Histaminergic modulation of striatal development

Sungwon Han

Lady Margaret Hall, University of Oxford

Thesis submitted for the degree of Master in Science (by Research) in Pharmacology

Trinity Term 2020

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ABSTRACT

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Inadequate synthesis of the neurotransmitter histamine in the brain has been suggested to be one of causes of Tourette's syndrome and several psychiatric diseases. Previous findings suggested that dysfunction of the corticostriatal circuits are associated with such mental disorders. Indeed, recent research has reported a hypofunction of histamine in patients with Tourette's syndrome and obsessive-compulsive disorder in human and animal studies. However, the functional role of histamine in young developing animal brains is poorly known. Firstly, this study investigated whether and to what extent histamine plays a significant role in the corticostriatal circuit in the developing mouse brain. Secondly, the study investigated whether and to what extent histamine affects neurogenesis in the striatum in the embryonic mouse brain. Towards the first aim, the study recruited three postnatal young age period mice (postnatal (P)3-6 days, P9-12 days and P21+ days) and applied extracelluar field recordings of the corticostriatal transmission. As a result, the study found that histamine negatively modulates the corticostriatal synaptic transmission in all of young age period mice, acting at the H_3 receptors. In addition, histamine facilitated long-term potentiation of the corticostriatal synapses in the P9-12 period, but blocked it in the P21+ period, whereas the baseline condition showed long-term facilitation in the P21+, not the P9-12 periods. Collective analysis of this long-term plasticity experiment revealed that the dorsolateral striatum (DLS) is more likely to be facilitated than the dorsomedial striatum (DMS). Histamine's negative modulation on the corticostriatal synaptic transmission is found in developing age periods, which was found in only adult mice brains in past studies. Also histamine's opposite effect on the corticostriatal long-term plasticity in the P9-12 and P21+ periods implies that histamine may cause significant change in the dynamics of synaptic properties in particular developing age periods. For the second aim, the study injected α-fluoromethylhistidine (α-FMH) into the ventricle of embryonic mouse brain at embryonic day (E)12.5 and E15.5. The study then collected their brains 2-3 days after the application of α-FMH to compare the size of the striatum and proliferative zones between control and α-FMH conditions. Finally, a reduced size of striatum was observed in E15.5 brains (medial section) treated with α-FMH than those in control conditions. However, the study could not make further conclusions due to the small number of samples.

CONTENTS

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LIST OF ABBREVIATIONS

ACSF	artificial cerebrospinal fluid
ADHD	attention deficit hyperactivity disorder
α-FMH	alpha-fluoromethylhistidine
ANOVA	analysis of variance
CNS	central nervous system
CP	caudate-putamen
CSF	cerebrospinal fluid
D-AP5	D-2-Amino-5-phosphonovaleric acid; D-2-Amino-5-phosphopentanoic acid; 5-Phosphono-D-norvaline; D-Norvaline; 5-Phosphono-; D(-)-APV; D(-)-AP-5
DNA	deoxyribonucleic acid
DTI	diffusion tensor imaging
ECL	enterochromaffin-like
EDS	excessive daytime sleepiness
EPSP	excitatory postsynaptic potential
fEPSP	field excitatory postsynaptic potential
GABA	gamma aminobutyric acid
$GABA_A$ receptor	gamma aminobutyric acid A receptor
GAD	glutamate decarboxylase (or glutamic acid decarboxylase)
GPe	globus pallidus externus
GPi	globus pallidus internus
HDC	histidine decarboxylase
IgE	immunoglobulin E
IVC	individually ventilated cage
KO	knockout
LGE	lateral ganglionic eminence
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NMDA	N-Methyl-d-aspartic acid; N-Methyl-d-aspartate
NREM	non-rapid eye movement
OCD	obsessive-compulsive disorder

PB	phosphate buffer
PBS	phosphate buffered saline
PCR	polymerase chain reaction
SNr	substantia nigra pars reticulatae
SPN	spiny projection neuron (also known as medium spiny neuron (MSN))
STN	subthalamic nucleus
TBS	theta burst stimulation
TMN	tuberomammillary nucleus

UNIT OF MEASUREMENT AND CONCENTRATION

Hz	hertz
m	minute
M	molarity; molar concentration
ms	millisecond
μM	micromolar; 10^{-6} mol/L; 10^{-3} mol/m^3
μm	micrometre; 10^{-6} m
mM	millimolar; 10^{-3} mol/L; 10^{0} mol/m^3
nM	nanomolar; 10^{-9} mol/L; 10^{-6} mol/m^3

DECLARATION

The author of this thesis, Sungwon Han, confirms that some data included in *Figures 8*, *11*, *12*, and *13* were also included in another article written by Sungwon Han, Ricardo Marquez-Gomez, Myles Woodman and Tommas J. Ellender and published in the Journal of Neuroscience (JN-RM-0740-20; DOI: 10.1523/JNEUROSCI.0740-20.2020; Article publication on 24 July 2020; Journal publication on 19 August 2020).

Ⅰ. Introduction

1. Histamine in the central nervous system (CNS)

1.1. Production of histamine and histaminergic neurons

Histamine is a biogenic amine that has essential functions in inflammatory and immune responses (Thurmond *et al*., 2008; O'Mahony *et al*., 2011), but is also active in the brain. In the brain, histamine can be found in both neurons and mast cells (Garbarg *et al*., 1976) where it is synthesised from the essential amino acid L-histidine through oxidative decarboxylation by histidine decarboxylase (HDC), a pyridoxal 5′-phosphate-dependent enzyme (Brown *et al*., 2001; Fleming *et al*., 2004; Thakkar, 2011) in neuronal bodies and terminals (Nieto-Alamilla *et al*., 2016) (***Figure 1***). The enzyme HDC is transcriptionally regulated by DNA methylation (Kuramasu *et al*., 1998; Suzuki-Ishigaki *et al*., 2000), and post-translationally processed (Olmo *et al*., 2000; Fleming *et al*., 2004) in peripheral tissues. However, transcriptional regulation of the HDC in the mammal brain is not commonly reported (Haas *et al*., 2008; Huang *et al*., 2018).

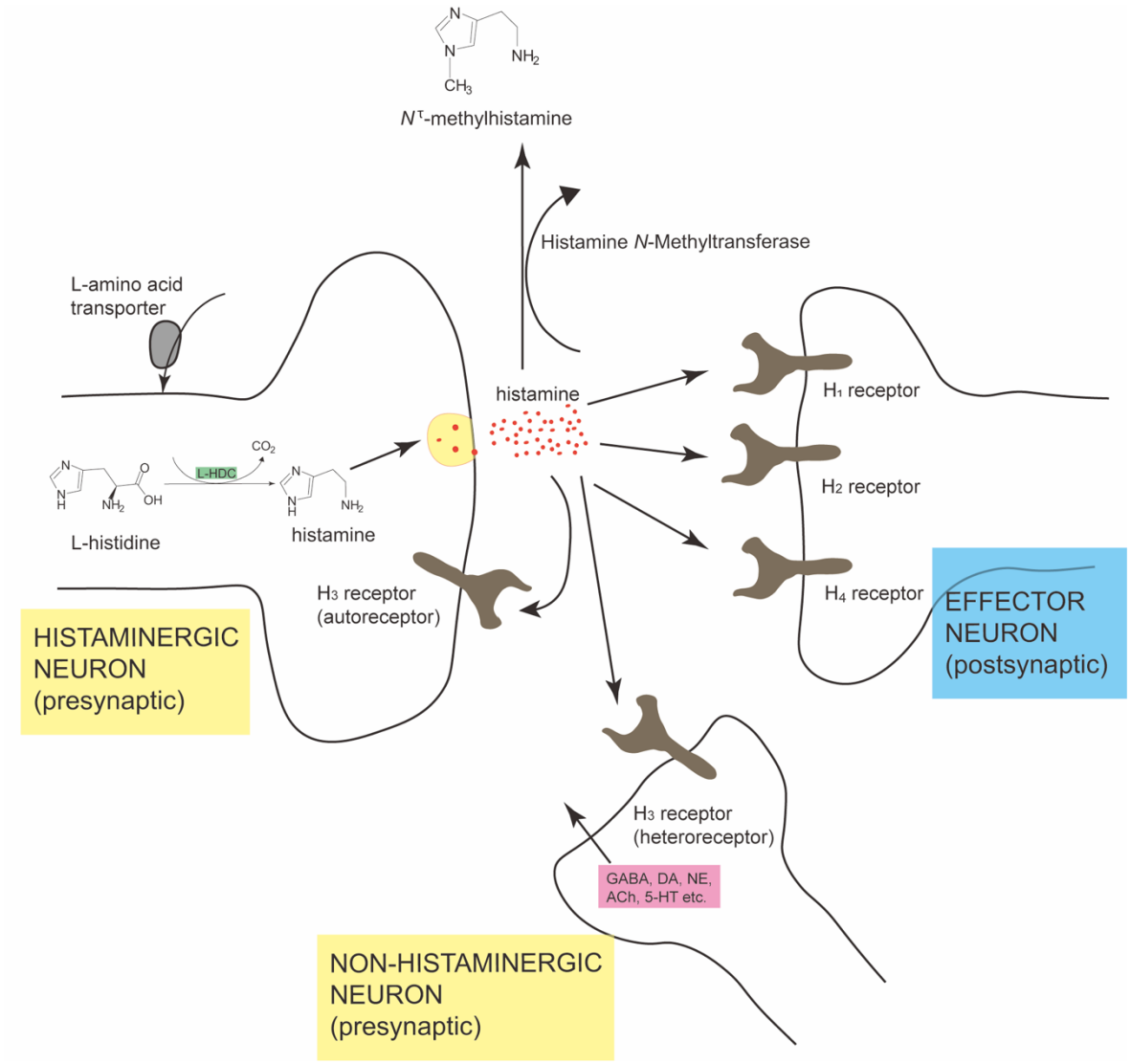


***Figure 1*. Histamine and histamine receptors.**

L-histidine enters the presynaptic neuron through the L-amino acid transporter. L-histidine is then synthesised to histamine by L-histidine decarboxylase (HDC), which then crosses synaptic cleft to bind to histamine receptors. The H_3 receptor has dual functions as an autoreceptor (on histaminergic neurons) and a heteroreceptor (on non-histaminergic neuron axon terminals). The heteroreceptor role of the H_3 receptor is to control several other neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA), dopamine (DA), norepinephrine (NE), acetylcholine (Ach) and serotonin (5-hydroxytryptamine; 5-HT) on terminals where they are located (i.e.: The H_3 receptor regulates glutamate release on the glutamate terminal, and GABA release on the GABA terminal), and this is the key pathway in this research.

There are various types of cells that release histamine throughout the body. Major cells including mast cells, basophils, enterochromaffin-like (ECL) cells, and

histaminergic neurons release histamine after several types of activation signals such as immunoglobulin E (IgE) crosslinking (mast cell & basophil), gastrin (ECL cell) and the N-methyl-D-aspartate (NMDA) receptors (histaminergic neurons) and so on (Huang *et al.*, 2018). Minor cells including dendritic cells, T cells, macrophages, neutrophils and epithelial cells are also reported to release histamine with no external stimulation (Konttinen *et al*., 2013; Huang *et al.*, 2018). Alternatively, these cells can be divided into 'non-professional and professional histamine producing cells' depending upon several properties such as the rate of histamine synthesis, requirement for release, and concentration range (Konttinen *et al*., 2013).

Histaminergic neurons in the brain are exclusively located in the tuberomammillary nucleus (TMN) of the hypothalamus (Inagaki *et al*., 1988; Brown *et al*., 2001; Takahashi *et al*., 2006), which can be confirmed by histological expression (***Figure 2***). Histaminergic afferents are found throughout the brain in adulthood (Haas & Panula, 2003). In earlier age periods, histaminergic afferents were found in the cortex (from postnatal (P)3-6 period) and the striatum (from P9-12 period) of mice (Han *et al*., 2020).

