunohistochemistry. Brain slices were washed with PBS 3 times, permeabilized with PBST(0.4% Triton in PBS) for 30min at room temperature, then incubated overnight at 4°C with primary antibody anti-GFP (Life technologies A11120, 1:200). The following day, slices were washed 3 times with PBS and incubated for 2hours with secondary antibody (Goat anti mouse IgG, Alexa Flour 488, life technologies A11001, 1:400). Slides were coated with homemade fluoromount aqueous mounting medium and covered with glass cover slides (VWR, 631-1575) and allowed to dry. Slides were observed under Apotome.2 Microscope (Zeiss, 423667-7144-002) (Figure 1b). Subjects were excluded from final analysis for missed electrode, virus, or fiber optic implant placement.

4.2. Recording the hyperdirect pathway

Aim:

The increasing burden of drug addiction on society and the challenge of treating addicts has been the focus of much research in the past decades. DBS has been employed to treat psychiatric disorders like OCD and treatment-resistant depression (Mallet et al., 2008; Mayberg et al., 2005). Recent research from our lab has highlighted the as a promising target for treating addiction (Pelloux & Baunez, 2017). Manipulating the STN through lesion or DBS has been shown to reduce motivation for drugs such as cocaine while simultaneously increasing motivation for natural rewards like sweet food (Baunez et al., 2005; Rouaud et al., 2010). Additionally, STN manipulations prevent key addiction behaviors, such as the escalation of drug intake and compulsive drug-seeking behavior (Pelloux et al., 2018; Degoulet et al., 2021.

Since the STN is an integral hub in the basal ganglia and receives direct cortical projections via the "hyper-direct pathway," it is crucial to investigate the specific role of this pathway in modulating addiction-related behaviors observed with STN manipulation. The current project aims to clarify the network's involvement in addiction, using calcium imaging (fiber photometry) to monitor neural dynamics in the hyper-direct pathway during motivational assessments for sucrose or cocaine in rats.

Although we conducted experiments during FR1 and PR schedules with both cocaine and sucrose, here we report only the results from the sucrose experiments. Recordings during cocaine self-administration were too noisy and lacked discernible signals due to poor light conduction caused by the optical rotary joints and homemade patch cords, which did not meet the minimum light conduction requirements.

The IL, PL, and ACg were the target regions for this study. A Cre-dependent genetically encoded calcium indicator (GECI) virus was injected into these areas, along

with Cav2-Cre into the STN for retrograde labeling. Optic fibers implanted above the STN enabled the recording of calcium activity in IL-STN, PL-STN, and ACg-STN projections during fixed and progressive ratio schedules for sucrose. We also recorded calcium signals from a population of STN neurons during these behaviors.

Main Results:

Here, we demonstrate that the hyperdirect pathway is activated during motivated sucrose reward behaviors. Specifically, the PL and ACg projections to the STN show decreased activity following the last correct response of the progressive ratio. Additionally, STN neuron activity decreases during entry into the food port. These findings offer a more detailed understanding of the specific STN networks involved in motivated behaviors, potentially informing more precise therapeutic targets for treating substance use disorders and providing insights into the side effects observed in PD patients undergoing STN-DBS.

The Neural Dynamics of the Subthalamic Nucleus hyperdirect pathway during 'natural' reward seeking behavior

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Abstract

DBS has been used for the treatment of some psychiatric disorders such as obsessive-compulsive disorders and treatment-resistant depression. Our lab's work on motivational processes has positioned the STN as a very interesting target for addiction treatment since its inactivation by lesion or DBS can reduce motivation for cocaine, while increasing motivation for sweet food and also prevent some criteria of addiction such as escalation (loss of control over drug intake) or modulate compulsive cocaine seeking. Since the STN is a hub of the Basal ganglia and receives direct cortical projections, referred to as the "hyper-direct pathway", it is important to clarify the role of this pathway in the effects observed after STN manipulations on addiction-like behavior. This project thus seeks to clarify the specific role of STN and its network in addiction-related behavior. We have used calcium imaging (fiber photometry) to observe neural dynamics of the hyper-direct pathway during behavioral assessments of motivation for sucrose in rats. The IL, PL, and ACg were targeted with an injection of a Cre-dependent-GECI adeno virus combined with a Cav2-Cre injected in the STN for retro labeling. Optic fibers were implanted above the STN, so that IL-STN, PL-STN, and ACg-STN projections' calcium activity could be recorded during fixed and progressive ratio schedules for sucrose. Results show differential activity in the various hyper-direct pathways. The PL and ACg projections to the STN show decreased activity following the last correct response of the ratio. Additionally, STN neuron activity decreases during entry into the food port. This should help better define the specific network involving the STN that should be targeted for the treatment of addiction.

Introduction:

DBS targeting the STN was first introduced as a treatment for the motor symptoms of PD in 1995 (Limousin et al., 1995). More recently, the STN has been implicated in non-motor disorders such as depression, OCD, and SUD, due to its role in motivational processes (Baunez & Lardeux, 2011). While DBS has proven effective, the precise mechanisms underlying its effects, particularly in non-motor symptoms, remain unclear.

The STN has been identified as a input structure within the basal ganglia, receiving direct cortical projections through the hyperdirect pathway (Nambu et al., 2002). Previous research from our lab has demonstrated that STN lesions and HFS can reduce motivation for cocaine without affecting the drive for natural rewards like food (Rouaud et al., 2010). These findings suggest that DBS may selectively modulate reward processing, making it a promising intervention for SUD, where conventional pharmacological treatments remain inadequate.

A key consideration when using DBS is the non-selective electrical input, which can activate not only the target site but also afferent, efferent, and passing neuronal fibers (Maurice et al., 1998, 1999; Li et al., 2012). This widespread activation can complicate our understanding of how DBS affects motivation and behavior. Given that the STN is connected to the PFC through the hyperdirect pathway (Nambu et al., 2002), this pathway my play a crucial role in integrating cognitive and motor processes, contributing to behavioral inhibition and decision-making (Groenewegen & Berendse, 1990). This suggests that the STN may act as a "gatekeeper" for action selection, particularly under conditions involving valuable rewards (Frank, 2006).

The hyperdirect pathway, composed of excitatory glutamatergic inputs from the PFC, is essential for controlling attention, inhibitory responses, and motivation (for review, Baunez & Lardeux, 2011). Its involvement in integrating cortical and striatal information suggests that the STN could be an important target for treating psychiatric disorders like OCD and addiction (Mallet et al., 2008; 2019). However, the precise contributions of the STN in integrating both direct cortical and indirect striatal information are still not fully understood.

The rodent mPFC can be divided into ACg, PL, and IL based on considerations such as cytoarchitecture and connectivity (Heidbreder & Groenewegen, 2003; Ongür & Price, 2000). More recent studies using viral tracing methods have mapped out the sub-territories of the STN receiving projections from the mPFC regions that terminate in the medial limbic area of the STN (Kita & Kita, 2014). To investigate the role of the hyperdirect pathway in addiction-related behaviors, this project focused on limbic projections from the cingulate, prelimbic, and infralimbic cortices. By employing fiber photometry, this study sought to monitor these pathways during motivated behaviors, allowing for real-time observation of neural dynamics in freely moving animals.

The primary goal of this thesis is to understand the pathological motivations driving drug-taking behavior, using the PR task, which requires increasing effort for a reward and models human addiction behaviors. Intervening at this stage of addiction may help vulnerable individuals before they reach the more severe stages of the addiction cycle, where relapse becomes prevalent after failed attempts to quit. By targeting the hyperdirect pathway, this study hopes to uncover new insights into how the STN influences motivation and behavioral control, offering potential pathways for therapeutic intervention in addiction.

Materials and Methods:

Animals

40 Adult Lister Hooded males (~380g, Charles River) used in the experiments were housed in groups of two in Plexiglas cages and maintained on an inverted 12h light/dark cycle (light onset at 7pm) with food and water available ad libitum, in a temperature and humidity-controlled environment. All experiments were conducted during the dark cycle (8am-7pm). Animal care and use conformed to the French regulation (Decree 2010-118) and were approved by local ethic committee at the University of Aix-Marseille, under the French ministry of Agriculture authorization #03129.01.

Surgeries

Once rats reached ~400g, they were anesthetized with ketamine (Imalgene, Merial, 100mg/kg, *i.p.*) and medetomidine (Domitor, Janssen 30 mg/kg, *i.p.*), reversed at the end of the surgical procedure with an injection of atipamezole (Antisedan, Janssen, 0.15 mg/kg, *i.m.*).

They also received an antibiotic treatment with amoxicillin (Duphamox, LA, Pfizer, 100 mg/kg, *s.c.*) and were administered meloxicam (Metacam, Boehringer Ingelheim, 1 mg/kg, *s.c.*) for analgesia. Animals were placed in the stereotaxic frame (David Kopf apparatus) for 0.50 µL bilateral injections of virus into the STN (with tooth bar set at -3.3 mm), at STN at the coordinates AP: −3.7/+5.3mm; L: ±2.4mm; DV: −8.35/+1.65mm, from bregma and interaural point respectively (and further averaged), and incisor bar set at −3.3mm. The PFC regions were injected with 1.0 µL of virus at the following coordinates: PL: AP: -3.2/+12.2mm; L: ±0.8mm; DV: -3.4/+6.6mm; ACG: AP: -1.5/+10.5mm; L: ±0.8mm; DV: -3.0/+7.0mm; IL: AP: -3.0/+12.0mm; L: ±0.6mm DV: -5.2/+4.8mm from bregma and interaural point respectively (and further averaged) (Paxinos & Watson 2007). The virus was allowed to incubate three weeks before fiber photometry experiments began. For recording fiber photometry, optic fibers (200µm, NA 0.37, ferrule 1.25mm, length: 10mm, Neurophotometrics) were implanted in 0.05 mm above each injection site and maintained within a head-cap made of dental cement on the skull.

Viruses

Experiment 1: This first experiment was to pilot the study and use fiber photometry for the first time in the lab, recoding from cell bodies of the IL and STN at the same time on contralateral sides. Rats (n = 2) were bilaterally injected with AAV9.Tre3.Gcamp7f and AAV9.mThyl (NeuroBioTool, Aix Marseille). The first injection was in the IL and the second injection was in the STN, on the contralateral side. Fiber probes were implanted above the injection site at IL and STN.

Experiment 2: In our first attempt to record the hyperdirect pathway, we bilaterally injected AAV1.Tre.GCamp7f + AAV1.mThyl into PFC areas (IL, n=2; PL, n=2; ACG, n=2). The optic fibers were implanted at the axon terminals in the STN.

Experiment 3: In order to better target the projection from the PFC to the STN (the hyperdirect pathway), in a third experiment we used Cre-dependent GCamp along with the retrograde canine adenovirus. Rats were bilaterally injected with pGP-AAV-syn-FLEX-jGCaMP8m-WPRE (Addgene # 162375) in PFC (IL, n=5; PL, n=5; ACg, n=6). The retrograde virus, Cav2-Cre (Plateforme de Vectorologie de Montpellier) was bilaterally injected into the STN to achieve projection specific infection of the hyperdirect pathway. Fibers were implanted above the STN to record axon terminal at the STN.