Histamine seems to be present in the brain from the prenatal period, and its level increases with age. Histamine levels in the rat brain were not matched to synaptogenesis (Aghajanian & Bloom, 1967) and were 5 to 6 times higher in the 1st postnatal week than in the adult age period (Pearce & Schanberg, 1969; Schwartz *et al*., 1971; Young *et al*., 1971). It was also found that histamine in the neonatal rat brain and the peripheral mast cell display slow turnover (Martres *et al*., 1975), whereas adult brain histamine demonstrated rapid turnover (Dismukes & Snyder, 1974; Pollard *et al*., 1974). Other studies reported that brain histamine is mainly found in the mast cells during the neonatal period (Young *et al*., 1971; Picatoste *et al*.,

1977), while brain histamine is mainly found in synaptosomes (Kataoka & De Robertis, 1967; Kuhar *et al*., 1971; Picatoste *et al*., 1977). This is supported by another ontogenic study using rats that shows that changes in the level of brain histamine are correlated to the number of the brain mast cells in the developmental period; the number of brain mast cells showed a rapid increase by postnatal day (P)5 followed by a rapid decrease until P21, while the level of brain histamine showed rapid increase by P5-10 and then a rapid drop by P20-25 (Ferrer *et al*., 1979).

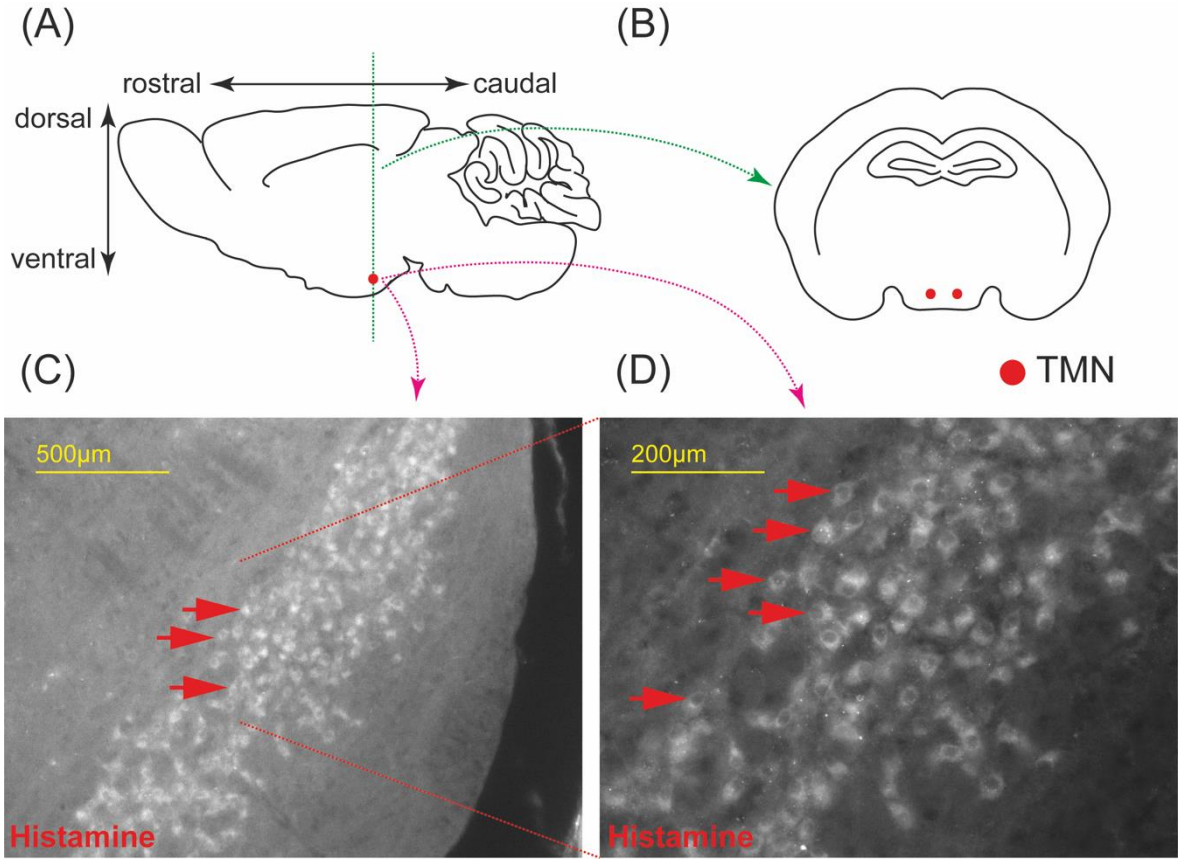


***Figure 2*. Histaminergic cells in the tuberomammillary nucleus (TMN) in a young adult mouse brain.**

Histological expression of histaminergic cells in the TMN. **(A)** The sagittal plane of mouse brain. The red point indicates the location of TMN. **(B)** The coronal plane of the mouse brain showing the TMN. This comes from the green line in the coronal section. **(C)** Microscopic image of the histaminergic cells in the TMN of postnatal 21 days mouse with red fluorescent protein antibody: Magnification ×4; Scale bar 500μm. **(D)** Zoom in image in magnification ×10 and scale bar 200μm. Histamine neurons were labelled using a histamine polyclonal antibody and Cy3 conjugated secondary antibody.

Histamine has been reported to have several roles in the brain. Often thought of as a neuromodulator in the mammalian brain (Taylor & Snyder, 1972; Schwartz, 1975; Taylor, 1975), histaminergic cells in the TMN release histamine widely throughout the brain and parts of the spinal cord (Watanabe *et al*., 1983; Panula *et al*., 1984; Wada *et al*., 1991; Nieto-Alamilla *et al*., 2016) where histamine activates metabotropic G-protein coupled receptors (Hill *et al*., 1997; Leurs *et al*., 2005).

1.2. Histamine receptors

Histamine is thought to be mainly acting at G-protein coupled metabotropic receptors, which include the H_1, H_2, H_3 and H_4 receptors (Schwartz *et al*., 1986; Roznieckі *et al*., 1999; Barnes, 2001; Brown *et al*., 2001; Haas & Panula, 2003; Connelly *et al*., 2009). The H_1 and H_2 receptors are located mainly postsynaptically whereas the H_3 receptors are thought to be mainly located presynaptically (Arrang *et al*., 1983; Brown *et al*., 2001; Bertlich *et al*., 2014; Schlicker & Kathmann, 2016), though other research reported that the H_3 receptor also acts postsynaptically in several brain regions such as the cerebral cortex, striatum, hippocampus, nucleus accumbens (NAc), lateral hypothalamus and zona incerta (Pillot *et al*., 2002; Arrang *et al*., 2007; González-Sepúlveda *et al*., 2013; Parks *et al*., 2014). The H_1 (G_q) receptor is coupled with the activation of phospholipase C and mediates activating protein kinase C (Megson *et al*., 2001), whereas the H_2 (G_s) receptor activates adenylate cyclase and phospholipase C (Wang *et al*., 1997). The H_3 ($G_{i/o}$) receptor inhibits various kinds of neurotransmitters such as acetylcholine, histamine, noradrenaline and serotonin in the central and peripheral tissues of various animals such as pigs, guinea pigs, rats, and humans (“the H_3 receptor as a heteroreceptor or

presynaptic autoreceptor") (Ishikawa & Sperelakis, 1987; Trzeciakowski, 1987; Schlicker *et al*., 1988; Tamura *et al*., 1988; Schlicker & Göthert, 1991; Molderings *et al*., 1992; Schlicker *et al*., 1994). The H_3 receptor also inhibits histaminergic neurons' impulse flow ("the H_3 receptor as a somadendritic autoreceptor") and histamine synthesis (Schlicker & Kathmann, 2016), and is expressed at high levels in embryonic periods. In a messenger ribonucleic acid (mRNA) expression study with rats, the peak level of H_3 receptor mRNA expression was found in the central and peripheral nervous system, adipose tissue, skin, thymus, respiratory, and tongue epithelia (Héron *et al*., 2001). Specifically, the adipose tissue showed the highest level of expression on embryonic day 20, but very low levels in early postnatal periods (Héron *et al*., 2001). The human H_4 receptor couples to co-expressed Gαi2 in Sf9 cells (Schneider & Seifert, 2016). The H_1 receptor knockout (KO) mouse shows deficits in sensitivity to pain (Inoue *et al*., 1996) and lower levels of anxiety than controls in the elevated plus-maze (Yanai *et al*., 1998), while the H_2 receptor deficient mice showed no change of gastric pH which implies compensation by the muscarinic acetylcholine M_1 receptor (Kobayashi *et al*., 2000). They did, however, show reductions in interleukin-12 and interleukin-6 and an increase in monocyte chemoattractant protein-1, which is a pro-inflammatory mediator, in antigen-presenting cells (Teuscher *et al*., 2004). The H_3 receptor KO mouse shows deficits in locomotion, wheel-running behaviour, and body temperature during the dark phase (Toyota *et al*., 2002), whereas the H_4 receptor deficient mice showed deficits of histamine-induced calcium mobilisation and chemotaxis in their mast cells as compared to control mice (Hofstra *et al*., 2003). The presence and function of the H_4 receptor in the brain is still disputed, and the absence of functional H_4 receptors in the human, guinea pig and mouse cortex has been reported (Feliszek *et al*., 2015),

though several research groups reported detection of the H_4 receptor at the mRNA level in brain tissue (Cogé *et al*., 2001; Liu *et al*., 2001; Zhu *et al*., 2001; Strakhova *et al*., 2009) and by an antibody investigation in the human cortex, mouse thalamus, hippocampus and cortex (Connelly *et al.*, 2009).

The presence of histamine receptors in the striatum changes dynamically as mice age. In a recent investigation using quantitative polymerase chain reaction (PCR), the striatum section of acute mice brain slices was analysed with mRNA quantification and qualification. As a result, transcripts for the H_3 receptor showed a dramatic increase in the P9-12 age period and further increase in P21-35, whereas transcripts for the H_1 and H_2 receptors showed constant mRNA expression in the P3-6, P9-12, and P21-35 periods (Han *et al*., 2020).

2. Histamine's function in the brain

A wide range of functions have been ascribed to histamine, including regulating wakefulness and sleep, attention, arousal, learning and memory, brain energy metabolism, feeding, drinking, neuroendocrine, locomotor activity, autonomic and vestibular functions, sexual behaviour and analgesia (White & Rumbold, 1988; Lin *et al*., 1989; Schwartz *et al*., 1991; Wada *et al*., 1991; Parmentier *et al*., 2002; Haas & Panula, 2003; Anaclet *et al*., 2009).

Histamine levels are correlated with alertness and sleep. In rodents, it was found that the highest level of histamine release occurred during wakefulness, and the lowest level during sleep in the caudate nucleus and mid-brain (Friedman & Walker, 1968), and the hypothalamus (Orr & Quay, 1975). Indeed, the histaminergic neurons in the TMN are highly active during wakefulness (Takahashi *et al*., 2006; Saper *et al*., 2010; Lin *et al*., 2011), but are silent during sleep (Haas & Panula, 2003; Takahashi *et al*., 2006; Takahashi *et al*., 2010; Sakai *et al*., 2010). Several studies used administration of α-fluoromethylhistidine (α-FMH), an irreversible inhibitor of the HDC enzyme that results in low levels of histamine in the brain, and observed depressed wakefulness and increased non-rapid eye movement (NREM) sleep in experiments with rats and cats, whereas administration of histamine in the TMN increased arousal and latency to sleep in experiments with cats (Kiyono *et al*., 1985; Lin *et al*., 1988).