Experiment 4: In the final experiment we again used Cre-dependent GCamp along with the retrograde canine adenovirus Rats were bilaterally injected with pGP-AAV-syn-FLEX-jGCaMP8m-WPRE (Addgene # 162375) in PFC (IL, n=4; PL, n=4; ACg, n=4). The retrograde virus, Cav2-Cre (Plateforme de Vectorologie de Montpellier) was bilaterally injected into the STN to achieve projection specific infection of the hyperdirect pathway.

Additionally, we injected the STN of rats (n=4) with the cell body specific AAV9-HSYN_RIBO-jGcamp8m (NeuroBioTool, Aix Marseille) in order to record the neural dynamic of the STN neurons only.

Importantly, in this final experiment, the stereotaxic surgery for virus injections were performed under general anesthesia (3.0-5.0 % isoflurane) while they also received an antibiotic treatment with amoxicillin (Duphamox, LA, Pfizer, 100 mg/kg, *s.c.*) and were administered meloxicam (Metacam, Boehringer Ingelheim, 1 mg/kg, *s.c.*) for analgesia.

Optic fibers also differed in these experiments, utilizing a larger ferrule and core diameter than in previous experiments (400µm, NA 0.5, ferrule 2.5mm; length: 10mm at STN and IL, 5mm at ACg and PL) (RWD)

Behavioral experiment

Food self-administration

Rats were trained to nose-poke for 65% sucrose pellets under a FR1 in standard rat operant chambers equipped with two nose-poke holes (MedAssociates). Nose-poke in the active hole leads to 5-sec illumination of an associated cue-light and delivery of the reward in the food magazine on the opposite wall. Nose-poke in the inactive hole had no consequences. The ratio was increased to FR5. FR5 sessions lasted 30 min. When rats showed a stable consumption (<20% of variation) during 3 consecutive days. A minimum of 4 sessions were recorded with fiber photometry for each rat (recording from right and left sides of the brain) during the 30min sessions of FR5.

Following this schedule, rats were subjected to the PR experiment, the ratios followed an arithmetically increasing schedule in steps of five, with three repetitions of each step (i.e., 1, 1, 1, 5, 5, 5, 10, 10, 10…). The sessions ended after 90min or after 5min without any active nose-poke. The last ratio completed was defined as the 'breakpoint'. A minimum of 4 session we recorded with fiber photometry for each rat (recording from right and left sides of the brain) during the entire sessions of PR.

Histology

At the end of the experiments, rats were deeply anesthetized via an i.p. injections with ketamine (Imalgene, Merial, 200 mg/kg) and medetomidine (Domitor, Janssen 60 mg/kg). They were perfused intra-cardiacally with 4% paraformaldehyde in PBS. Brains were extracted and after cryo-protection in 30% sucrose, they were frozen into liquid isopentane (-80°C), and finally cut in 40µm coronal slices with a cryostat.

Immuno-histochemistry staining was used to verify viral expression. After PBS rehydration (3 x 5 min), brain sections underwent a 90 min permeation step (PBS, 1% bovine serum albumin (BSA) 2% normal goat serum (NGS), 0.4% TritonX-100), PBS washes (3 x 5min) and incubation with primary antibody (mouse anti-GFP, A11120, Life technologies; 1:200, in PBS 1% BSA, 2% NGS, 0.2% TritonX-100) at 4°C overnight. Sections were then washed with PBS (3 x 5 min), followed by 2h incubation at room

temperature with secondary antibody (Goat anti-mouse Alexa 488, A11011, Life technologies, 1:400 in PBS 1% BSA, 2% NGS) and finally washed with PBS (3 x 5 min).

Brain sections of all animals were then mounted on to glass slides with homemade mounting medium and examined with an epifluorescence microscope (Zeiss, Imager.z2). Optic fibers' location and fluorescence expression are illustrated in Figure 3b. Histological verification was not conducted for Experiment 4, as the experiments with these animals are ongoing.

Fiber photometry procedures

We used a commercially available fiber photometry system for experiments 1-3 (Neurophotometrics). The 470-nm excitation light was adjusted to approximately 80–100 μW at the tip of the patch cord (fiber core diameter, 200 μm; Doric Lenses). In experiment 3, we use homemade fiber optic patch cords (fiber core 200 μm) polished to conduct 80-100 μW at the tip. Fibers were connected to a fiber optic rotary joint (HRJ-OL_FC-FC, Doric Lense) to reduce torque on animals and avoid bending or twisting of the patch cord in operant chambers. Fluorescence emission was passed through a 535-nm bandpass filter and focused onto the complementary metal-oxide semiconductor camera sensor through a tube lens. Samples were collected at 25 Hz using a custom Bonsai workflow. Timestamps of task events were collected simultaneously through an additional TLL from Med Associates interface, which sent 5V pulses coincident with task events. Signals were saved using Bonsai software and exported to MATLAB (MathWorks) for analysis.

In experiment 4, we used the commercially available fiber photometry system from RWD along with a pigtailed rotary joint (FRJ_1x1_PT, Doric Lense). The same parameters were used for signal acquisition; however the analysis was performed with the internal GUI from RWD.

Statistical analysis

We first extracted mean fluorescence intensity values recorded from calcium-dependent signal (470 nm) and isosbestic control signal (415 nm) LEDs. As the isosbestic

signal also undergoes decay across a session with photobleaching, we can use this to correct the calcium-dependent signal for photobleaching. To smooth out the potential effects of photobleaching and motion artifacts, each signal smoothed using a moving mean algorithm. To remove the slope and low frequency fluctuations in signals we performed baseline correction of each signal using the adaptive iteratively reweighted Penalized Least Squares (airPLS) algorithm. We then removed the first 60s of the data as this consistently had high variability in the signal and would disrupt the correction. We standardized each signal using the mean value and standard deviation using non-negative robust linear regression, we fitted standardized z410 to z470 signals to the regression function to obtain the change in fluorescence response (zdF/F or z-scores). This method was adapted from Martianova et al., 2019, with custom changes to fit our analysis.

Using the dF/F signal, we extracted the signal from each trial aligned with events such as reward delivery and entry into the food port. For Experiment 3, signals were also extracted around error and perseverative responses. We calculated the area under the curve (AUC) for the z-scores during the 3 seconds before and after each event. Prism software was used for statistical analysis, with a t-test employed to compare AUC values from the STN data, and a two-way ANOVA with post-hoc Bonferroni tests for the three hyperdirect pathways.

Results

Experiment 1

Histological verification from the first experiment confirmed the presence of fibers and virus in the STN and IL prefrontal cortex in one rat. One rat was excluded from the analysis. During a 30-min FR5 reinforcement schedule, the remaining rat self-administered sucrose while GCaMP signals were recorded. From this session, 800 seconds of data were analyzed (Figure 1). We detected spiking transients aligned with reward delivery during the behavioral session. Calcium activity was notably higher in the IL cortex, although STN neurons also exhibited increases in calcium signals during some reward delivery events. Peaks in the IL cortex were approximately twice as high as those observed in the STN (Figure 1b).

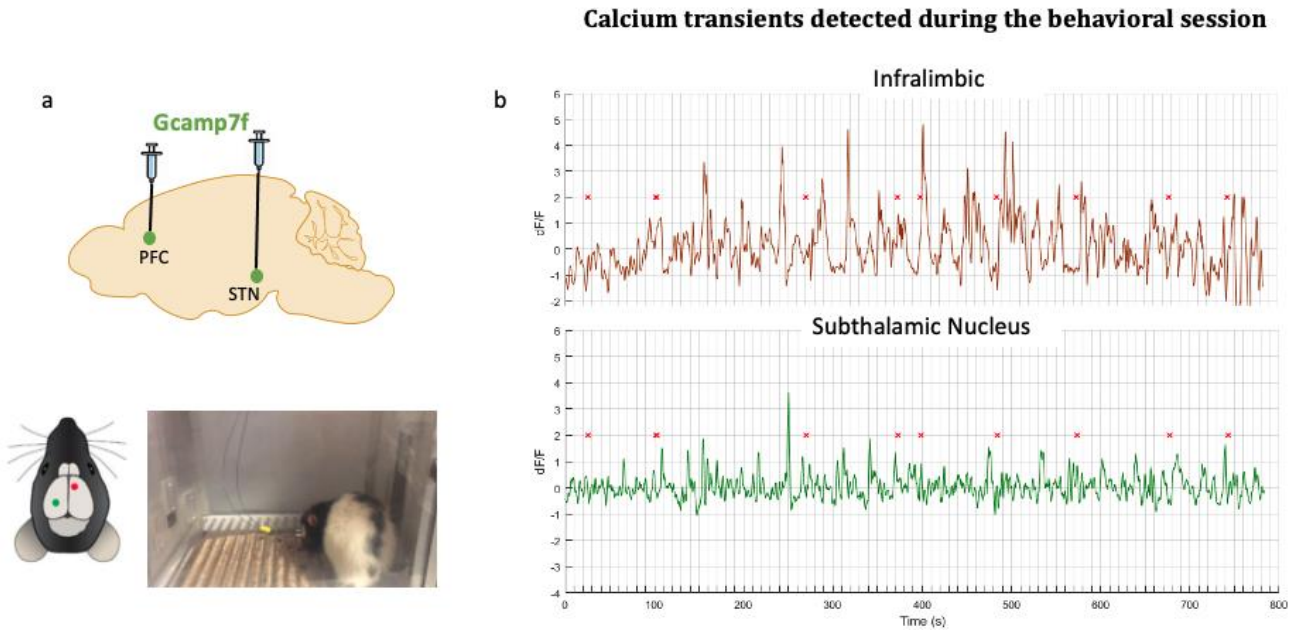


Figure 1. zdF/F signal from the IL and STN cell bodies of a rat confirm that Gcamp signals can be recorded in the freely behaving animals during a self-administration task. A) representation of the virus and fiber placement in Rat 25. The picture of a rat in the operant chamber, connected to fiber photometry patch cords before the behavioral experiment. This rat was performing self-administration for sucrose in a FR5 schedule of reinforcement. X represents the entry into the reward port. B) dF/F signals from Rat 25 during a single FR5 session, over a 800s period. zdF/F were analysed from the IL and STN on the contralateral sides during the same behavioral session.

Experiment 2

In the second experiment, rats were infected with an anterograde GCamp virus in the PFC and axon terminals were recorded in at the STN. One rat from each group was used for this analysis after histological verification of virus in the PFC and fiber implants at the STN. A single 30min session was analysed for each rat

with viruses injected into the PL (n=1), IL (n=1), and ACg (n=1) areas. During the 30 min session of sucrose self-administration experiment (highlighted in yellow), GCamp signals were recorded for 15min before, after, and during the FR1 session. No peaks in the signal were observed during the recording period for any of the rats (Figure 2).