Histamine also regulates several aspects of cognition such as learning and memory. In studies conducted with rats, it was reported that α-FMH application prolongs the response latency in active avoidance response tasks (Kamei *et al*., 1993). In studies on rats and mice, intraperitoneal or oral administration of histidine

and the H_1 and H_3 receptors antagonists resulted in enhanced memory in maze navigation, object recognition and passive avoidance tasks (Huang *et al*., 2003; Yamamoto *et al*., 2007; Bertoni *et al*., 2008; Pascoli *et al*., 2009; Xu *et al*., 2009), though a negative impact was also found in recognition and active/passive avoidance tasks (Kamei *et al*., 1990; Blandina *et al*., 1996). As for object recognition, male HDC-KO mice showed a lower level of performance in a non-reinforced object exploration task (Dere *et al*., 2003). Later studies discovered that the H_1 receptor KO mice and the H_2 receptor KO mice showed impaired performance in object recognition, with another discovery that long-term potentiation (LTP) in the CA1 area of the hippocampus was reduced in both the H_1 KO and the H_2 KO, as compared to that in control mice (Dai *et al*., 2007).

2.1. Psychiatric disorders caused by reduction of histamine

Histamine has been reported to cause or be associated with various mental diseases including sleep disorders, cognitive depletion and Alzheimer's disease, schizophrenia, additive behaviour, multiple sclerosis, motor disorders and Parkinson's disease, Huntington's disease, attention deficit hyperactivity disorder (ADHD), depression, Tourette’s syndrome and obsessive-compulsive disorder.

In humans, a decreased level of histamine has been found in those with sleep-related disorders. Chronic narcolepsy and hypersomnia patients showed lower levels of cerebrospinal fluid (CSF) histamine than normal (Nishino *et al*., 2009; Kanbayashi *et al*., 2009), which was consistent with a study that showed rat CSF histamine levels increased as a result of a lack of sleep and administration of the H_3 receptor (Soya *et al*., 2008). An inverse H_3 receptor agonist, pitolisant, increased the

level of wakefulness and cortical arousal in orexin$^{-/-}$ (hypocretin$^{-/-}$) mice, and enhanced excessive daytime sleepiness (EDS) in patients with narcolepsy, as compared to a placebo group (Lin *et al*., 2008). All of these previous finding indicate that a decreased level of histamine is associated with sleep pathologies.

2.2. Tourette's syndrome and obsessive-compulsive disorder

Decreased histamine levels in the brain are suggested to cause Tourette's syndrome and obsessive-compulsive disorder (OCD) (Rapanelli & Pittenger 2016; Pittenger, 2017). An investigation of deoxyribonucleic acid (DNA) samples extracted from the blood of Tourette's syndrome patients showed a functional mutation of the HDC gene (W317X) encoding L-histidine decarboxylase, which synthesizes histamine (Ercan-Sencicek *et al*., 2010). The study showed that the mutant HDC resulted in a decrease in enzymatic activities of wild-type HDC using a fluorescence-based assay reporting histamine concentration (Ercan-Sencicek *et al*., 2010).

Later studies discovered histamine's contribution to Tourette's syndrome or OCD-like symptoms. One study found that depletion of the HDC contributed to Tourette's syndrome with tic behaviour in the HDC KO mice and impaired prepulse inhibition in both mice and humans (Baldan *et al*., 2014). Another study reported that disrupted histaminergic cells in the mice brain are linked to grooming (Rapanelli *et al*., 2017). It was also confirmed that no significant discrepancy was found between wild type mice and the HDC KO mice in morphological and cytological phenotypes, but that histamine deficiency contributes to behavioural alterations (Abdurakhmanova *et al*., 2017). In this report, T2-weighted magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) were used to assess differences in microstructural

changes in the white matter of the brain between the HDC KO mice and controls, and no significant difference was found (Abdurakhmanova *et al*., 2017). However, in open field behavioural measurement, the HDC KO mice showed shorter rearing times (Day 1) and fewer vertical counts (Day 1-2) as compared to controls, while no significant difference between these two groups was found on the third day (Abdurakhmanova *et al*., 2017). These discrepancies between humans and mice imply that the HDC KO mouse model does not recapitulate all the symptoms described in humans (Abdurakhmanova *et al*., 2017).

It was also found that histamine can modulate different synapses in adult mice (Ellender *et al*., 2011). They observed that histamine negatively modulates both corticostriatal and thalamostriatal input acting at the H_3 receptors, and that it modulates short-term plasticity (paired pulse ratio) selectively (D_2 SPN only, not D_1 SPN) (Ellender *et al*., 2011).

The HDC mutation is a rare genetic cause as it was not found outside the patient group (Ercan-Sencicek *et al*., 2010). On the other hand, recent research has suggested the possibility of other genetic causes (i.e.: cadherin gene (CDH2) and De Novo mutation) of Tourette's syndrome and obsessive-compulsive disorder (Moya *et al*., 2013; Willsey *et al*., 2017). However, considering histamine's interaction with other brain monoamines such as dopamine, serotonin and norepinephrine in the central nervous system (CNS) (Haas *et al*., 2008; Escobedo-Avila *et al*., 2014; Baldan *et al*., 2014; Flik *et al*., 2015), further study of histamine's role in the brain is necessary to understand the causes and mechanisms of psychiatric diseases.

Together, these previous investigations suggest that histamine plays many important roles in psychiatric diseases by acting at histaminergic neurons and their

receptors. However, most of them were reported with adult animals, which did not provide details of histamine's impact throughout development.

3. Synaptic transmission and plasticity

Synaptic transmission happens among neurons with changing electrical and chemical properties. Excitatory dendritic and somatic inputs are caused by the positively-charged cation influx, and this depolarises the plasma membrane. As the axon potential reaches the presynaptic neuron (axon terminal), extracellular Ca^{2+} enters the presynaptic neuron through calcium channels, which allows vesicles to diffuse neurotransmitters to the postsynaptic neuron through the synaptic cleft (***Figure 3A***). Depending on the dynamics of neurotransmitters and receptors, synaptic transmission is either excitatory or inhibitory (***Figure 3B***). The sum of excitatory and inhibitory inputs to dendrites can lead to the generation of axon potentials (***Figure 3B***). Following the quantal hypothesis, the postsynaptic response (I) depends on the neurotransmitter release probability (Pr) from a pool of releasable quanta (N) of defined quantal amplitude (Q) (Dobrunz & Stevens, 1997; Glasgow *et al*., 2019). The strength of an evoked postsynaptic response can be demonstrated as:

$$I = Q\,Pr\,N$$

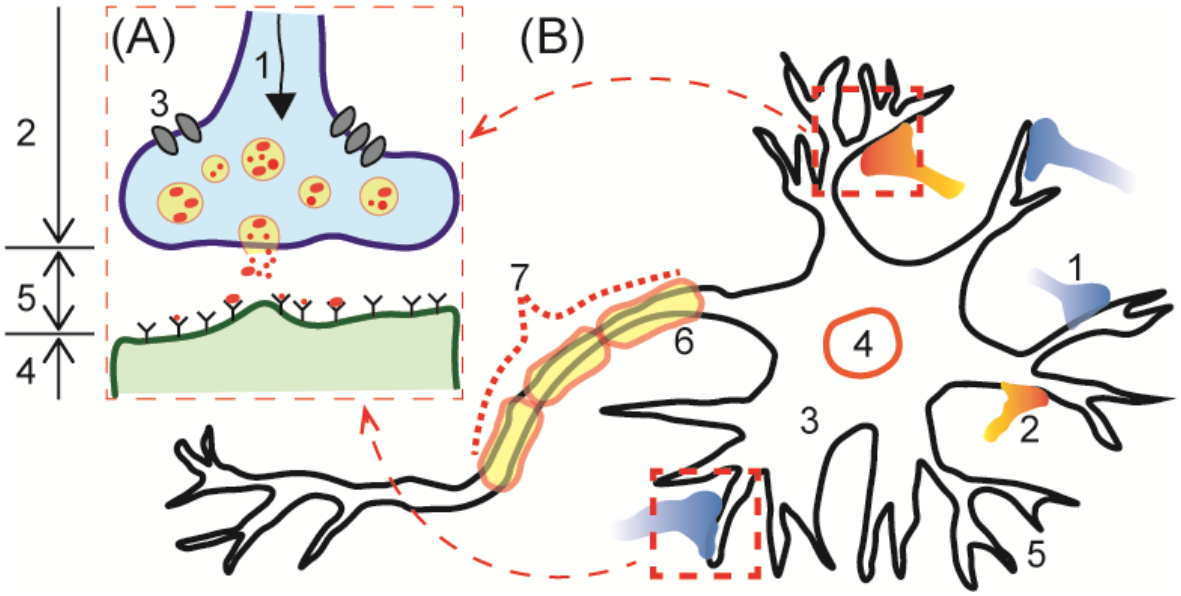


***Figure 3*. Diagram of synaptic transmission.**

(A) Presynaptic and postsynaptic neurons. When action potential (A1) comes down to the axon terminal, presynaptic neuron (A2), calcium channels open (A3). Ca^{2+} infiltrates from outside into presynaptic neuron through calcium channels and then let vesicles (yellow circles inside presynaptic neuron) release neurotransmitter (red dots inside vesicles) to postsynaptic neuron (A4) through synaptic cleft (A5). Neurotransmitters bind to receptors on the postsynaptic neuron, which stimulates postsynaptic neuron and produces signal. **(B)** Neuron. Depending upon types of neurotransmitters and receptors, synaptic transmission become excitatory (B1, blue) or inhibitory (B2, red-yellow). (B3) Soma (cell body). (B4) Nucleus. (B5) Dendrite. (B6) Myelin. (B7) Axon.

3.1. Short-term plasticity

Synapses are plastic and can therefore increase or decrease in strength. There are two forms of plasticity: Short-term plasticity and long-term plasticity. Short-term synaptic plasticity refers to synaptic potentiation or depression lasting several milliseconds to minutes (Zucker & Regehr, 2002). This is thought to correlate with sensory inputs, behavioural transient changes and short-term memory (Citri & Malenka, 2008). There are several types of short-term plasticity: paired-pulse

facilitation and depression, facilitation and depression following trains of stimuli, and modulation of transmission by presynaptic receptors (Citri & Malenka, 2008).

If two continuous stimulations are given within a short interval (typically 20-100ms), the second action potential (pulse) can be strengthened or depressed (Katz & Miledi, 1967; Zucker & Regehr, 2002). One hypothesis to explain this change is based on the dynamics of calcium regulation in synapses, though there are various mechanisms which affect the change of the second pulse compared to the first (Glasgow *et al*., 2019). The ratio of the peak amplitude of the two continuous pulses is referred to as “paired pulse ratio (PPR)”, and this relates to changes of synaptic properties depending upon the release probability (*Pr*) in the presynaptic site. If a significant number of residual calcium ions remain inside the presynaptic neuron (axon terminal), the second stimulus will interact with a relatively higher amount of them, resulting in a longer peak amplitude for the second action potential (***Figure 4B up***). This is called paired pulse facilitation (PPF). If the number of vesicles in the presynaptic neuron decreases significantly after the first action potential and the second stimulus reach the axon terminal and before the restoration of the vesicles, the second stimulus will interact with relatively fewer calcium ions, which results in a shorter peak amplitude for the second action potential (***Figure 4B middle***). This is called paired pulse depression (PPD). PPF and PPD are parts of examples of short-term plasticity. If continuous stimuluses are given within a sufficient interval (more than 1s), presynaptic vesicles are sufficiently restored and as a result, the first and second action potentials are the same or similar to each other (***Figure 4B bottom***).