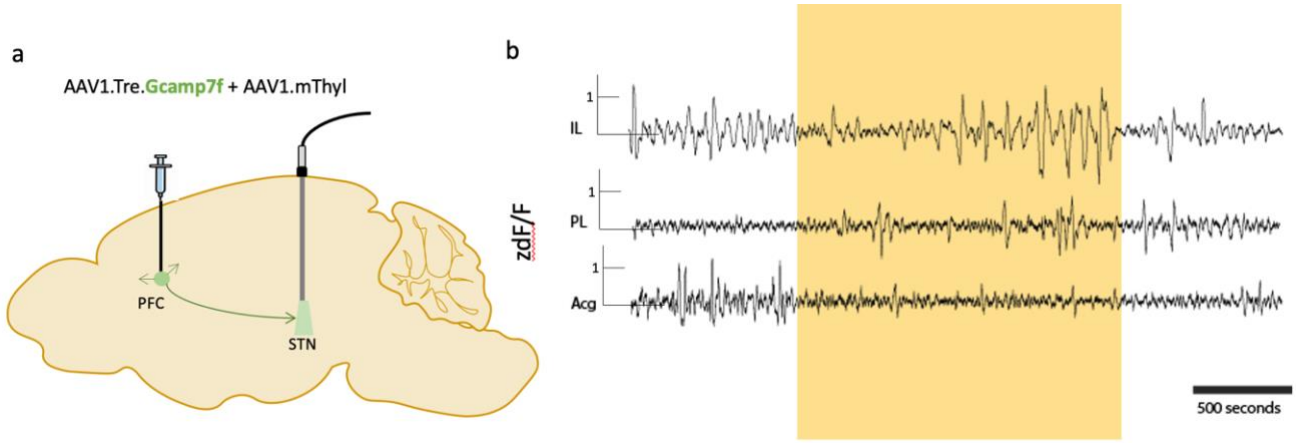


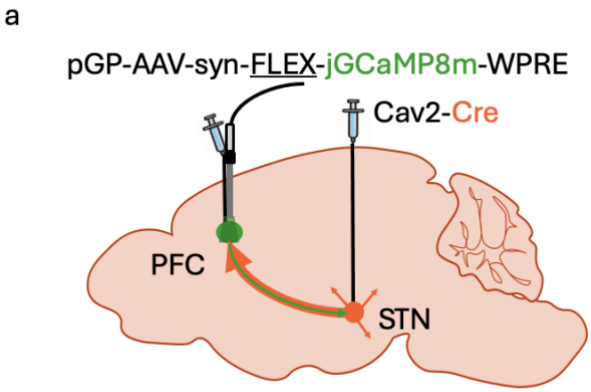
Figure 2. Recording GCamp signals at axon terminals for rats infected with anterograde virus in the PFC yields no significant peaks. a) Schematic of the virus injection in the PFC areas (IL n=1, PL n=1, Acg n=1) and fiber placement above terminals at the STN. b). Recordings during a single FR1 session which lasted 30 min. Yellow highlight the time of the behavioral experiments, so that recordings were taken 15 min before and after the behavioral session. zdf/f signals were all relatively flat during the recordings of the axon terminals.

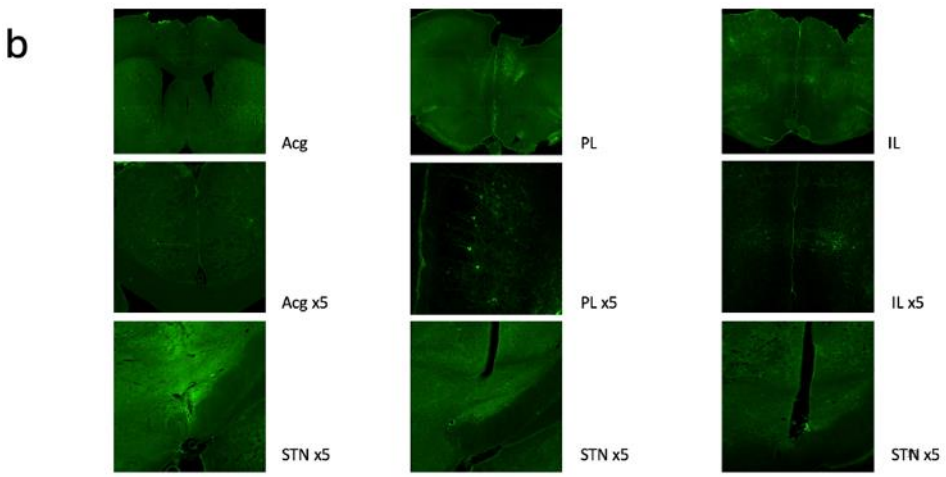
Experiment 3

In the third experiment, rats were infected with Cre-dependent GCaMP8m in the PFC areas and Cav2-Cre in the STN (Figure 3a). After histological verification, sparse labeling of PFC cells was observed (Figure 3b). We selected the best-labeled subjects (n=1 from each region, 1 session) with the least noisy dF/F signals and

normalized these into zdF/F (Figure 3c). Signals from 5 seconds before and after events (valid responses, error responses, perseverative responses, delivery of sucrose reward, and entry into the food port) were averaged across a single recording session during FR5 sucrose self-administration (Figure 3d).

In the ACg projection, there was a transient increase in GCaMP signal in the 5 seconds before both valid and error responses. In the PL projection, the GCaMP signal increased precisely at the moment of an incorrect response (0 seconds). The IL projections showed a trend toward increased activity 5 seconds after both the delivery of a sucrose reward and incorrect responses.





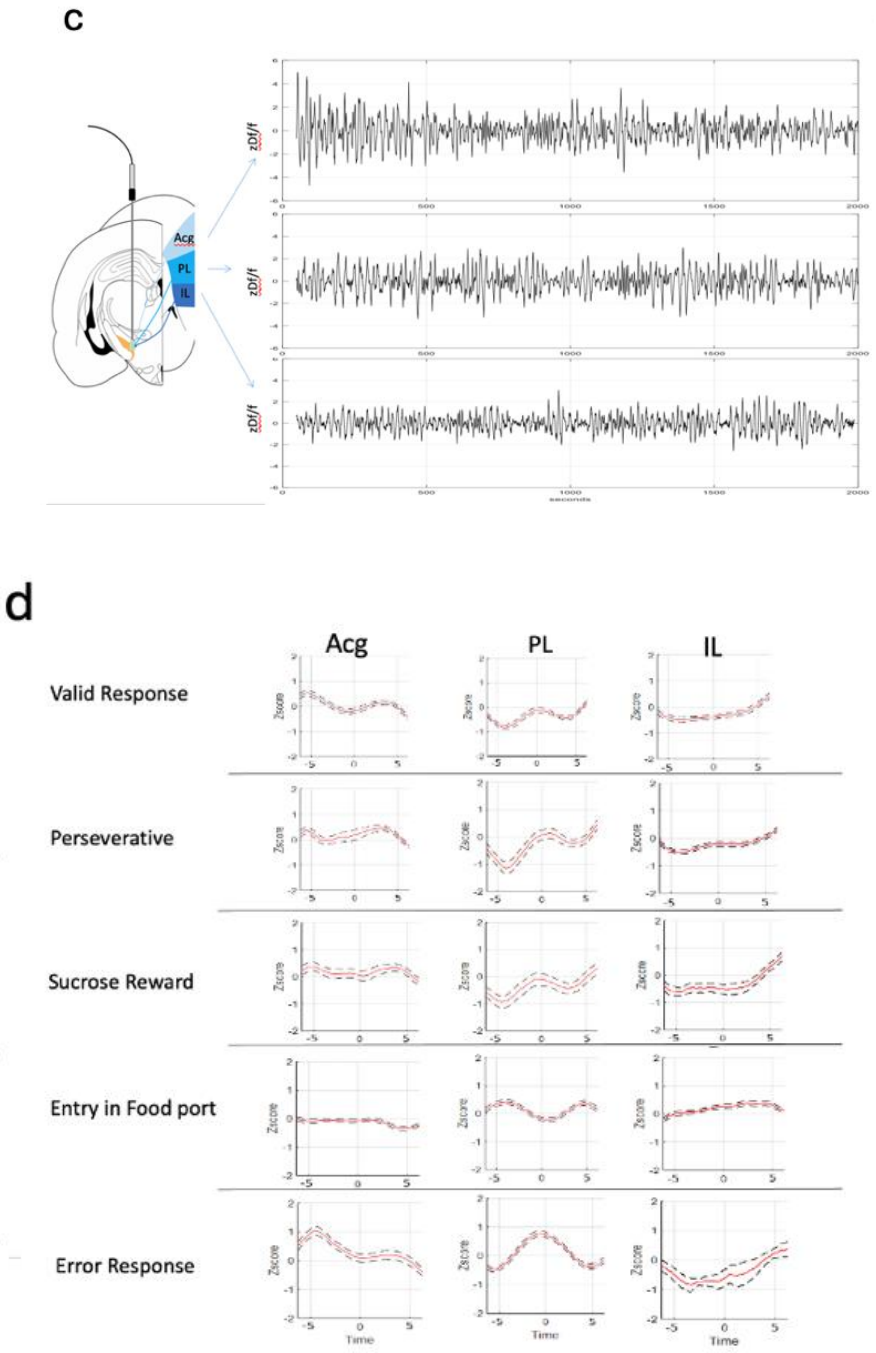


Figure 3. Recording the terminals of the hyperdirect pathway. a) illustration of the viral methods used to transfect the hyperdirect pathway with the GECI Gcamp8m. Fibers for recording were implanted above the STN. B) Histological verification of the virus in the PFC regions and placement of the fiber at the level of the STN. C) A single sessions whole 30min fiber photometry signal (zdf/f) from each the ACg n=1, PL n=1, and IL n=1. D) Isolation of the signals around the event, from the ACg, PL, and IL terminals. The mean is represented in black, while the standard deviation from the mean is represented in red.

Experiment 4

In the fourth and final experiment, we recorded hyperdirect pathway activity using Cre-dependent GCaMP8m in the PFC regions (ACg = 4, IL = 4, PL = 3) and Cav2-Cre injected into the STN during a PR task for sucrose rewards. Z-scores were measured for 3 seconds before and after both entry into the food port and reward delivery. Signal changes were evaluated by comparing the average area under the AUC before and after each event.

Results from the two-way ANOVA revealed a significant differences in the hyperdirect pathway signals during the 3 seconds surrounding last correct response of the ratio ($F(2,516) = 4.334$, $p=0.0136$; Figure 4a). There was also a significant effect of time ($F(1,516)=45.39$, $p < 0.0001$), and a significant interaction between time and pathway ($F(2,516)=5.860$, $p=0.003$). Post-hoc analysis revealed a significant decrease in the ACg-STN z-score signal during last correct response of the ratio ($t = 6.676$, $df = 516$, $p<0.0001$) and in the PL-STN signal ($t = 4.607$, $df = 516$, $p<0.0001$). There was no significant change in the IL-STN pathway z-score signal during reward delivery ($t = 1.057$, $df = 516$, $p=0.8737$; Figure 4).

There was also no significant difference in the hyperdirect pathway signals during food port entries ($F(2,510) = 2.317$, $p=0.0996$; Figure 4c). There was no significant effect of time ($F(1,516)=0.04972$, $p= 0.8236$), nor a significant interaction between time and pathway ($F(2,516)=1.405$, $p = 0.2464$). Post-hoc analysis showed no significant difference in the z-score signals pre- versus post-food port entry for the ACg ($t = 1.253$, $df = 510$, $p=0.6319$) PL ($t = 1.109$, $df = 510$, $p=0.8039$), or IL ($t = 0.2419$, $df = 510$, $p=1.0$; Figure 4d).