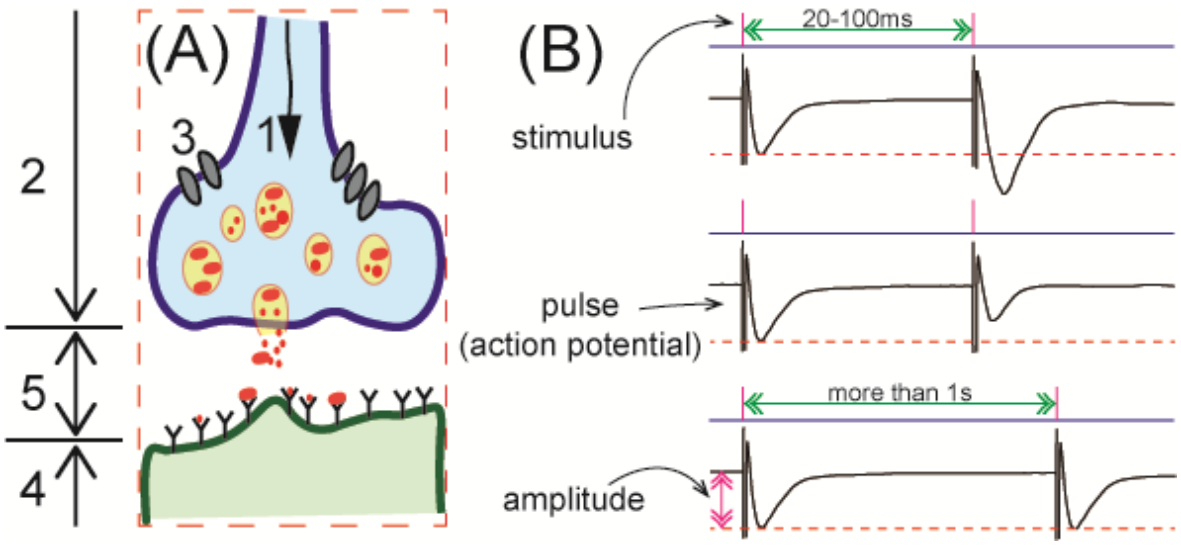


***Figure 4*. Paired Pulse Ratio.**

(A) Presynaptic and postsynaptic neurons. When an action potential (A1) comes down to the axon terminal, presynaptic neuron (A2), Extracellular Ca^{2+} ions enters the presynaptic neuron through calcium channels (A3) and then the vesicles (yellow circles inside presynaptic neuron) release neurotransmitters (red dots inside vesicles) to the postsynaptic neuron (A4) through the synaptic cleft (A5). Neurotransmitters bind to receptors on the postsynaptic neuron, which stimulates postsynaptic neuron and produces signal. **(B)** Paired Pulses. If a significant amount of residual Ca^{2+} ions remain in the axon terminal, the second pulse (action potential) interacts with a higher amount of residual Ca^{2+} ions, which results in paired pulse facilitation (B up). By contrast, if the amount of residual Ca^{2+} ions in the axon terminal decreased significantly, the second pulse interacts with a smaller amount of residual Ca^{2+} ions, which results in paired pulse depression (B middle). Both paired pulse facilitation and depression happen when the paired stimulations are given in quick succession (20-100ms). However, if the gap between paired stimulations is longer (i.e.: more than 1s), the presynaptic vesicles are restored enough and there is no significant change between the first and second peak amplitudes.

Another type of short-term plasticity is formed by repetitive stimulation on synapses, which results in transient enhanced transmitter release that lasts from seconds (augmentation) to several minutes (post-tetanic potentiation; PTP) (Feng, 1941; Hughes, 1958; Rosenthal, 1969; Magleby & Zengel, 1975; Zucker & Lara-Estrella, 1983; Magleby, 1987; Griffith, 1990; Zucker & Regehr, 2002; Citri & Malenka, 2008). PTP occurs when tetanic trains of stimulation at high frequency (10-200Hz) within 200ms to 5s produce short-term plasticity, whereas augmentation occurs at lower frequency (Magleby, 1987; Zucker & Regehr, 2002; Regehr, 2012). It is believed that the tetanic stimulation increases the release probability in the presynaptic axon terminal due to the increase in calcium ions induced by the subsequent action potentials, and that this increase in calcium ions causes presynaptic biochemical changes (Magleby & Zengel, 1982; Zucker & Regehr, 2002; Citri & Malenka, 2008).

3.2. Long-term plasticity

Long-term synaptic plasticity refers to long-lasting potentiation or depression of synaptic strength. The Pavlovian conditioning theory (Pavlov, 1927) is based on a correlation between presynaptic activities and postsynaptic firing generating associative memories in the brain (Hebb, 1949), suggesting that synaptic plasticity results from two coincident events' association with a behavioural action (Pavlov, 1927). Later studies demonstrated that repetitive activation of excitatory synapses in the rabbit hippocampus induced enhanced synaptic change which lasted hours or days (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973).

The excitatory synaptic strength is mediated by changes of function and the number of three major glutamate receptors on the postsynaptic neuron: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, N-methyl-D-aspartate (NMDA) receptors and kainate receptors (Hollmann & Heinemann, 1994). These receptors bind glutamate that is released from the presynaptic neuron, and depolarise the postsynaptic membrane (Hollmann & Heinemann, 1994; Dingledine *et al*., 1999). AMPA receptors consist of four subunits (GluR1, GluR2, GluR3 and GluR4), which have membrane channels that are permeable to monovalent cations (Na^+ and K^+) (Glasgow *et al*., 2019). Those that lack the GluR2 subunit are permeable to Ca^{2+} (Cull-Candy *et al*., 2006). NMDA receptors consist of an essential NR1 subunit and multiple NR2 subunits, and all NMDA receptors are permeable to Na^+, K^+ (Lüscher & Malenka, 2012) and Ca^{2+} (Rao & Finkbeiner, 2007). Kainate receptors consist of two high-affinity subunits and three low-affinity subunits (Hollmann & Heinemann, 1994), and activation of the presynaptic kainate receptors regulates the amount of neurotransmitter released (Schmitz *et al*., 2001; Huettner, 2003; Mayer, 2005). When action potential descends to the presynaptic axon terminal, the neurotransmitter glutamates are released from the presynaptic neuron to the postsynaptic membrane. In low frequency conditions, less action potential stimulates the axon terminal which results in the release of fewer glutamates. These open the postsynaptic AMPA receptors, allowing Na^+ ions to enter the postsynaptic neuron and generate depolarisation. The postsynaptic NMDA receptors, however, are blocked by Mg^{2+} ions in this small amount of released glutamate. In high frequency conditions, more action potential stimulates the axon terminal, releasing more glutamate that leads to postsynaptic depolarisation. This removes the Mg^{2+} ion block of the postsynaptic NMDA receptors, and Ca^{2+} ions enter the postsynaptic neuron

through the NMDA receptors. When the stimulation is more intense, synaptic properties change including protein synthesis, which can result in long-lasting synaptic potentiation or depression.

There are various types of long-term plasticity: NMDA receptor dependent long-term potentiation/depression, metabotropic glutamate receptor dependent long-term depression, endocannabinoid-mediated long-term depression and metaplasticity (Citri & Malenka, 2008). Long-term plasticity is induced by activation of both the presynaptic and postsynaptic neurons. When the axon potential reaches the presynaptic terminal, the neurotransmitter glutamate is released from the presynaptic neuron. The NMDA receptors are blocked by Mg^{2+} ions at resting membrane potentials (Mayer *et al.*, 1984; Nowak *et al.*, 1984). However, when enough stimuli are given, Mg^{2+} ions are expelled from the NMDA receptors and glutamate binds with them. This enables calcium influx to the postsynaptic neuron and causes intracellular signalling which may be linked to changes in synaptic properties (Lüscher & Malenka, 2012). In contrast, long-term depression is induced by activation of the presynaptic terminal in the absence of postsynaptic activation (in some paradigms). As the force driving calcium influx grows and ability of the Mg^{2+} ions to block the NMDA receptors is no longer stable at resting potentials, Ca^{2+} enters the postsynaptic neuron and produces intracellular signalling (Jahr & Stevens, 1993; Sabatini *et al*., 2002; Bloodgood & Sabatini 2007; Bloodgood *et al*., 2009). It is believed that long-term facilitation is associated with higher levels of intracellular postsynaptic Ca^{2+} caused by high frequency synaptic stimulation, whereas long-term depression is associated with smaller amount of it, triggered by low frequency synaptic stimulation.

Repeated series of brief bursts within 200ms intervals, known as theta-burst stimulation (TBS) (Larson *et al*., 1986) were found to cause long-lasting synaptic

changes in adult mice corticostriatal synapses (Hawes *et al*., 2013), and affect activity patterns of voluntary behaviour in rats (Tort *et al*., 2008). TBS in 10Hz or 50Hz frequency also demonstrates physiological activity properties in the young brain (Khazipov *et al*., 2004; Hanganu *et al*., 2006; Yang *et al*., 2009). This thesis explored how histamine impacts the short-term and long-term plasticity of the striatum in the mouse brain.

3.3. Recording methodologies

Synaptic input among neurons is one of the essential mechanisms to understand changes and development in the brain. There are several types of technological approaches to observing neuronal activities. Biochemical measurements provides neuroanatomic information (i.e.: *in situ* hybridization & single cell transcriptomics), cell-type specific and synaptic information (Fenno *et al*., 2011; Lin & Schnitzer, 2016). Electrophysiology in general offers high temporal resolution. However, extracellular electrophysiology is limited by its poor spatial resolution, whereas whole-cell patching is only able to observe single or simultaneous double neurons, which is not ideal for understanding network-level interactions (Miles & Poncer, 1996; Markram *et al*., 1997). Multi-cell recording is useful to understand the ensemble of neuronal activities, whereas single-cell recording is good to measure single channel conductance or kinetics (Graziane & Dong, 2016). As whole-cell recordings dialyse the intracellular components, this study chose extracellular field recording to minimise artificial changes to cells.

4. The basal ganglia and striatum

Dysfunction in the basal ganglia is thought to contribute to disorders such as Parkinson's disease, Huntington's disease, obsessive-compulsive disorder, Tourette's syndrome and drug addiction (Albin *et al*., 1989; DeLong, 1990; Graybiel & Rauch, 2000; Aouizerate *et al*., 2004; DeLong & Wichmann, 2007; Medina *et al*., 2014; Mink, 2001; Yael *et al*., 2015). The basal ganglia consist of an interconnected network of subcortical nuclei which are located in the ventral or subpallial part of the telencephalon, and they play critical roles in motivation, motor planning and cognitive functions (Graybiel *et al*., 1994; Hikosaka *et al*., 2000; Packard & Knowlton, 2002; Yin & Knowlton, 2006; Nicola, 2007; Kreitzer & Malenka, 2008; Medina *et al*., 2014; Bolam & Ellender, 2016). The striatum is the main input nucleus of the basal ganglia, receiving excitatory glutamatergic input from the cortex and thalamus as well as dopaminergic input from the midbrain (Bolam *et al*., 2000; Gerdeman *et al*., 2003; Gerfen, 2000; Bolam & Ellender, 2016). The striatum contains GABAergic interneurons (Kreitzer & Malenka, 2008) and approximately 95% of striatal neurons consist of GABAergic spiny projection neurons (SPNs) (also known as GABAergic medium spiny neurons (MSNs)), which can be distinguished as either the dopamine receptor 1 (D_1)-expressing SPNs or dopamine receptor 2 (D_2)-expressing SPNs. These respectively form the so-called direct and indirect pathways depending upon their projection pathway and target (Gerfen *et al*., 1990; Smith *et al*., 1998). The other 5% are composed of cholinergic and GABAergic interneurons.

The direct pathway is composed of GABAergic SPNs (GABAergic MSNs) sending axonal projections from the striatum to the *globus pallidus internus* (GPi) and *substantia nigra pars reticulatae* (SNr), which are the output nuclei of the basal

ganglia (Bolam & Ellender, 2016). The D_1-expressing neurons directly project to the GPi and SNr, whereas the D_2-expressing neurons project to the GPi and SNr through the *globus pallidus externus* (GPe) and subthalamic nucleus (STN). Previous studies reported that activating the direct or indirect pathways lead to opposing effects on movement, reinforcement, and reward-related behaviours (Hikida *et al*., 2010; Kravitz *et al*., 2010; Lobo *et al*., 2010; Ferguson *et al*., 2011; Kravitz *et al*., 2012). Malfunction of the basal ganglia causes motor tics, cardinal features of Tourette's syndrome and OCD, though the tic disorder has other sources such as the motor cortex and cerebellum (McCairn *et al*., 2013). A recent study investigated the distinct properties of D_1 and D_2 SPNs in early age periods. The study found that excitatory inputs from the cortex and thalamus to both the D_1 and D_2 SPNs are already functional in postnatal (P)3-6 days age groups by showing recordings of mEPSC amplitude, though the amplitude increased more in the thalamostriatal circuit between P3-6 days and P9-12 days than that in the same period scheme (Krajeski *et al*., 2019).

4.1. The dorsolateral striatum (DLS) and the dorsomedial striatum (DMS)

A number of studies investigated pathways in the striatum in action selection among mice (Hilario *et al*., 2012), rats (Yin *et al*., 2004; Yin *et al*., 2005a; Yin *et al*., 2005b; Yin *et al*., 2006; Corbit *et al*., 2007; Corbit & Janak, 2010; Corbit *et al*., 2012), non-human primates (Miyachi *et al*., 1997; Miyachi *et al*., 2002), and humans (Tricomi *et al*., 2009; McNamee *et al*., 2015). Accumulated evidence suggests that different parts of the striatum are associated with different types of behaviour. First, the nucleus accumbens is involved in stimulus-outcome associated actions such as Pavlovian learning (Setlow *et al*., 2003; Roitman *et al*., 2005; Balleine & O'Doherty,

2010; Liljeholm & O'Doherty, 2012), meaning that sensory stimuli and predicted outcomes are conditioned, though the 'outcome' that is experienced and the 'behaviour' are independent from each other (Cox & Witten, 2019). Second, the dorsomedial striatum (DMS) is involved in action-outcome associated action (or “goal-directed behaviour”) (Yin *et al*., 2005a; Yin *et al*., 2005b; Balleine *et al*., 2007; Yin *et al*., 2009; Redgrave *et al*., 2010; Balleine & O'Doherty, 2010; Thorn *et al*., 2010; Liljeholm & O'Doherty, 2012; Dolan & Dayan, 2013), meaning that the action is induced or motivated by the degree to which the outcome, which is thought to be caused by the ‘action’, is valuable (Cox & Witten, 2019). Third, the dorsolateral striatum (DLS) is involved in stimulus-response associated action (or “habit”) (Barnes *et al*., 2005; Yin & Knowlton, 2006; Yin *et al*., 2009; Redgrave *et al*., 2010; Balleine & O'Doherty, 2010; Thorn *et al*., 2010; Liljeholm & O'Doherty, 2012; Dolan & Dayan, 2013; O’Hare *et al*., 2016) meaning that the ‘stimuli’ becomes the automatic basis of the ‘response’ (Cox & Witten, 2019).

Based on this idea, there have been various experimental approaches to distinguish differential functions of each part of the striatum, depending upon differential sources of input from other parts of brain. For example, a study with rats using a T-maze indentified that the DMS and DLS are associated with different behaviour parameters (Thorn *et al*., 2010). Indeed, the prelimic cortex (PL) was associated with aversive stimulus behaviour, whereas the anterior cingulate cortex (ACC) was associated with several types of behaviour (Friedman *et al*., 2015). This implies the importance of further discoveries related to specific neural circuitry models of the loop in the basal ganglia covering the striatum, cortex and thalamus.

In terms of neural circuitry investigation, dopaminergic projection has been adopted to study the differential roles of the DMS and DLS. For example, it has been

found that dopaminergic activation triggers Pavlovian conditioning as a teaching signal (Steinberg *et al*., 2013; Chang *et al*., 2016; Saunders *et al*., 2018), dopaminergic neurons demonstrated reward prediction errors (Cohen *et al*., 2012; Howe & Dombeck, 2016; da Silva *et al*., 2018; Engelhard *et al*., 2019), and optogenetic manipulation of D_1-SPN enhanced spontaneous movement, whereas D_2-SPN inhibited it (Kravitz *et al*., 2010; Roseberry *et al*., 2016; Bartholomew *et al*., 2016). The role of histminergic neurons for the DMS and DLS functions, however, have not yet been investigated.

4.2. Long-term plasticity in the DMS and DLS

The long-term potentiation in the striatum was found in the corticostriatal circuit (Calabresi *et al*., 1992; Charpier & Deniau, 1997). It was believed that LTP plays a critical role in the enhancement of stimulus-response associated behaviour in the striatum (Reynolds & Wickens, 2002; Mahon *et al*., 2006). Furthermore, other studies reported differential properties of the DMS and DLS in long-term plasticity. Specifically, the DMS is more likely to represent long-term plasticity in both skill and response learning, whereas the DLS is available for both long-term plasticity and long-term depression (Lovinger, 2010). The NMDA and D_1 receptors are also more commonly found in the DMS, whereas the A2A, CB1 and D_2 receptors are more commonly found in the DLS (Lovinger, 2010). This different proportion of receptors in sub-regions might be related to different properties of long-term plasticity depending upon the location.

5. Cortical, thalamic, and striatal development of the rodents brain

The development of the rodent brain can be understood through evidence of neurogenesis in the cortical, thalamic and striatal regions, which shows the contribution of these brain regions to physiological functions.

5.1. Formation of the cortical layers and connection with the thalamus

In the mammalian brain, including the rodent brain, the cerebral cortex shows rapid and coalescing formation during its period of development (Northcutt & Kaas, 1995; Krubitzer & Huffman, 2000; Antón-Bolaños *et al*., 2019). The cortex is largely classified as the six-layered neocortex, whose neurons including projection neurons are born before adulthood in the ventricular zone (VZ) and subventricular zone (SVZ) of the lateral ventricle (Mountcastle, 1957; Rakic, 1988; López-Bendito & Molnár, 2003). The radial glial cells in the VZ and SVZ migrate to their final destinations in the cerebral cortex (Germain *et al*., 2010), and each cerebral cortical layer is formed over the developing age periods. Layer VI is found in the deepest location (the most inner part of the brain), and this layer develops first, whereas layer I is found closest to the outer surface (Gilmore & Herrup, 1997). Layer I is produced during the embryonic day (E)10.5 to E12.5, and layers II and III are formed between E13.5 and E16. Layers IV, V and VI are formed in E11.5 to E14.5 (Germain *et al*., 2010; Kwon & Sabatini, 2011).

In the mouse brain, neurons in the cortex are associated with sensory inputs through different thalamic nuclei. Specifically, first, neurons in layer IV of the primary somatosensory cortex (S1) are somatotopically corresponded with whisker input

through the ventrobasal complex (VB) (Woolsey & Van der Loos, 1970; López-Bendito & Molnár, 2003; Antón-Bolaños *et al*., 2019). Second, neurons in the primary auditory cortex (A1) are corresponded with acoustic input through the medial geniculate nucleus (MGN) (López-Bendito & Molnár, 2003). Third, neurons in the visual cortex (V1) are corresponded with visual input through the retina and the dorsal lateral geniculate nucleus (dLGN) (López-Bendito & Molnár, 2003). The connection between the cortex and the thalamus can be found by the period of neurogenesis. The thalamic neurons in the rat brain are born between E13 and E19 (Altman & Bayer, 1979), which is the same as the corticogenesis period (López-Bendito & Molnár, 2003). The neocortex and dorsal thalamus begin to connect to each other during the embryonic period, which in the mouse brain is between E13 and E18 (López-Bendito & Molnár, 2003).

5.2. Development of the corticostriatal brain and motor activities

In mice brain development, three developmental age periods can be distinguished in terms of the corticostriatal function in motor activities: postnatal days (P)3-6, P9-12, and P21+. Until (P)5, the striatal neurons are formed, and their intrinsic voltage-gated clustered calcium activities have few excitatory synaptic inputs, which can be seen in the limited movement of mice and rat pups (Khazipov *et al*., 2004; Dehorter *et al*., 2011). Synapse-driven depolarization begins in P5-P7, which is linked to the increased activities of oscillatory patterns (Khazipov *et al*., 2004; Dupont *et al*., 2006; Yang *et al*., 2009). From P10, SPNs generate a different type of corticostriatal activity as the SPN excitatory synapse develops rapidly, with its inputs to the striatum, and motor activities switch to continuous then discontinuous

(Brockmann *et al*., 2011; Peixoto *et al*., 2016). They generate intrinsic voltage-gated clustered calcium activity without synaptic components (Brockmann *et al*., 2011). From P21 onwards, they are regarded as young adults with some distinct features. It is thought that the separation of layer 5 is over in P21 (Rice *et al*., 1985), and barrels (S1), sublayers in layer 5, and trilaminar plate (S1) start to form from P22 (Rice *et al*., 1985).

6. The current study

The aim of this study is to investigate if and how the neuromodulator histamine affects the development of the neurons and circuits of the striatum. To investigate the role of histamine in postnatal synaptic transmission, this study has used electrophysiology with acute brain slices from different developmental stages, namely postnatal day (P)3-6, P9-12, and P21+, combined with a superfusion of histamine (10μM). As Tourette's syndrome is a childhood-onset developmental mental disorder characterised by multiple motor and phonic tics (Tamara, 2013; Georgitsi *et al*., 2016), it is valuable to investigate histamine's impact during the early age periods of mice. Secondly, to investigate the role of histamine in the generation of striatal neurons, this study has used pharmacological inhibition of the HDC enzyme in embryonic C57Bl/6 mice. These approaches allowed this paper to answer the following research questions:

(1) Does histamine modulate the corticostriatal synaptic transmission during early postnatal development?

(2) Does histamine modulate the short-term plasticity of corticostriatal synapses?

(3) Does histamine modulate the long-term plasticity of corticostriatal synapses?

(4) At which receptor(s) on the corticostriatal synapses does histamine act?

(5) Does inhibition of the HDC enzyme affect the development of the striatum?

Ⅱ. Materials and methods

1. Mice and animal welfare

All mice were C57Bl/6 wildtype mice of both sexes (male and female), which were bred in an individually ventilated cage (IVC) housed at the animal facility in the building of Biomedical Services at the University of Oxford, with controlled temperatures and daily cycles (12 hours light - 12 hours dark). In order to minimise the effects of litter size, maternal care, and sex, each specific group's data were assigned animals randomly. All the procedures followed the Animals (Scientific Procedures) Act (1986) in the UK.

2. Brain slices and ACSF

Brain slices including a sufficient size of the striatum were collected from postnatal mice in three age groups: postnatal day (P)3-6, P9-12, and P21 and later. The mice were anaesthetised with isolurane and then decapitated, based on the Animals (Scientific Procedures) Act (1986) in the UK. A vibrating microtome (Microm HM650V) was used to cut the brain slices in coronal sections of 350μm. The fresh brain slices were then placed in artificial cerebrospinal fluid (ACSF) containing 65mM Sucrose, 85mM NaCl, 2.5mM KCl, 1.25mM NaH_2PO_4, 7mM $MgCl_2$, 0.5mM $CaCl_2$, 25mM $NaHCO_3$ and 10mM glucose, pH 7.2-7.4, bubbled with carbogen gas (95% O2 + 5% CO2). These slices were immediately transferred to a storage beaker with different properties of ACSF containing: 130mM NaCl, 3.5mM KCl, 1.2mM NaH_2PO_4,

2mM $MgCl_2$, 2mM $CaCl_2$, 24mM $NaHCO_3$ and 10mM glucose, pH 7.2-7.4, at 32ºC and bubbled with carbogen gas until being used for recording.