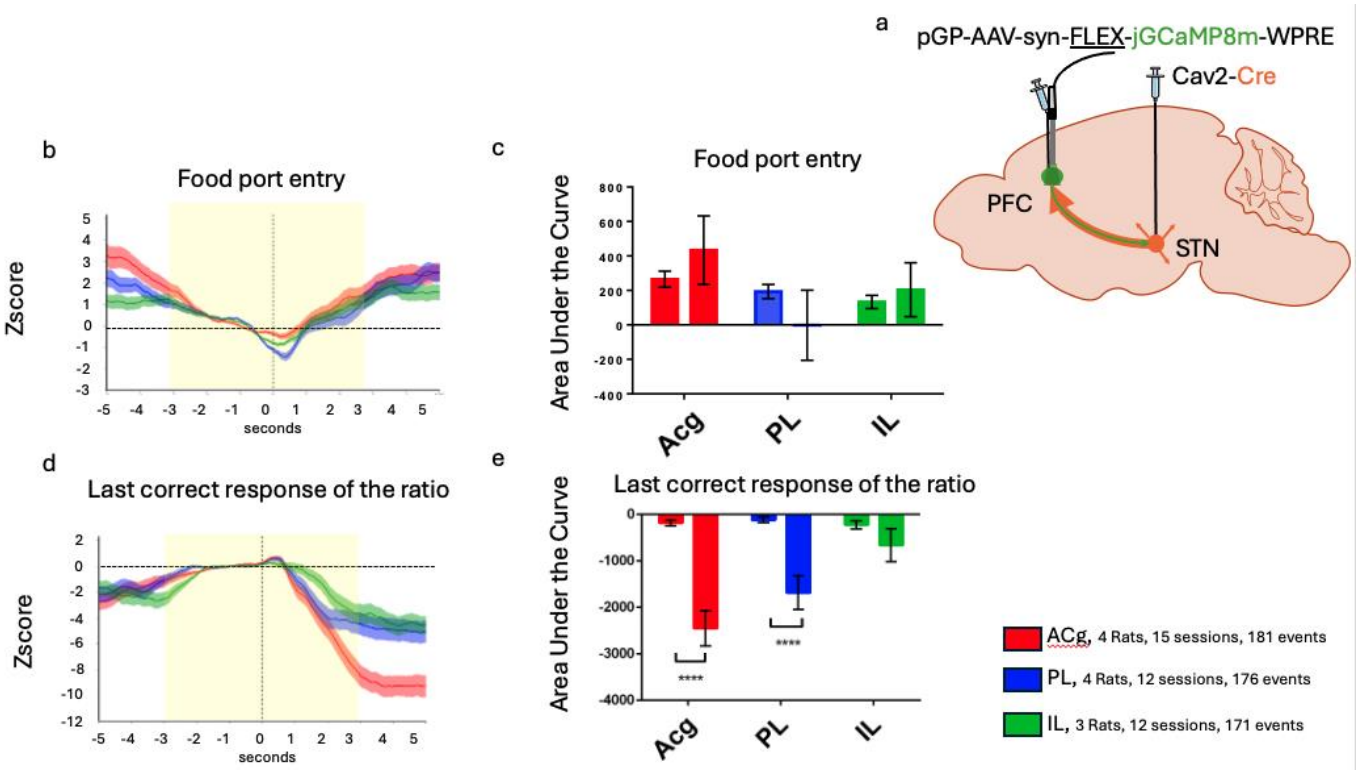


Figure 4. Calcium signals of the hyperdirect pathway surrounding food port entry (b-c) and last correct response of the ratio (d-e) revealed only the PL and ACg pathways are modulated during motivated food seeking behaviors during a PR task for sucrose. **(a)** Schematic of the virus injections and optic implant. **(b,d)** Z-score signals of the ACg projection (red), PL projection (blue), and IL projection (green) are shown in 10-second windows surrounding each event. **(c/e)** Area Under the Curve, 3 sec pre vs post the event. Two-way ANOVA revealed a main effect the pathways during the 3s surrounding the last correct response ($F_{(2,516)}$ = 4.334, p=0.0136) but not during food port entry($F_{(2,510)}$ = 2.317, p=0.0996). Post-hoc analysis revealed a significant increase in the ACg-STN z-score signal after the correct response (p<0.0001) and in the PL-STN signal (p<0.0001) but not in the IL-STN pathway (p=0.8737). Data in the graph are expressed as mean ± SEM. * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001

Recordings from STN neurons revealed no significant change in GCaMP signal 3s pre- versus post- last correct response of the ratio (n = 2 rats, t = 0.1520, df = 369, p=0.8793). However, there was a significant decrease in signal surrounding food port entries (n = 1 rat, t = 4.945, df = 382, p<0.0001).

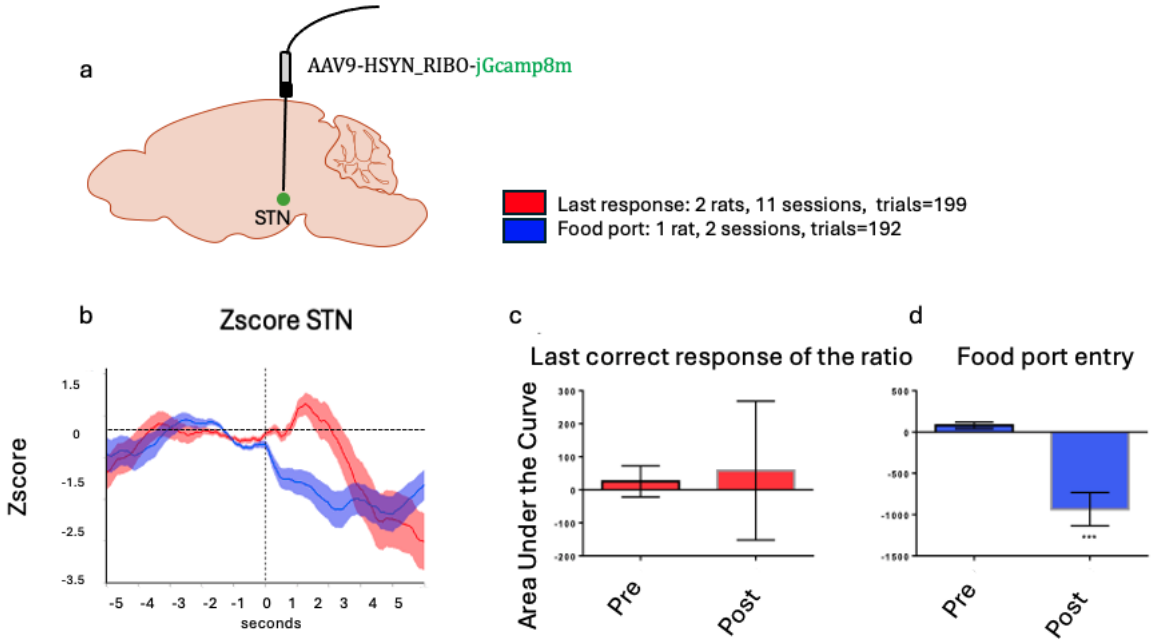


Figure 5. STN calcium activity decreases after entry into the food port. **(a)** Schematic of the virus injections and optic implant. **(b)** zscores from the STN neurons 10 seconds surrounding the events, food port entry (blue) and last correct response of the ratio (red). **(c/d)** Area Under the Curve, 3 sec pre vs post the event. **(c)** Two-tailed, T-test revealed no significant increase in STN calcium activity around the last correct response ($t = 0.1520$, $df = 369$, $p=0.8793$). However, there was a significant decrease in signal surrounding food port entries ($t = 4.945$, $df = 382$, $p<0.0001$). Data in the graph are expressed as mean ± SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Discussion

This study aimed to investigate the activity of the hyperdirect pathway and neurons of the STN during motivated reward-seeking behavior. Overall, we found that the different hyperdirect pathways displayed similar activity profiles, with only slight variations in their individual responses to reward delivery and food port entry events. During the PR task, there was a significant decrease in activity in the PL and ACg hyperdirect pathways in the 3s following last correct response of the ratio, but no such increase was observed in the IL pathway. In the STN, there was a significant decrease in activity following food port entry, but no significant change after last correct response of the ratio.

In the first pilot experiment, we observed the strongest calcium signals, suggesting that cell bodies are a more efficient targets for fiber photometry. This finding led us to focus on cell bodies in the final experiments. The pilot also showed increased IL activity during reward delivery, although the signal was not isolated in a window as in later experiments, since our data analysis techniques became more refined over time.

The second experiment, which recorded calcium signals from hyperdirect pathway terminals without using a retrograde virus, resulted in poor signal quality. This may have been due to insufficient transfection at the level of the terminals, despite adequate infection at the cell body.

In the third experiment, we made progress by employing a retrograde system to target the hyperdirect pathway and using the next-generation GECI GCaMP8m, which has a higher light emission than the previously used GCaMP7f. However, the use of homemade patch cords and rotary joints designated for optogenetic use resulted in poor signal quality, and only a few recorded sessions which could be analyzed. Additionally, histological verification revealed only sparse labeling of PFC neurons.

In the final experiment, we improved our setup by using a new fiber photometry system and upgraded patch cords, which provided a better signal-to-noise ratio.

The role of the hyperdirect pathway in Motivation

The PFC plays a crucial role in motivated behaviors, encompassing everything from simple Pavlovian conditioning to more complex instrumental conditioning. Lesioning the mPFC and the STN leads to the same attentional deficits described after a bilateral STN lesion (Chudasama et al., 2003; Baunez and Robbins, 1997, 1999) providing evidence that the hyperdirect pathway likely contributes to attentional processes. Furthermore, studies have shown that STN activity is modulated by visual distractors in an instrumental task (Bočková et al., 2011; Beck et al., 2018). This modulation could account for the decreased activity observed in the PL and ACg regions surrounding the delivery of rewards, particularly when a cue light signals the impending reward.

The IL cortex is important for the expression of extensively-trained instrumental behaviors, regardless of whether these behaviors manifest as stimulus-response habits or goal-directed actions. On the other hand, the PL cortex plays a key role in modulating

instrumental behavior (Balleine & Dickinson, 1998; Killcross & Coutureau, 2003; Green et al., 2021). While there is extensive evidence for the role of the IL and PL in these processes, the evidence for the ACg is more limited. However, some studies suggest that the ACg is important for inhibiting behavior, particularly following difficult or error trials (Newman et al., 2015), as well as during conditions of uncertainty (van Holstein & Floresco, 2020; Brockett et al., 2020).

Research has also highlighted the ACg's role in learning from reinforcement. In rats, ACg lesions impair the learning of stimulus-reward associations (Bussey et al., 1997). This suggests that the lowered activity observed in the ACg may reflect the brain's response to the expectation or anticipation of rewards, emphasizing the importance of this region in motivational processes. Moreover, optogenetic inactivation of PFC pyramidal neurons that project to the STN increases inappropriate responses, whereas activation of the PFC-STN pathway reduces errors in mice performing a go/no-go task (Li et al., 2020).