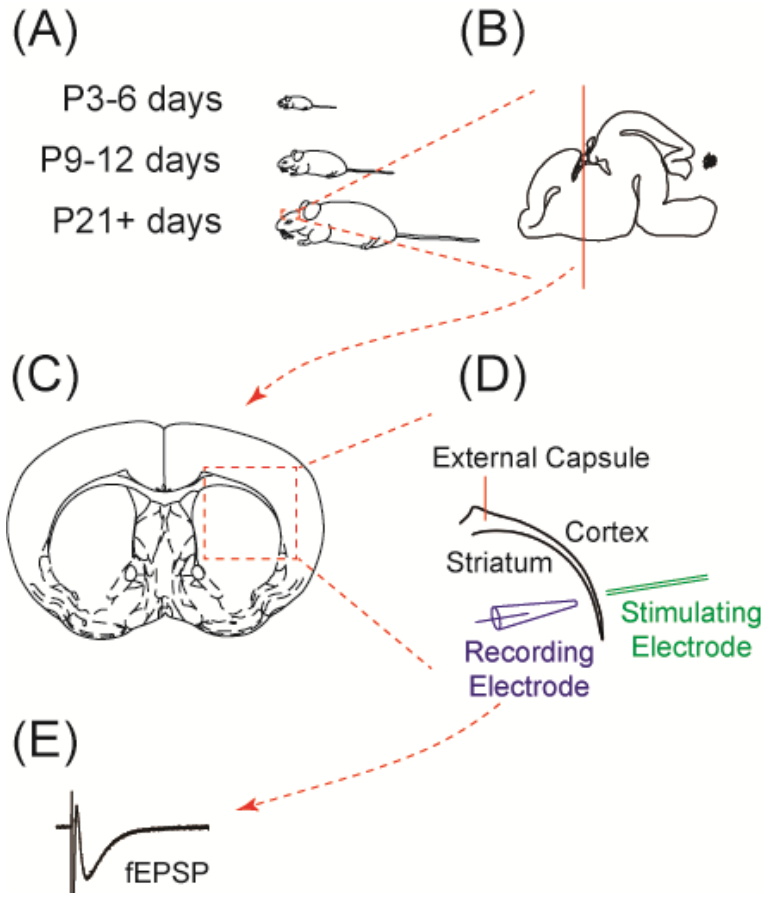


***Figure 5*. Experimental approach to study corticostriatal transmission.**

(A) The mouse brains were collected at three developing age groups: Postnatal day (P)3-6, P9-12, and P21+ days and used for experiments. **(B)** Diagram of sagittal plane of mouse brain. **(C)** Coronal sections were made including both cortex and striatum at 350μm - 400μm thickness. **(D)** Diagram of the recording conditions. A stimulating electrode was placed in the cortex close to the external capsule and the recording electrode was placed in the striatum. This recording configuration allows for the stimulation of large groups of cortical projection neurons and the recording of a field excitatory postsynaptic potential (fEPSP) using the recording electrode placed in the striatum. **(E)** An example fEPSP trace, which is obtained from the recording electrode.

3. Stimulation and recording protocols

A bipolar stimulating electrode (FHC Inc., USA) or a glass electrode was placed on the external capsule or the cortex (Layer 4-6) to activate excitatory cortical afferents towards the striatum. A DS2 isolated voltage stimulator (Digitimer, UK) ranging from 10V to 100V and 200μs in duration and stimulation strength was used to generate electrical stimulating pulses. On each recording of the brain slice, the half-maximum of field excitatory postsynaptic potentials (fEPSPs) was first measured and calculated based on several recordings before recording for the study started.

Cortical afferents were activated electrically every 5 or 10 seconds during drug superfusion and synaptic plasticity experiments. Continuous training stimulations included 6 pulses given at 20Hz repeated at 30s intervals up to 5 times. Long-term synaptic plasticity stimulations consisted of stimulating cortical afferents at 5s or 10s intervals, and the first 5 minutes were recorded to obtain a stable baseline of fEPSP amplitude. The theta-burst stimulation (TBS) paradigm in 10Hz or 50Hz or 100Hz frequency was given immediately after the baseline recording. These TBS consisted of 13 pulses given at 10Hz or 50Hz or 100Hz, and repeated 20 times with a 200ms interval. After this TMS stimulation, afferents were activated every 5s or 10s for at least 40 minutes to record the amplitude of fEPSP and evaluate potential long-term changes over time.

Electrical stimulation was performed by placing a metal stimulating electrode in the external capsule for activation of the corticostriatal afferents. The activation of excitatory afferents was performed in the presence of blockers of inhibitory GABAergic transmission including the $GABA_A$ receptor antagonist SR95531 (10μM) to inhibit the channel opening for the $GABA_A$ receptor. Fibres were activated every 10

seconds and fEPSP was recorded in the placed cells in the striatum. For paired pulse stimulation, two stimulating pulses were consecutively given at 50ms interval and repeated twice. Baseline responses were measured for 5 minutes after which the striatum was washed in histamine (10μM) for 35 minutes. For the thioperamide experiment, the first 5 minutes featured a superfusion of only thioperamide (10μM), and then histamine (10μM) and thioperamide (10μM) were used for the next 35 minutes.

4. Field recording devices

An interface chamber (Scientific Systems Design, Hofheim, Germany) was used for extracellular field recording, with continuous superfusion of ACSF bubbled with carbogen gas with the same composition as the storage solution (32 °C and perfusion speed of 2 ml/min). The acute brain slice was placed on the net of the chamber (the no. (C6) at ***Figure 6***). Data was collected using glass pipettes, pulled from standard wall borosilicate glass capillaries and containing ACSF in the interface conditions using a Multiclamp 700A amplifier (Axon Instruments, Molecular Devices, CA, USA), filtered at 4kHz and acquired at 10kHz using a X-series USB-6341 A/D board (National Instruments, Texas, USA) and WinWCP software (University of Strathclyde, RRID:SCR_014713) at 10kHz.

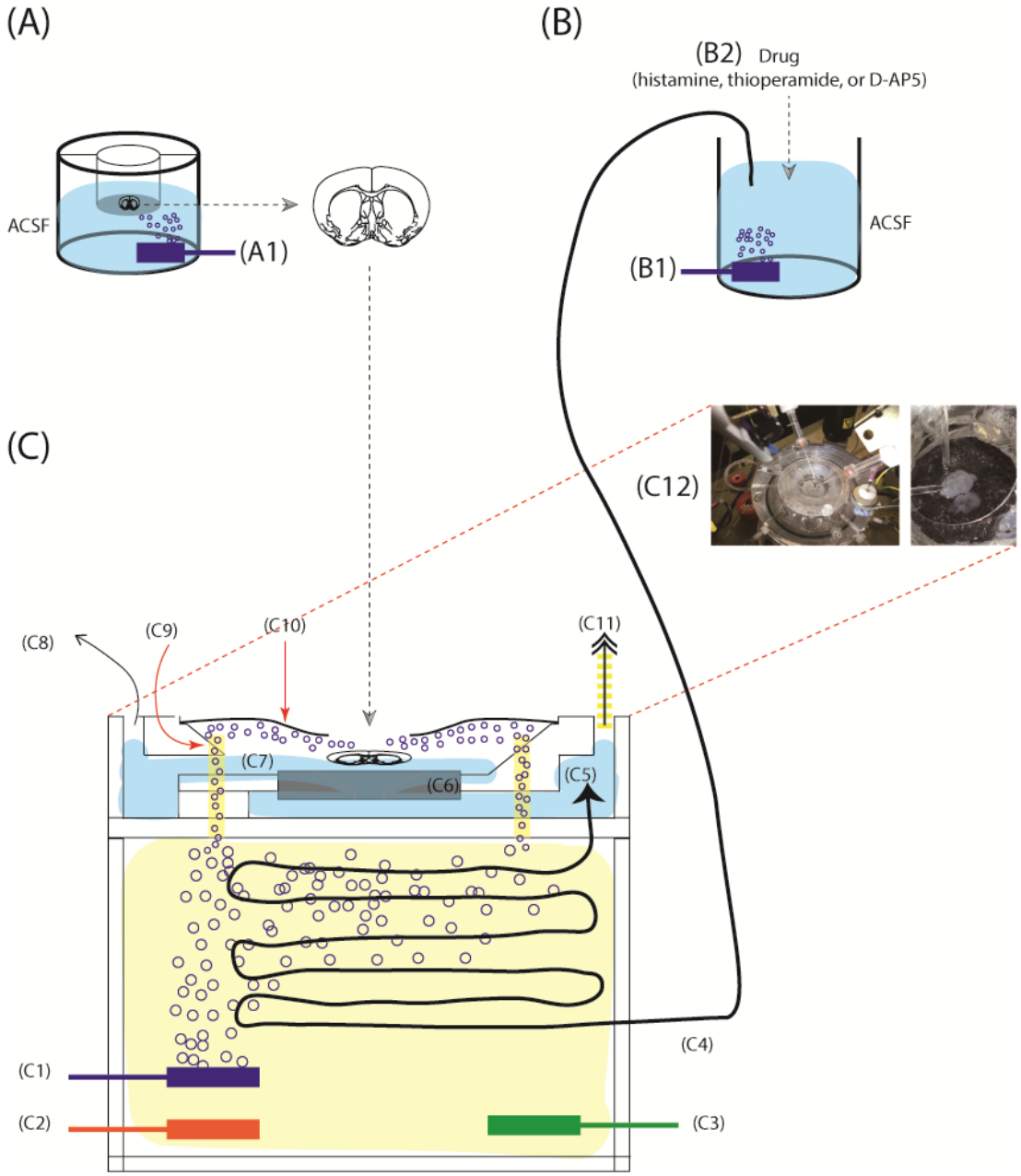


***Figure 6*. Experimental setup for field recordings.**

The recordings of fEPSP were collected in an interface chamber. **(A)** Fresh brain slices were immediately kept in a beaker with artificial cerebrospinal fluid (ACSF). An air tube (A1) was settled to provide enough air (95% oxygen + 5% carbon dioxide). Acute brain slice (A2) was placed on the net (C6) of interface chamber for recording. **(B)** A bottle was used to provide ACSF with an air tube (B1), and drug (B2: histamine, thioperamide or D-AP5) was superfused into this bottle. **(C)** The interface chamber. The lower part of the interface chamber was filled with distilled water (light yellow colour). Air was added to the lower part of the interface chamber by an air tube (C1). A heater (C2) was used to raise temperature of filled distilled water with measure its temperature by a temperature sensor (C3). ACSF was circulated by tube (C4), which passed lower part of the chamber with receiving heat by warm distilled water. ACSF reached upper part of the chamber (C5) including the net (C6) and placed brain slice (C7), and then exited the chamber (C8) for circulation. Vapour from the lower part of

the chamber reached the brain slice via holes (C9). A cover (C10) kept this vapour to provide moisture to the brain slice. There was another exit hole to release air bubbles of circulating ACSF (C11). C12: The real example photo of interface chamber.

5. Injection of α-fluoromethylhistidine (α-FMH) and data analysis of the striatum size

5µg/µL of α-fluoromethylhistidine (α-FMH) was prepared in H_2O and then injected into the ventricle of embryo brains after anesthetising the pregnant mouse. 60-70% of embryos (i.e.: seven of 10 embryos) were injected with α-FMH while the others were not for controls. Three days after injection, the pregnant mouse was anesthetised and decapitated. Immediately after that, all embryos were decapitated and then submerged in ice-cold 0.1M phosphate buffer (PB), pH 7.4, followed by ice-cold 4% 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide HCl (Thermo Fisher Scientific) in 0.1M PB, pH 7.4. The brains were left in the same fixative for 3 days followed by 3% paraformaldehyde in 0.1M PB for 1 day. After rinsing, the sections were incubated with DAPI (4′,6-diamidino-2-phenylindole) to label nuclei. Images were taken by a microscope for analysis. The striatum was distinguished by “caudate-putamen” and “lateral ganglionic eminence, ventricular and subventricular zones (striatal neuroepithelium)” for comparing size between control and α-FMH conditions. The size analysis was divided into three section groups: rostral, medial and caudal sections. Between rostral and medial sections, for those who had a smaller size of caudate-putamen than that of lateral ganglionic eminence, ventricular & subventricular zones (striatal neuroepithelium) were regarded as rostral sections. Between medial and caudal sections, those whose cortical mantle section became curved were classified as caudal sections. The size was taken by the Java-based

image-processing software "ImageJ", developed by the National Institutes of Health (Bethesda, Maryland, United States of America) and the University of Wisconsin. Due to the importance of accuracy and animal welfare, the *in utero* injections of α-FMH to the ventricle of embryo brains were carried out by the author and the author's supervisor, Dr. Tommas J. Ellender. Apart from this, all procedures were performed by the author under the supervision of Dr. Ellender.

6. Histamine fluorescence antibody processing

Mice were anaesthetized and decapitated and their brains were removed and briefly submerged in ice-cold 0.1M PB, pH 7.4, followed by ice-cold 4% 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide HCl (Thermo Fisher Scientific) in 0.1M PB, pH 7.4. The brains were left in the same fixative for 3 days followed by 3% paraformaldehyde in 0.1M PB for 1 day. Sagittal vibratome sections (60μm) were made and incubated with 10% normal goat serum in phosphate buffered saline (PBS) with Triton-X100 for 2 hours. Then, the primary antibody (with 0.3% PBS-Tx) was incubated at 1:5000 for 48 hours, and then washed 3 times with PBS (Histamine antibody: Cat #22939, Lot #1532001, Immuno Star). Goat anti-rabbit secondary (goat anti rabbit 555; 1:500) was subsequently added for 2 hours after wash-in with PBS. The section was then mounted on slides with Vectashield.

7. Drugs and chemicals

Field recording experiments used the following drugs: histamine (10μM), the H_3 receptor antagonist thioperamide (10μM), D-(-)-2-Amino-5-phosphonopentanoic

acid (D-AP5) (50μM), the NMDA receptor antagonist, and SR95531 (200nM), the $GABA_A$ receptor antagonist. The concentration of these materials (10μM & 50μM) was decided by consulting previous studies (Jafri *et al*., 1997; Brown & Haas, 1999; Atzori *et al*., 2000; Doreulee *et al*., 2001; Yu *et al*., 2009; Ellender *et al*., 2011; Zhuang *et al*., 2018) and several pilot experiments of the current study. The concentration of histamine (10μM) was decided in order to secure a sufficient level of histamine's effect. All drugs were purchased from Tocris Biosciences (Bristol, UK).

8. Analysis of recorded fEPSPs

Recorded fEPSP data were analysed in the software Igor Pro 8 (Wavemetrics, RRID:SCR_000325). Most fEPSP recordings showed a stimulation artefact, a first negativity, direct activation of neurons and axons presynaptic fibre volley, and a second negativity, synaptic transmission (Malenka & Kocsis, 1988; Flagmeyer *et al*., 1997). The amplitude of the action potential was calculated by the gap between the peak amplitude and the baseline. Rise time was measured by the time gap between the lowest amplitude point between fibre volley and the peak point of fEPSP, whereas the decay time was measured by the time gap between the peak and the end point of fEPSP. The duration was the sum of the rise time and decay time. As for short-term plasticity analysis, the values of the amplitude of the second to the last fEPSPs were divided by the value of the first fEPSP on every recording.

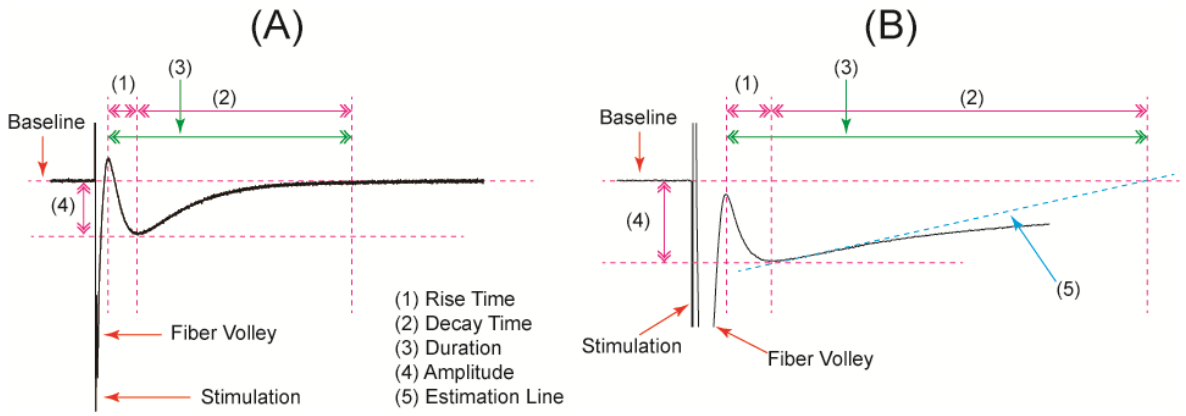


***Figure 7*. Example trace of field excitatory postsynaptic potential (fEPSP) and the analysis of the various parameters.**

The electrophysiological properties were calculated manually from filtered and averaged traces (~20 sweeps) in the data were loaded to the software "Igor Pro". **(A)** Parameters measured from fEPSP. **(B)** Parameters measured from fEPSP with the estimation line. Baseline: The average of value at y-axis before stimulation. *(1)* Rise Time: The time gap between the lowest amplitude point between fibre volley and the peak point of fEPSP. *(2)* De cay Time: Time gap between the peak and the end point of fEPSP. *(3)* Duration: Sum of rise time and decay time. *(4)* Amplitude: The amplitude of fEPSP was measured by gap between baseline and the peak. *(5)* Estimation Line: When the end point of fEPSP did not return completely to baseline, an estimated linear curve was fitted to the decaying phase of the fEPSP by connecting and expanding the two time points of the fEPSP curve at 22.67ms and 24.85ms or appropriate points.

9. Statistics

All numerical data are presented as means ± SEM. The 'n' refers to the number of brain sections tested. Continuous data were assessed for normality, and appropriate parametric statistical tests (analysis of variance (ANOVA), paired t-test and independent t-test) or non-parametric statistical tests (Wilcoxon Signed Ranks Test and Mann-Whitney U Test) were performed using IBM SPSS Statistics 26 (*$p<0.05$, **$p<0.01$).

Ⅲ. Result

1. Histamine reduces the corticostriatal fEPSP amplitude at all developmental ages by acting at the H_3 receptor.

Previous studies showed a negative modulation of histamine in the corticostriatal circuit due to their acting at the presynaptic H_3 receptors (Doreulee *et al*., 2001; Ellender *et al*., 2011). These results were found using adult mice, and it was not known yet whether the same effect of histamine would be found in earlier age periods or not. Therefore, this study used acute coronal slices of mouse brains from three developmental age groups (postnatal day (P)3-6, P9-12, & P21+) to investigate histamine's effect on the corticostriatal synaptic transmission in early age periods.

Three postnatal age periods were selected based on previous studies in this study: Postnatal (P)3-6, P9-12 and P21+. The first postnatal week (P3-6) shows the fewest excitatory synaptic inputs, but most of the striatal SPNs are born in this period. The second postnatal week (P9-12) is when excitatory inputs enter the rapid maturation period. The young adulthood period (P21+) is regarded to start to have mature striatal SPNs and circuits (Tepper *et al*., 1998; Khazipov *et al*., 2004; Dehorter *et al*., 2011; Kozorovitskiy *et al*., 2012; Peixoto *et al*., 2016; Peixoto *et al*., 2019).

First, this study superfused only artificial cerebrospinal fluid (ACSF) for 5 minutes, and then added histamine (10μM) for the next 35 minutes. The histamine's concentration (10μM) was determined by referring to previous studies which showed dose-response report IC50/EC50 values of ~2-3μM with maximum effects at ~5μM (Jafri *et al*., 1997; Brown & Haas, 1999; Atzori *et al*., 2000; Doreulee *et al*., 2001; Yu *et al*., 2009; Ellender *et al*., 2011; Zhuang *et al*., 2018). The study placed a stimulus

electrode on the cortex (around Layer V/VI) or the external capsule, and placed the recording electrode in the striatum close to the external capsule with the stimulus electrode (***Figure 8A***). During the 40-minute recording, the stimulus electrode stimulated the external capsule every 5-10 seconds, and recorded the fEPSP response evoked in the striatum. This fEPSP demonstrates synaptic activation of large numbers of corticostriatal excitatory synapses on the striatal SPNs, including both the D_1 and D_2 SPNs (Malenka & Kocsis, 1988; Flagmeyer *et al*., 1997). The stimulation was given either as a single pulse or twice in close succession with a 50ms interval. In order to isolate the glutamatergic afferents, the study included 200nM of gabazine (SR-95531), the $GABA_A$ receptor antagonist.

This study discovered that in all three age groups a superfusion of histamine (10µM) lead to a progressive reduction in fEPSP amplitude (***Figure 8***). Indeed, when analysing the average amplitude at the end (35-40 minutes) of each recording compared to the baseline (00-05 minutes), the study found that there is a significant reduction in the normalised fEPSP amplitude in all three age groups (normalised change in fEPSP amplitude, P3-6: to 87.95 ± 4.57%, P9-12: to 83.87 ± 5.46% and P21+: to 83.29 ± 4.04%: p=0.046, p=0.042 and p=0.009 respectively, paired t-test, n=6 / 5 mice, n=5 / 5 mice, and n=6 / 6 mice, ***Figure 8B-D***).

To determine at which histamine receptor histamine is acting, the study used thioperamide, which is a potent and selective H_3 and H_4 antagonist. Given that it is not yet clear whether the H_4 receptors are located in the central or peripheral regions of the brain despite previous reports of expressions of the H_4 receptors in the brain (Cogé *et al*., 2001; van Rijn *et al*., 2006; Strakhova *et al*., 2009; Marson, 2011), thioperamide likely only acts at the H_3 receptors in the brain. Previous studies also showed that histamine modulates the corticostriatal transmission through the H_3

receptors in adult mice (Doreulee *et al*., 2001; Ellender *et al*., 2011). Thioperamide (10μM) was superfused from the beginning to the end, whereas histamine (10μM) was added between 5 minutes and 40 minutes (for 35 minutes).

As a result, this study found that thioperamide application blocked the histamine modulation on the fEPSP amplitude in all three age groups (normalised change in fEPSP amplitude, P3-6: to 95.19 ± 2.44%, P9-12: to 100.39 ± 2.17% and P21+: to 99.97 ± 3.70%: p=0.096, p=0.862 and p=0.993, paired t-test, n=7 / 2 mice, n=8 / 3 mice and n=5 / 2 mice, ***Figure 8B-D***).

Lastly, the study recorded fEPSP for 40 minutes in ACSF without adding any drug to confirm whether the reduction in fEPSP amplitude was truly made by histamine, or could be ascribed to other causes. As a result, the study found that there was no significant change of normalised fEPSP amplitude (normalised change in fEPSP amplitude, P3-6: to 100.82 ± 2.22%, P9-12: to 100.38 ± 1.48% and P21+: to 103.93 ± 1.60%: p=1.000, p=0.715 and p=0.109, Wilcoxon Signed Rank Test, n=4 / 4 mice, n=4 / 3 mice and n=3 / 3 mice, ***Figure 8B-D***).

These results suggest that histamine is able to negatively modulate corticostriatal transmission from the earliest postnatal days, and histamine acts on the H_3 receptor in these developmental ages. As this study showed that blocking the H_3 receptor prevented histamine's negative modulation on normalised fEPSP amplitude, this result is based on the presynaptic glutamatergic neuron terminal (non-histaminergic neuron) (see ***Figure 1***).