The significant increase in PL and ACg pathway activity in the 3s following reward delivery suggests that these regions play a critical role in processing reward-related signals. This increase likely reflects the involvement of these cortical regions in motivational and reinforcement learning processes.

The absence of significant changes in the IL pathway during the same period suggests that this pathway may not be directly involved in immediate reward processing during the PR task. Given that the PR task is a highly trained activity requiring extensive learning and substantial effort to earn rewards, the observed differences between the PL and the IL and Acg pathways may indicate ongoing instrumental learning. Perhaps, if we perform this experiment again with cocaine as the reward, we would observe a significant change in the IL pathway indicating a shift to more habit-related behaviors driven by motivation. This finding implies that the IL pathway may have a more specialized function related to other aspects of behavior or decision-making that were not assessed in this task but could potentially emerge in an addiction-like behavior.

The role of the STN in motivation

The earliest evidence for the involvement of the STN in motivation emerged from electrophysiological recordings in monkeys during operant oculomotor tasks. These studies demonstrated changes in STN activity when monkeys anticipated a food reward (Matsumura et al., 1992). Specifically, certain STN neurons were activated only when the target predicting the reward was fixated. Further research revealed that some STN neurons responded to both the anticipation and delivery of rewards (Darbaky et al., 2005; Espinosa-Parrilla et al., 2015).

A significant decrease in STN activity observed upon food port entry suggests that the STN plays a crucial role in reward valuation. When animals enter the food port, it indicates the subject is consuming the reward, and this decrease in STN activity may reflect the coding of the reward's value following consumption. Previous studies have shown that STN neuron activity correlates with feeding behaviors in mice, influenced by their homeostatic status and the type of food available; modulation of this activity using optogenetics can effectively regulate food intake (Wu et al., 2020). However, these studies also indicated that STN activity increases in response to sweet foods, while activity decreases when animals are sated. Notably, STN lesions were found to increase the "wanting" for sweet food (Pelloux et al., 2014), suggesting that a decrease in STN activity may represent a reduction in the motivational value applied to the reward. In another study in monkeys, a specific population of STN neurons was identified as responsible for reward modulation, with their activity increasing or decreasing based on the most favorable conditions of the task. The absence of significant changes in STN activity following the actual delivery of the reward contrasts with former research indicating that STN neurons encode the motivational value of stimuli (Lardeux et al 2009; 2013; Breysse et al 2015; Nougaret et al., 2022).

Although lesions of the STN did not affect overall food consumption, they significantly heightened motivation for food (Baunez & Robbins, 1997; Baunez et al., 2005). These findings underscore the STN's role in modulating reward-seeking behaviors, particularly in situations that demand increased effort to obtain rewards. Additionally, our results are supported by previous work which has shown that there is a decrease firing rate in the STN during food port entries in electrophysiology experiments (Lardeux et al., 2013).

In patients with PD, STN-DBS has been associated with weight gain, food cravings, and binge eating (Witjas et al., 2005; Ardouin et al., 2006; Lim et al., 2008; Zahodne et al., 2011; Kistner et al., 2014; Aiello et al., 2015). This weight gain does not appear to stem from increased hunger or enhanced pleasure but rather from a modulation of homeostatic mechanisms that heighten the incentive salience of food. This suggests that the STN may influence the effort put into obtaining food, making it more desirable without necessarily enhancing the subjective experience of pleasure. Some studies support the idea that STN DBS-induced weight gain may result from off-target stimulation of neighboring nuclei, including the lateral hypothalamus, altering the release of feeding-related hormones (Růžička et al., 2012; Markaki et al., 2012). Additionally, increased motivation for food intake has been reported in patients with strokes or tumors affecting the STN (Barutca et al., 2003; Etemadifar et al., 2012), as well as in rats subjected to STN lesions (Baunez et al., 2002, 2005).

Moreover, individuals who experience damage to the STN due to strokes or tumors may exhibit hyperphagia and heightened appetite, reinforcing the STN's role in reward processing and appetite regulation (Barutca et al., 2003; Etemadifar et al., 2012). This evidence highlights the STN's involvement in both processing actual rewards and anticipating rewards based on subjective expectations.

Overall, these findings suggest that the hyperdirect pathway, especially the PL and ACg components, is actively involved in reward-seeking behavior, while the STN appears to be more engaged in the consumption of the reward and the assessment of its incentive value. This distinction in the roles of the hyperdirect pathway and the STN highlights the intricate and complex nature of the neural circuits that regulate motivation and reward processing, indicating that different brain regions may contribute uniquely to various phases of motivated behavior. The next, and final phase of this thesis will investigate if modulation of the hyperdirect pathway with optogenetic tools can change the food motivation observed in these fiber photometry experiments.

4.3. Manipulating the hyperdirect pathway

Aims :

After having investigated the role of each hyperdirect pathway in the motivation for sucrose with fiber photometry, the last step of my PhD work will be to selectively manipulate these pathways, using optogenetic tools in the same behavioral progressive ratio test used during the fiber photometry recordings. We will then determine if motivated sucrose taking behavior can be altered by selective manipulation of the hyperdirect pathway and which one (IL-STN, PL-STN or ACg-STN) is the most efficient at altering motivation for sweet rewards. If the hyperdirect pathway contributes to the effects mediated by STN inactivation on increased motivation for sweet rewards, the inhibition of the hyperdirect pathway should induce similar effects to those observed after STN inactivation. It should thus increase motivation for sucrose.

Introduction

The STN has been extensively studied for its role in motor control, particularly in the context of treating PD through HF-DBS. While this intervention has proven highly effective in alleviating motor symptoms in PD (Limousin et al., 1995), the potential non-motor effects of STN DBS have garnered increasing attention. More recent research has explored the STN's role in cognitive and motivational processes, including its involvement in addiction-like behaviors (Baunez & Lardeux, 2011; Pelloux & Baunez, 2013).

The STN is a key structure within the basal ganglia and serves as a critical relay between the cortex and the motor system, receiving direct input from the PFC through the hyperdirect pathway (Nambu et al., 2002). Given the STN's connections to both motor and limbic areas, it has been hypothesized that it plays a dual role in modulating both movement and motivation, including drug-seeking behaviors. Prior research has shown that STN inactivation through either lesions or HF-DBS can reduce cocaine intake in rodents, without decreasing the motivation for natural rewards like food (Baunez et al., 2005; Rouaud et al., 2010). This suggests that the STN may selectively modulate the

motivational processes associated with addictive substances, while sparing or even enhancing motivation for non-drug rewards.

However, the precise mechanisms through which the STN influences addiction-like behavior remain unclear. One key question concerns the role of the hyperdirect pathway, which allows direct cortical input to the STN, bypassing traditional reward circuits such as the NAc and VP. This direct connection has been implicated in impulse control and decision-making processes (Frank, 2006) and may be critical to understanding the effects of STN DBS on motivated behaviors.

This project seeks to further elucidate the role of the STN and its hyperdirect pathway in motivated behaviors, with a particular focus on understanding how these circuits contribute to the consumption of natural rewards like sucrose versus. By utilizing optogenetics, we aim to selectively manipulate the hyperdirect pathway during behavioral tasks that assess motivation. This approach will provide valuable insights into how the STN influences reward processing and could pave the way for novel therapeutic strategies targeting addiction and other compulsive behaviors.

Materials and Methods

Animals

16 Adult Lister Hooded males (~400g, Charles River) used in the experiments were housed in groups of two in Plexiglas cages and maintained on an inverted 12h light/dark cycle (light onset at 7pm) with food and water available ad libitum, in a temperature and humidity-controlled environment. All experiments were conducted during the dark cycle (8am-7pm). Animal care and use conformed to the French regulation (Decree 2010-118) and were approved by local ethic committee at the University of Aix-Marseille, under the French ministry of Agriculture authorization #03129.01.

Surgery

Animals were anesthetized with ketamine (Imalgen, Merial, 100mg/kg, i.p.) and medetomidine (Domitor, Janssen, 0.5mg/kg, i.p.). Once fully sedated, they were placed in a

Kopf stereotaxic apparatus for bilateral optogenetic viral injections and optic fibers implants.

For the optogenetic experiments, animals underwent bilateral microinjections of a virus at a rate of 0.15 µl/min. To specifically target the hyperdirect pathway neurons, we utilized AAV5 carrying the recombinant protein under the Ef1a-promoter control, with expression being Cre-dependent (UNC Vector Core - 4342), in combination with a retrograde canine adenovirus (Plateforme de Vectorologie de Montpellier).

For inhibitory experiments, 1.0 µl of AAV5-EF1a-DIO-eNpHR3.0-RPF (4 × 10^12 pp) was injected into the PFC at the following coordinates: PL (n=4): AP: -3.2/+12.2 mm; L: ±0.8 mm; DV: -3.4/+6.6 mm ; ACg (n=4): AP: -1.5/+10.5 mm; L: ±0.8 mm; DV: -3.0/+7.0 mm ; IL (n=4): AP: -3.0/+12.0 mm; L: ±0.6 mm; DV: -5.2/+4.8 mm. Control animals (n=4) received injections of AAV5-EF1a-DIO-RPF (4 × 10^12 pp) into the same PFC regions. Additionally, 0.50 µl of the retrograde virus Cav2-Cre-GFP (2 × 10^9 pp) was injected into the STN of all rats (n=16) at the coordinates: - AP: −3.7/+5.3 mm; L: ±2.4 mm; DV: −8.35/+1.65 mm. Coordinates are presented from the bregma and interaural points (averaged), with the incisor bar set at −3.3 mm, based on the Paxinos & Watson (2007) atlas. Optic fibers were implanted 0.4 mm above the injection site within the STN. Fibers were secured with screws and dental cement.

Following surgery, animals were revived with an injection of atipamezole (Antisedan, Janssen, 0.15 mg/kg, intramuscularly), a medetomidine antagonist. A three-week incubation period was allowed for viral expression before commencing optogenetic manipulations.

Sucrose self-administration

Rats were trained to nose-poke for 65% sucrose pellets using a FR1 reinforcement schedule in standard operant chambers (MedAssociates). Each chamber was equipped with two nose-poke holes. A nose-poke in the active hole triggered a 5-second illumination of a cue light, a 5-second time-out period, and the delivery of the reward to a food magazine located on the opposite wall. Nose-pokes in the inactive hole had no consequences. When the rats achieved a minimum of 100 rewards and demonstrated

stable consumption (with less than 20% variation) for three consecutive days, the ratio was increased to FR5 for an additional three days.

Following this, the rats were tested in a PR schedule over a period of 15 days. In this schedule, the ratio increased arithmetically in steps of five, with three repetitions at each level (e.g., 1, 1, 1, 5, 5, 5, 10, 10, 10, etc.). The session ended after 90 minutes or after 5 minutes without any active nose-poking. The final ratio completed by the rat was defined as the "breakpoint."

The experiment was structured in two phases: during the first five days of PR training, rats performed the task without any light inhibition (laser off). On the fifth day, half of the rats continued with five additional days of PR self-administration with the laser turned on during the session, followed by five days with the laser off. The second group experienced the opposite sequence: the laser remained off for the first 10 days, and then was turned on for the final five days of self-administration.

Optogenetic Light Stimulation

Light stimulation during the experiments was performed using a 528nm laser, controlled by a signal generator and connected through an optical coupler (Thorlabs, FCMM625-50A) and rotary joints (Doric Lenses) to alleviate torsion caused by animal movements. Before each experiment, light output was measured with a power meter (Thorlabs, PM20A). Laser inhibition was delivered at 10mW, measured at the tip of the optic fiber. The laser operated in a cycle of 8 seconds on and 2 seconds off throughout the entire progressive ratio (PR) session. Inhibition was performed over five sessions.

Histology

At the end of the experiments, rats were deeply anesthetized via an intraperitoneal injection of ketamine (Imalgene, Merial, 200 mg/kg) and medetomidine (Domitor, Janssen, 60 mg/kg). The animals were then perfused intracardially with 4% paraformaldehyde in PBS. Following extraction, the brains were cryoprotected in 30% sucrose and subsequently frozen in liquid isopentane (-80°C). The brains have yet to be sectioned for immunohistochemistry staining, which will be used to confirm viral expression. All Nphr3.0-infected rats that completed the study were included in the

analysis (ACg: n=3, PL: n=4, IL: n=4). Control rats were excluded from the analysis as they did not reach the progressive ratio (PR) phase of the behavioral test.

Statistical Analysis

Optogenetic data were analyzed using a two-way repeated measures ANOVA with 'inhibition' (laser on vs. laser off) as the within-subject factor.

Results

In these optogenetic experiments, we investigated how inhibiting the hyperdirect pathway affects motivation for sweet reward intake. Our results revealed that inhibiting the ACg, IL, and PL pathways projecting to the STN significantly reduced motivation for sweet food.

Specifically, in rats expressing NpHR3.0 in the ACg and Cav2-Cre in the STN, we observed a significant reduction in the number of rewards obtained in the progressive ratio (PR) task. A significant main effect of laser inhibition was found ($F(1, 39) = 9.267$, $P = 0.0042$), indicating a reduction in motivation when the laser was on. There was no significant main effect of subjects ($F(2, 3) = 0.5941$, $p = 0.5570$) and no significant interaction effect ($F(2, 39) = 1.1502$, $p = 0.8611$).

Inhibition of the IL projection to the STN also resulted in a significant reduction in the number of rewards in the PR task. A main effect of laser inhibition was observed ($F(1, 49) = 28.81$, $P < 0.0001$), indicating a reduction in motivation for sweet reward when the laser was on. In this group, there was a significant main effect of subjects ($F(3, 49) = 13.55$, $P < 0.0001$), although no significant interaction effect was found ($F(3, 49) = 2.005$, $P = 0.1255$).

Finally, inhibition of the PL projection to the STN significantly reduced the number of rewards during laser inhibition. A main effect of laser inhibition was observed ($F(1, 52) = 20.77$, $P < 0.0001$), indicating reduced motivation for sweet rewards when the laser was on. A small but significant effect of subjects was observed ($F(3, 52) = 3.057$, $P = 0.0363$), with no significant interaction effect ($F(3, 52) = 0.07916$, $P = 0.971$).

Overall, these results show that inhibiting the IL, ACg, and PL hyperdirect pathways leads to a reduced breakpoint in the PR task, indicating decreased motivation for sweet food.

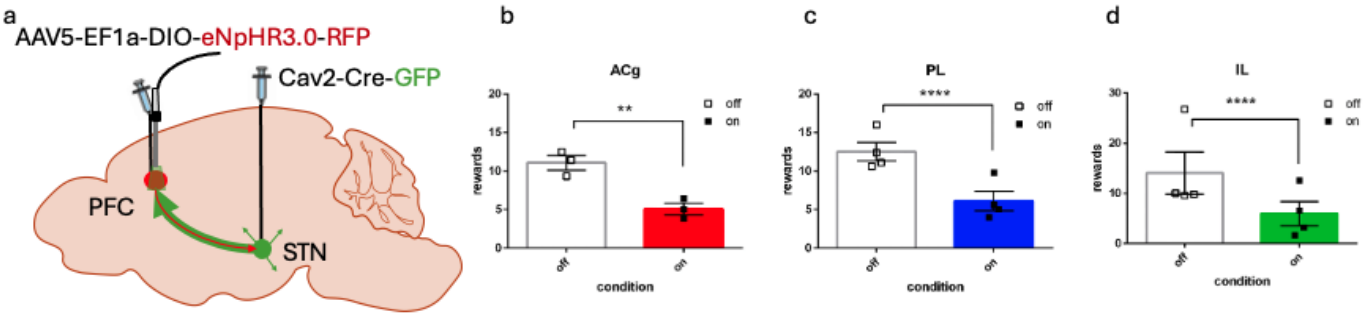


Figure 1. Optogenetic inhibition of the hyperdirect pathways significantly reduced motivation for sweet food in a progressive ratio task. **(a)** Schematic of the virus injections and optic implant. **(b-c)** 2-way ANOVA 'inhibition' (laser on vs. laser off) as the within subject factor. Inhibition of the ACg ($F_{(1, 39)} = 9.267$, $P = 0.0042$), PL ($F_{(1, 52)} = 20.77$, $P < 0.0001$), and IL ($F_{(1, 49)} = 28.81$, $P < 0.0001$) significantly reduced the rewards earned. Error bars represent SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Discussion

In this study, we demonstrated that optogenetic inhibition of the IL, PL, and ACg components of the hyperdirect pathway led to a significant decrease in rewards earned during a PR reinforcement task. These findings suggest that the hyperdirect pathway does not contribute to the increased motivation for rewards observed after STN lesions or HFS, as reported in prior studies (Baunez et al., 2005; Rouaud et al., 2010).

Interestingly, the behavioral similarities between DBS and lesions indicate that STN DBS mimics the inactivation of the STN in terms of its motivational functions. This inactivation has previously been associated with heightened motivation for food (Baunez et al., 2005; Rouaud et al., 2010). Our findings suggest that rather than simply enhancing general motivation, STN inactivation may specifically affect the incentive properties of

rewards that drive food-seeking behaviors (Pelloux et al., 2014). This hypothesis is supported by electrophysiological studies on STN activity during reinforcement tasks (Lardeux et al., 2008, 2009).

The results of our experiments indicate that the hyperdirect pathway is not responsible for the increased motivation for sweet rewards seen after STN inactivation. In fact, inhibiting this pathway produced the opposite effect, suggesting that the inhibition of the hyperdirect pathway might work to activate the STN and reduce food motivation. The PFC is extensively involved in motivated behaviors, ranging from simple Pavlovian conditioning to more complex instrumental conditioning (Kouneiher et al., 2009). Therefore, the inhibition of the hyperdirect pathway could indeed, decrease the motivation for the sucrose as we have observer in these experiments. The heightened motivation observed with STN inactivation may instead be related to the indirect pathway and its glutamatergic connections to the VP, a region known to influence food intake. Notably, VP inactivation has been shown to increase eating behavior (Stratford et al., 1999; Smith & Berridge, 2005).

The hyperdirect pathway is more likely involved in inhibiting impulsive behaviors. The mPFC plays a pivotal role in curbing habitual responses (Isoda & Hikosaka, 2007; Duan et al., 2015). Optogenetic manipulations of STN-projecting neurons have shown that activation of these neurons reduces inappropriate licking during no-go trials, while their inactivation increases it, suggesting a role in impulse control. These findings point to a critical role for pyramidal neurons in the prefrontal cortex in regulating impulsivity (Li et al., 2020), reinforcing the idea that the hyperdirect pathway is more involved in impulse regulation than in hedonic motivation.

Current research has focused on whether STN-DBS could be an effective treatment for SUD, by modulating the motivational circuits linked to drug craving and consumption, while preserving normal reward-seeking behaviors (Pelloux & Baunez, 2017). However, STN-DBS has been associated with weight gain, food cravings, and binge eating in PD patients (Witjas et al., 2005). Our findings suggest that the weight gain observed following STN HFS may be due to its modulation of the STN, but likely not through the hyperdirect pathway, offering insights into potential treatment strategies for addiction and the metabolic side effects of DBS.

5. Discussion

Throughout this thesis work, I have used DBS, optogenetic tools, and fiber photometry to better understand the functional roles of the STN and the hyperdirect pathway in motivation. Using a selective way to inhibit STN activity and the hyperdirect pathway aimed at better understanding the physiological and functional effects of the STN HF-DBS. The results obtained raised many questions.

5.1. The STN as a hedonic hotspot

In the first study, we demonstrated that STN-DBS at 130 Hz can be self-administered by both naïve rats and those with a history of cocaine use, indicating that HF-STN stimulation is rewarding. Optogenetic inhibition, but not optogenetic stimulation, of STN neurons also increased ICSS responses, suggesting that inhibition of STN activity contributes to the reward effect. The increase in ICSS during 130 Hz DBS is likely due to its impact on reward-processing circuits. Interestingly, optogenetic inhibition produced similar effects, highlighting the role of STN inhibition in enhancing reward-related behavior. These findings support the involvement of the STN in encoding subjective pleasure ("liking") associated with rewards.

As discussed in the introduction, classical ICSS studies identified key reward centers such as the medial forebrain bundle, lateral hypothalamus, and VTA, due to their role in increasing responding during electrical stimulation (Olds & Milner, 1954). The STN's location within the cortico-basal ganglia loop, combined with its glutamatergic inputs from the thalamus and PFC and dopaminergic inputs from the VTA, may explain its role in reward processing. The STN's connections with the dopaminergic system (Parent & Hazrati, 1995; Karachi et al., 2005) could contribute to its involvement in cost-benefit decision-making and motivation-related behavior. Interestingly, pharmacological blockade of the dopaminergic system does not eliminate facial expressions of pleasure, as shown in studies by Peciña et al. (1997), suggesting that dopamine, typically associated with motivation, is not necessary for experiencing pleasure.

DBS has been shown to reduce L-DOPA addiction in PD patients with dopamine dysregulation syndrome (Limousin et al., 1995; Lawrence et al., 2003; Lhommée et al., 2012; Eusebio et al., 2013). Our findings that 130 Hz stimulation is rewarding and affects sensitization may help explain why STN-DBS improves L-DOPA addiction in PD patients. This highlights the STN's role in dopamine regulation, whether DA is deficient (as in PD) or stimulated (as in cocaine consumption or L-DOPA treatment). While dopamine plays a role in synaptic plasticity within the VTA and increases DA transmission to the NAc (Ungless et al., 2001; Bellone & Lüscher, 2005, 2006; Mameli et al., 2007, 2011; Yuan, 2013; Lammel et al., 2011), current evidence does not support the use of dopamine agonists for treating cocaine dependence (Minozzi et al., 2015). The STN's ability to reduce dopaminergic dysregulation, while preserving natural reward-seeking behaviors, positions STN-DBS as a unique treatment for CUD.

Studies show that STN lesions or DBS can have opposite effects on reward motivation depending on the subject's preferences and the type of reward. For example, STN lesions increase motivation for alcohol in high-preference rats but reduce it in low-preference rats (Lardeux & Baunez, 2008). Similarly, 130 Hz STN-DBS has been shown to reduce alcohol intake after escalation (Vignal et al., 2024). STN-DBS, lesions, or inactivation increase motivation for sucrose while decreasing it for cocaine (Rouaud et al., 2010; Baunez et al., 2005). These findings suggest that the STN plays a dissociative role in modulating motivation for different rewards. Our study suggests that an increase in the incentive salience of the reward may be the mechanism by which DBS enhances responding for certain rewards but not others.

The STN encodes food reward salience (Lardeux et al., 2013; Darbaky et al., 2005; Pelloux et al., 2014). In contrast to Pelloux et al. (2014), who found that STN lesions reduce the "liking" component of sweet rewards, our findings show that both STN HFS and inhibition increase ICSS responding, suggesting that these manipulations increase reward sensitivity.

In cocaine-experienced rats, both 30Hz and 130Hz stimulation were rewarding, while only 130Hz was rewarding in naïve rats. This suggests that lower-frequency stimulation may provide an alternative reward following drug exposure. Previous studies demonstrate that STN manipulation reduces compulsive cocaine-seeking behavior (Rouaud et al., 2010; Baunez et al., 2005; Pelloux et al., 2018; Degoulet et al., 2021). Our

findings suggest that 30 Hz STN stimulation may act as an alternative reward and reduce compulsive drug-seeking in addicted individuals.

We also investigated the effects of high-frequency optogenetic stimulation of the STN on food-motivated behavior. Light stimulation was applied at 130Hz to mimic the electrical DBS parameters in terms of frequency. Interestingly, high-frequency optogenetic stimulation did not increase ICSS behavior. In contrast, other hedonic hotspots stimulated by high-frequency stimulation do elicit ICSS responses (Song et al., 2024). This suggests that the STN is unique in that inhibiting its cells appears to promote ICSS behaviors.

This phenomenon may be linked to the STN's connections to the brainstem and its nociceptive properties, particularly regarding its ability to modulate pain responses. Previous studies have documented nociceptive responses within the STN, which has significant clinical implications for controlling chronic pain—an issue commonly observed in Parkinson's disease patients (Pautrat et al., 2018). Furthermore, recent evidence indicates that nociceptive perception can be modulated by STN lesions (Pautrat et al., 2018). Thus, STN stimulation may not only influence reward processing in terms of hedonic pleasure but also play a role in pain relief or perception.

Moreover, our results align with evidence showing that STN-DBS at 130 Hz can reduce cocaine relapse in rats (Pelloux et al., 2018) and compulsive drug-seeking at lower frequencies (Degoulet et al., 2021). Additional studies have shown that STN HFS interferes with the reactivity to cocaine in the reward circuit (Hachem-Delaunay et al., 2015). This decreased reactivity to cocaine may account for its reduced rewarding properties under STN HFS, suggesting that the modulation of the STN could alter the way the brain responds to addictive substances like cocaine. This supports the potential of STN-DBS in modulating reward sensitivity and treating addiction. Additionally, our data show that 30 Hz stimulation appears rewarding in rats with a history of cocaine use. This could be attributed to the well-documented phenomenon of reward sensitization, where previously drug-exposed animals may experience heightened sensitivity to the rewarding effects of stimulation (Kenny, 2006). In this context, rats with a history of cocaine use might exhibit a shift in reward sensitivity, allowing 30 Hz stimulation to be perceived as rewarding in this group.

While electrical DBS and optogenetic inhibition both suggest that STN inhibition is necessary for the reward effect, STN-DBS may also increase activity in STN output structures or inhibit neurons of the substantia nigra (Benazzouz et al., 2000; Tai et al., 2003; Maurice et al., 2003). The STN DBS also impacts afferent structures, altering cortical activity through antidromic activation of the hyperdirect pathway (Li et al., 2012; McIntyre et al., 2004). We observed a significant increase in perseverative responses during HFS-DBS, but not during optogenetic inhibition, indicating that the non-selective activity of HFS may be affecting connected STN structures, leading to compulsive-like behavior that was not observed during the selective inhibition of STN neurons during optogenetic experiments.

A key limitation of this study is the ambiguity around whether we measured "liking" or "motivation." ICSS experiments primarily measure motivation, but it remains unclear if the increase in behavior reflects enjoyment of the reward or the drive to obtain it. Future studies could explore this by recording ultrasonic vocalizations or facial expressions to assess hedonic reactions. ICSS studies with increased fixed ratios or progressive ratio schedules could differentiate between primary and secondary motivation.

Results from optogenetic manipulations confirm that the STN is more involved in secondary motivation (Tiran-Cappello et al., 2021). While optogenetic manipulations did not alter behavior under FR-5 schedules, they affected willingness to work for food and cocaine in PR tasks, further supporting STN involvement in secondary motivation. Studies using Pavlovian training have examined the impact of STN lesions on a specific aspect of food motivation: the attribution of incentive salience to reward-related cues. In these experiments, where a CS, like a lever, is paired with a food reward (US), lesions to the STN have been shown to increase the number of presses on the CS, indicating heightened motivation to obtain the reward (Baunez et al 2002; Uslaner et al., 2008). Similarly, in studies using the CPP paradigm, where an environment (CS) is associated with a rewarding stimulus (US), STN lesions lead to a stronger preference for the food-associated environment (Baunez et al., 2002).

This heightened attribution of incentive value is further supported by electrophysiological recordings in rats, showing that STN neurons respond to both reward delivery and CS incentive stimuli (Teagarden et al., 2007; Lardeux et al 2009;

2013). Additionally, in Parkinson's disease patients, the placebo effect—which influences reward expectancy—was found to modulate STN neuronal activity (Frisaldi et al., 2014).

Our findings demonstrate that both high-frequency STN-DBS and optogenetic inhibition increase ICSS responding, confirming the STN's role in reward processing. The increase in ICSS in cocaine-experienced rats suggests that DBS may offer an alternative reward and reduce drug-seeking. These findings have significant implications for the use of STN-DBS in treating addiction-related behaviors.

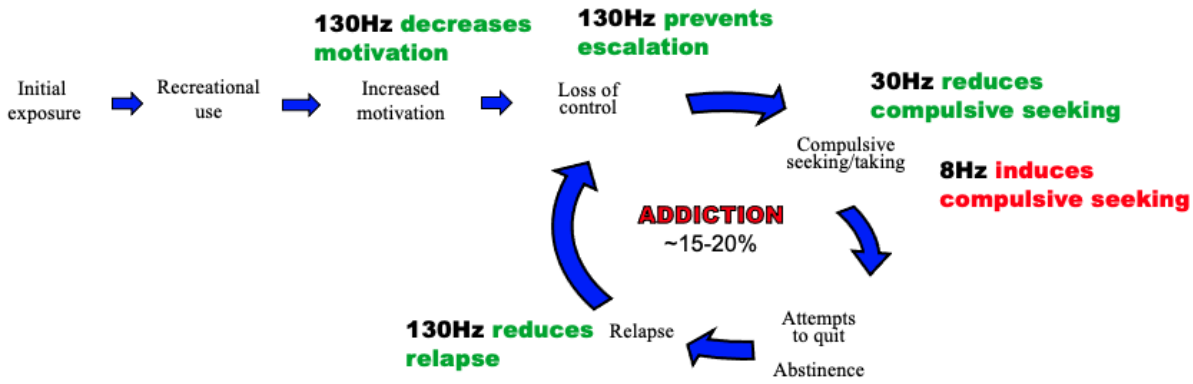


Figure 16. Frequency-dependent effects of STN DBS on different stages of addiction-like behaviors in rats (Rouaud et al, 2010; Pelloux et al, 2018 ; Degoulet et al, 2021).

5.2. Hyperdirect activity during motivation

The second study investigated the activity of the hyperdirect pathway and STN neurons during motivated reward-seeking behavior. We found that different components of the hyperdirect pathway exhibited unique activity patterns during reward-driven tasks. Notably, during the PR task, there was a significant decrease in activity in the PL and ACg pathways within 3 seconds following reward delivery of the last correct response of the ratio, while the IL pathway showed no significant change. In contrast, STN activity decreased significantly after food port entry but did not change following reward delivery.

These findings underscore the important role of the hyperdirect pathway in motivation. The PFC is extensively involved in motivated behaviors, encompassing everything from simple Pavlovian conditioning to more complex instrumental conditioning. Lesions in the mPFC and STN lead to similar attentional deficits, suggesting that the hyperdirect pathway contributes to attentional processes (Chudasama et al., 2003; Baunez & Robbins, 1997, 1999). Additionally, STN activity has been shown to be influenced by visual distractors during instrumental tasks (Bočková et al., 2011; Beck et al., 2018). This modulation could account for the decreased activity observed in the PL and ACg regions surrounding the delivery of rewards, particularly when a cue light signals an impending reward, after the last correct response of the ratio is achieved.

The PL cortex plays a role in modulating instrumental behavior (Balleine & Dickinson, 1998; Killcross & Coutureau, 2003; Green et al., 2021). Conversely, the ACg has been linked to behavioral inhibition, particularly following difficult or error trials (Newman et al., 2015) and under uncertain conditions (van Holstein & Floresco, 2020; Brockett et al., 2020). Research indicates that the ACg is vital for learning from reinforcement, as lesions in this area impair stimulus-reward association learning in rats (Bussey et al., 1997). In the 5-CSRTT, bilateral excitotoxic lesions and pharmacological inactivation of the STN significantly impaired accuracy, suggesting an attentional deficit (Baunez & Robbins, 1997). The decreased activity in the PL and ACg following reward delivery suggests that these hyperdirect connections are associated with the attentional processes impacted by STN inactivation.

In contrast, the IL cortex is crucial for the expression of well-trained and habitual instrumental behaviors. (Balleine & Dickinson, 1998; Killcross & Coutureau, 2003; Green et al., 2021). We observed no changes in the IL hyperdirect pathway activity during responses in the third fiber photometry experiment. The lack of significant changes in the IL pathway during the PR task indicates that there was not a shift from instrumental learning towards more habit-driven behaviors, which are supposed to be expressed in this pathway. However, as explained in previous chapters, we hypothesized that during PR for cocaine, we should observe an increased activity in the IL pathway.

Evidence for the STN's involvement in food motivation comes from electrophysiological recordings in monkeys, which showed changes in STN activity in anticipation of food rewards (Matsumura et al., 1992). Specific STN neurons responded

only when the target predicting a reward was fixated, while others reacted to both anticipation and reward delivery (Darbaky et al., 2005; Espinosa-Parrilla et al., 2015). Additionally, different populations of STN neurons have been shown to respond to sucrose or cocaine and to predict future errors (Lardeux et al., 2013). However, these different populations of neurons could not be discriminated in our task, as fiber photometry measures the bulk signal from a region. An alternative method to record calcium activity would be to install a mini camera lens in the brain, allowing for the recording of individual cells. Nevertheless, the depth of the STN and the size of the implant would cause significant damage to the brain, potentially yielding inaccurate results.

When recording from STN neurons, the significant decrease in activity upon food port entry indicates its role in reward valuation. Food port entries imply that the animals have consumed the reward, and this decrease in STN activity may reflect the coding of the reward's value post-consumption. Previous studies have shown that STN neuron activity correlates with feeding behaviors in mice, influenced by homeostatic status and food type, where optogenetic modulation can effectively regulate food intake (Wu et al., 2020). However, STN activity increases in response to sweet foods and decreases when animals are sated. Notably, STN lesions do not affect overall food consumption but significantly increase motivation for food (Baunez & Robbins, 1997; Baunez et al., 2005). These results underline the STN's role in modulating reward-seeking behaviors, especially when increased effort is required to obtain rewards.

Moreover, another study reported a decrease in STN firing rate during entry into the food port (Lardeux et al., 2013). These similar results observed provided additional support to the claim that STN activity is modulated, by entry into the food port. In our PR task, the motivation of the rats was tested by increasing the effort required to receive the rewards. STN lesions have been shown to increase the “wanting” for sweet food (Baunez et al 2002, 2005; Pelloux et al., 2014), suggesting that decreased STN activity may reflect a reduction in the motivational value assigned to the reward.

In patients with PD, STN-DBS is associated with weight gain, food cravings, and binge eating (Witjas et al., 2005; Ardouin et al., 2006; Lim et al., 2008; Zahodne et al., 2011; Kistner et al., 2014; Aiello et al., 2015). This weight gain does not appear to stem from increased hunger or pleasure but rather reflects a modulation of homeostatic mechanisms that enhance the incentive salience of food. This suggests that the STN may influence the

effort involved in obtaining food, making it more desirable without necessarily enhancing the subjective experience of pleasure. Some studies suggest that STN-DBS-induced weight gain may result from off-target stimulation of neighboring nuclei, including the lateral hypothalamus, affecting the release of feeding-related hormones (Růžička et al., 2012; Markaki et al., 2012). Additionally, increased motivation for food intake has been reported in patients with strokes or tumors affecting the STN (Barutca et al., 2003; Etemadifar et al., 2012), as well as in rats with STN lesions (Baunez et al., 2002, 2005).

Furthermore, individuals who experience damage to the STN due to strokes or tumors often exhibit hyperphagia and heightened appetite, reinforcing the STN's role in reward processing and appetite regulation (Barutca et al., 2003; Etemadifar et al., 2012). This evidence underscores the STN's involvement in processing and anticipating rewards based on subjective expectations.

Clinical evidence supporting the involvement of the STN in addiction has been observed in patients with PD. In these individuals, STN HF-DBS has been shown to reduce compulsive medication use, also called dopaminergic dysregulation syndrome (DDS) (Witjas et al., 2005; Lhommée et al., 2012), as well as CUD (Mira et al., 2024). These findings also indicate that the STN's connections with the brain's reward system may help explain the therapeutic effects of STN HF-DBS. The STN's role in modulating interactions between different regions of the reward circuitry could be key to understanding how it influences the brain's response to addictive substances, such as cocaine, during HFS.

Overall, these findings suggest that the hyperdirect pathway, particularly the PL and ACg components, plays an active role during food reward-seeking behavior, while the STN appears to be involved in the consumption of the reward and the assessment of its incentive value. This distinction in the roles of the hyperdirect pathway and the STN underscores the complexity of the neural circuits that regulate motivation and reward processing, with different brain regions contributing uniquely to various phases of motivated behavior. Further investigation could delve deeper into the STN and its network during the PR task, particularly by analyzing the wealth of data obtained from fiber photometry during these behavioral experiments. Specifically, examining calcium signals across different ratios may yield valuable insights. In conclusion, the results highlight the importance of the hyperdirect pathway, especially the PL and ACg components, in reward-seeking behavior, while the STN appears crucial in reward

consumption and valuation. This distinction emphasizes the complexity of neural circuits governing motivation and reward, with each brain region playing a unique role in the different stages of motivated behavior.

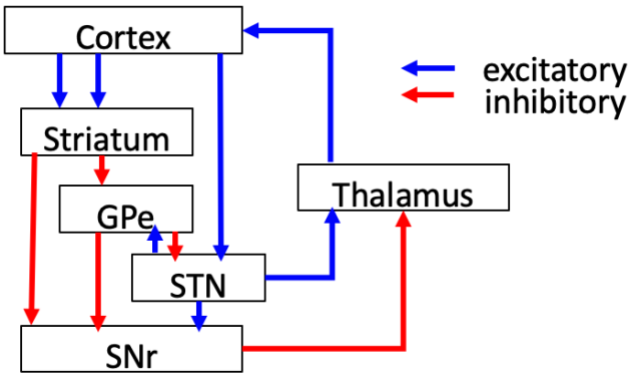


Figure 17. A schematic of the basal ganglia circuitry. This diagram illustrates the key structures within the basal ganglia, including the Cortex, Striatum, GPe, STN, SNr, and Thalamus. The blue arrows represent excitatory (glutamatergic) connections, while the red arrows indicate inhibitory (GABAergic) pathways. The basal ganglia circuitry plays a critical role in regulating motor control, decision-making, and reward processing.

5.3. Hyperdirect inhibition

In the final study, we demonstrated that optogenetic inhibition of the IL, PL, and ACg components of the hyperdirect pathway led to a significant decrease in rewards earned during a PR reinforcement task. These findings suggest that the hyperdirect pathway does not contribute to the increased motivation for rewards observed after STN lesions or HFS, as reported in prior studies (Baunez et al., 2005; Rouaud et al., 2010).

Interestingly, the behavioral similarities between DBS and lesions indicate that STN DBS mimics the inactivation of the STN in terms of its motivational functions. This inactivation has previously been associated with heightened motivation for food (Baunez et al., 2005; Rouaud et al., 2010). Excitotoxic lesions significantly increased motivation for food, as evidenced by more perseverative (excessive) and premature responses, as well as a higher breaking point under PR schedules of reinforcement (Baunez & Robbins, 1997; Baunez et al., 2005). These results highlight the STN's role in modulating reward-seeking behaviors, especially under conditions that require increased effort to obtain rewards. Our findings in the first study suggest that, rather than simply enhancing general motivation, STN inactivation may specifically affect the incentive properties of rewards that drive food-seeking behaviors (Pelloux et al., 2014). This hypothesis is supported by electrophysiological studies on STN activity during reinforcement tasks (Lardeux et al., 2008, 2009).

The results of our optogenetic experiments suggest that the hyperdirect pathway does not account for the increased motivation for sweet rewards observed following STN inactivation via lesion and HFS. In fact, inhibiting this pathway produced the opposite effect, indicating that the absence of excitatory glutamatergic inputs from the hyperdirect pathway reduces food motivation. Indeed, optogenetic stimulation of the STN decreased motivation for sucrose in a PR task, while inhibition increased it (Tiran-Cappello et al., 2018).

Additionally, our findings show that optogenetic inhibition of the hyperdirect pathways as a whole decreased the motivation for food rewards. The results from the fiber photometry experiments indicate that the PL and ACg components are specifically implicated in motivation for food rewards. This raises questions about the specificity of the hyperdirect pathway in food-seeking behaviors. The lack of histological verification in these experiments may explain these results, as the targeting of specific components of the hyperdirect pathway could have been nonspecific.))This is particularly relevant at the cortical level, where the PL is located directly above the IL, and at the STN level, particularly in rats, where the borders of these projection areas overlap and display a functional gradient (Afsharpour ,1985; Parent & Hazrati, 1995; Hamani, 2004; Kita et al., 2014; Karachi et al., 2005; Haynes & Haber 2013, Darbaky et al., 2005). Additionally, the

tripartite model dividing the STN into distinct regions remains a topic of debate within the STN community (Wallén-Mackenzie et al., 2020).

Without electrophysiological recordings, the lack of a defined rhythm in the STN during these optogenetic manipulations of the hyperdirect pathway leaves us without a pattern to determine whether the resulting STN activity has physiological relevance to the observed decrease in motivation. It is possible that the patterns produced by these two different manipulations generate a similar high-frequency activity in the STN, which could explain the similar results observed. The STN appears to be sensitive to specific ranges of oscillations. In the context of PD, low-frequency DBS (<20 Hz) has been reported to exacerbate symptoms, while high-frequency stimulation exerts therapeutic effects (Eusebio et al., 2008; Timmerman et al., 2004).

As discussed earlier, our group's work has shown that low-frequency oscillations in the STN develop during extended cocaine use, and blocking these oscillations with DBS or lesions prevents escalation and re-escalation of cocaine intake (Pelloux et al., 2018). Thus, the ability to affect motivation through STN stimulation likely lies within a specific rhythm rather than a general increase in activity (Tiran-Cappello et al., 2018).

The PFC is extensively involved in motivated behaviors, ranging from simple Pavlovian conditioning to more complex instrumental conditioning (Kouneiher et al., 2009). Therefore, inhibition of the hyperdirect pathway could indeed decrease motivation for sucrose, as we observed in these experiments. Activation of medial PFC projections to the VTA and NAc has been shown to reduce reward-seeking behavior (Ferenczi et al., 2016).

The heightened motivation observed with STN inactivation may instead be related to the indirect pathway and its glutamatergic connections to the VP, a region known to influence food intake. STN neurons share reciprocal connections with the VP (Haber & Knutson, 2010), providing further evidence that the STN may be a hub of the reward system. The VP, like the STN, contains cells that display distinct reward modulations depending on expected outcomes, including both reward-positive and reward-negative types (Tachibana & Hikosaka, 2012). Notably, VP inactivation has been shown to increase eating behavior (Stratford et al., 1999; Smith & Berridge, 2005).

Moreover, the hyperdirect pathway is involved in inhibiting impulsive behaviors. The mPFC plays a pivotal role in curbing habitual responses (Isoda & Hikosaka, 2007; Duan et al., 2015). Optogenetic manipulations of STN-projecting neurons have shown that activation of these neurons reduces inappropriate licking during no-go trials, while their inactivation increases it, suggesting a significant role in impulse control. These findings highlight the critical role of pyramidal neurons in the prefrontal cortex in regulating impulsivity (Li et al., 2020), reinforcing the idea that the hyperdirect pathway is more focused on impulse regulation than on hedonic motivation.

Functional MRI studies in humans further underline the PFC's involvement in motivational processes (Kouneiher et al., 2009). Our findings suggest that the weight gain observed following STN-HFS in PD patients may be attributed to its modulation of the STN, likely not through the hyperdirect pathway. This observation offers valuable insights into potential treatment strategies for both addiction and the metabolic side effects of DBS. However, it is important to note that all studies in this thesis were conducted using adult male rats, excluding any potential sex differences that may have been observed.

This work provides valuable insights into the role of the STN in reward processing and motivational behaviors. Throughout this thesis, we have demonstrated that 1) STN DBS is rewarding, and 2) the STN plays a key role in the valuation of food rewards. Additionally, we highlighted the involvement of the hyperdirect pathways in motivation, showing that 1) the PL and ACg components of the hyperdirect pathway are implicated in motivated food-seeking behavior, and 2) inhibition of the hyperdirect pathway has an opposite effect on food motivation compared to STN inhibition. These findings underscore the need for further research into the complex functions of the STN and its network to better understand the effects observed in humans with DBS implants. Moreover, this research contributes to our understanding of how STN DBS could be applied in the treatment of patients with CUD and OCD.

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