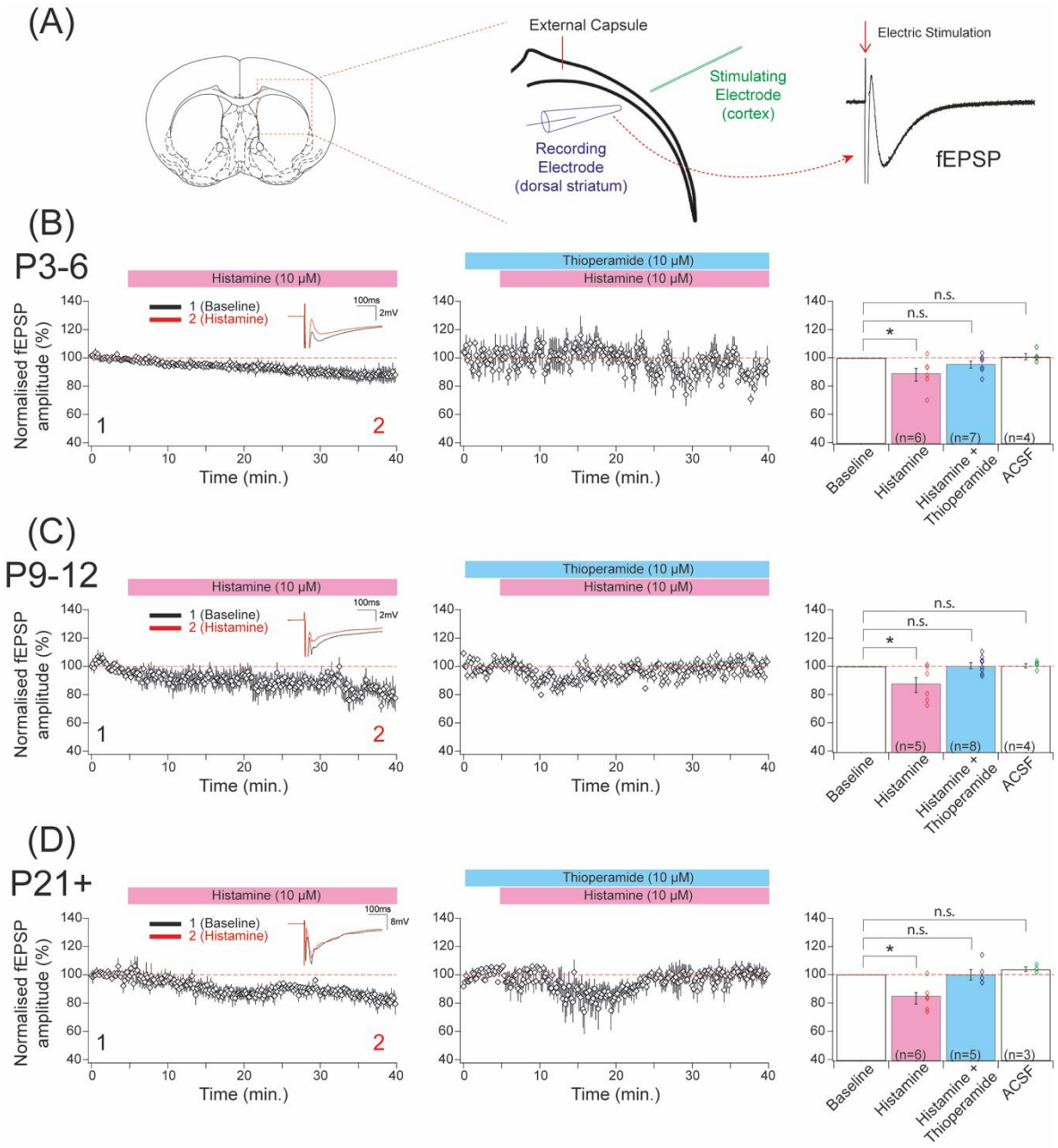


***Figure 8*. Histamine reduces corticostriatal fEPSP amplitude at all development ages.**

(A, left) An example acute brain slice which had a sufficient amount of striatum was used for experiment. **(A, middle)** Recording electrode was placed on the dorsal striatum and stimulating electrode was placed on the external capsule or cortex. **(A, right)** An example fEPSP, which is obtained by the recording electrode. **(B, left)** Histamine superfusion (10μM) significantly reduced the amplitude of corticostriatal fEPSPs in P3-6. Two example fEPSP traces correspond to the mean of fEPSP in the first 5 minutes (00-05 min; black) and the last 5 minutes (35-40 min; red). **(B, middle)** Thioperamide (10μM), the H_3 receptor antagonist, blocked the histamine-mediated reduction of normalised fEPSP amplitude. **(B, right)** The bar graph of the baseline, the effect of histamine alone, the effect of histamine together with thioperamide, and only ACSF condition in the corticostriatal fEPSP amplitude. The values are means of

the first 5 minutes recording for baseline (00-05 min), and the last 5 minutes of recordings for only histamine (35-40 min), or histamine in combination with thioperamide (35-40 min), or only ACSF (35-40 min). Histamine's negative modulation on the corticostriatal fEPSP amplitude and thioperamide's blocking were found also in the P9-12 (C) and P21+ age (D) groups. Paired t-test & Wilcoxon Signed Rank Test: *p<0.05; n.s.: non-significant.

2. Short-term plasticity did not change after histamine application.

To examine whether histamine acts at the presynaptic or postsynaptic side of the synaptic terminal, the current study stimulated the corticostriatal afferents with short pulses of electrical stimulation given at 20Hz frequency. A total of 6 pulses were given and the changes in fEPSP amplitude were analysed. If the amplitude of the fEPSP increased within the train this is called short-term facilitation and if the amplitude of the fEPSP decrease within the train this is called short-term depression. It is often assumed that a change in the paired pulse ratio is a reflection of presynaptic changes (Thomson, 2000). In order to block the $GABA_A$ receptors, the current study included 200nM of gabazine (SR-95531).

This study took the recording with ACSF, and then again after a 40 minute superfusion of histamine (10μM). As a result, this study found that the relative ratio is facilitated in ACSF conditions in the P3-6 age group (change in fEPSP amplitude ratio between the 1^{st} and 2^{nd} pulses, P3-6 ACSF: to 1.48 ± 0.1, p=0.040, paired t-test, n=6 / 6 mice, ***Figure 9B***). Histamine did not cause a significant change in the relative ratio, as compared to that of the ACSF condition in the P3-6 age group ($F(1, 130)=8.172$, p=0.059, ***Figure 9B***), and the P9-12 age group ($F(1, 100)=0.592$, p=0.444, ***Figure 9C***). However, histamine changed the ratio significantly in the P21+ age group ($F(1, 100)=7.309$, p=0.008, ***Figure 9D***).

In conclusion, these results suggest that histamine does not cause changes in short-term plasticity in field recordings, as compared to control conditions in all three postnatal weeks.

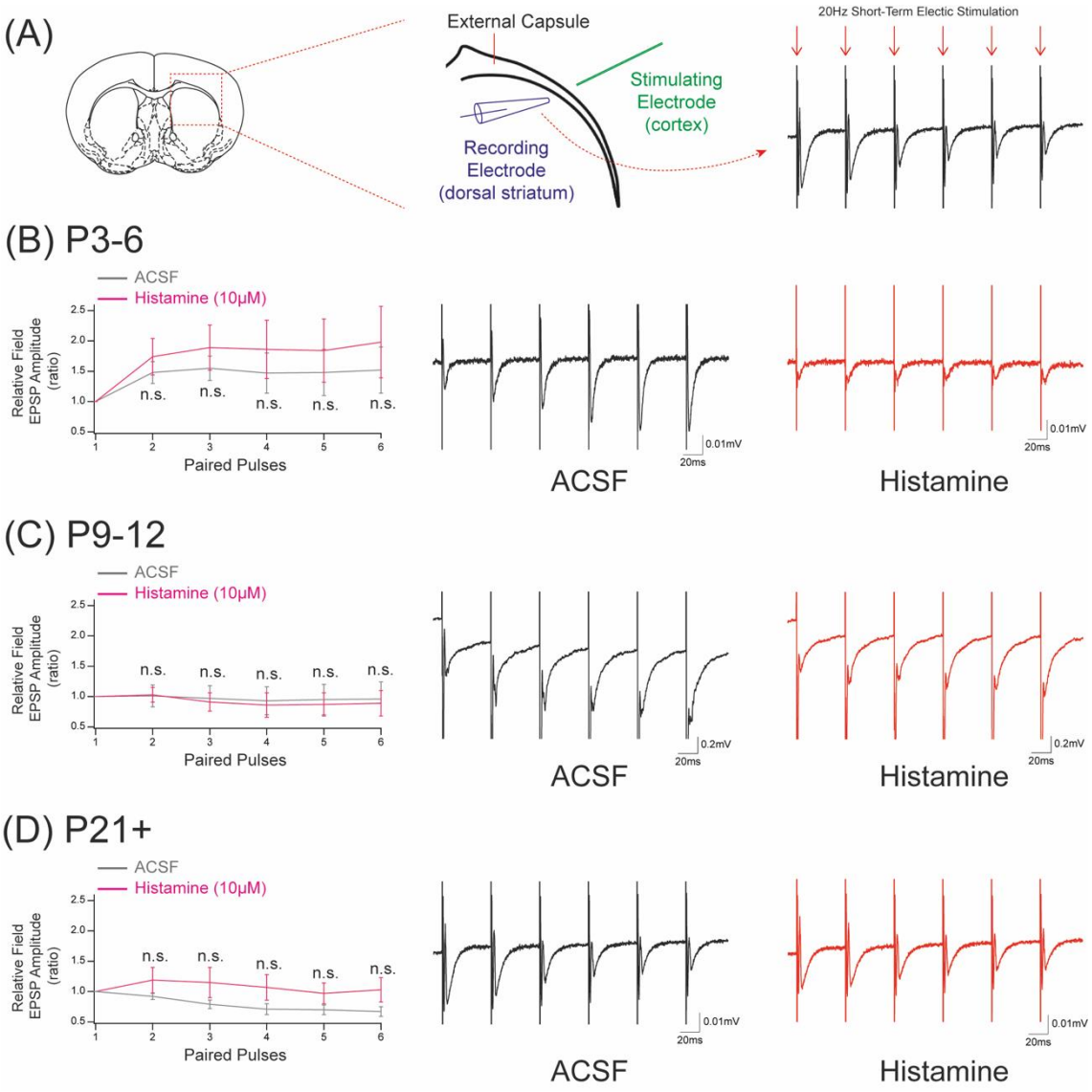


***Figure 9*. Histamine leads to facilitated relative fEPSP ratio of early ages (P3-6) in short term (20Hz) stimulation.**

(A, left) An example acute brain slice which had a sufficient amount of the striatum was used for the experiment. **(A, middle)** Recording electrode was placed on the dorsal striatum and stimulating electrode was placed on the external capsule or cortex. **(A, right)** An example of continuous fEPSPs, which are obtained by the recording electrode with 20Hz stimulation scheme. **(B-D, left)** Comparison of the relative fEPSP amplitude ratio in each of 3 age groups. Histamine showed a higher ratio than ACSF did, but the gap was not statistically significant. **(B-D, middle)** Example traces of 6 consecutive stimulations in 20Hz and corresponding fEPSPs in ACSF (baseline) condition. **(B-D, right)** Example traces of 6 consecutive stimulations in 20Hz and corresponding fEPSPs in histamine condition. Paired t-test & two-way ANOVA: *p<0.05; n.s.: non-significant.

3. Low frequency (10Hz) theta-burst stimulation (TBS) did not lead to long-term plasticity.

The results of this study confirm that histamine modulates synaptic transmission in early developing ages, though they could not identify an effect of histamine on short-term plasticity. This study also questioned whether histamine affects long-term plasticity or not by using three repeated bursts condtions: 10Hz (low frequency), 50Hz (high frequency) and 100Hz (high frequency) (see ***Introduction*** and ***Materials and Methods***). This idea was called 'theta-burst stimulation (TBS)' (Larson *et al*., 1986), and studies with TBS found that TBS triggers long-term potentiation in the dorsostriatal circiut of the adult brain (Hawes *et al*., 2013), demonstrates the striatal and hippocampal activities of rats in decision-making behaviour tasks (Tort *et al*., 2008), reflects physiological properties of young brains (Khazipov *et al*., 2004; Hanganu *et al*., 2006; Yang *et al*., 2009), and showed an increased level of dopamine in the striatal circuit and enhancement in motor activities (Cacace *et al*., 2017). However, none of the previous studies reported long-term plasticity in the corticostriatal synapses of the mouse brain in early age periods or the effect of histamine. Similar to previous experiments, acute brain slices were collected from young developing age groups (P3-6, P9-12 and P21+) and the corticostriatal synapses were recorded by placing a recording electrode on the dorsal striatum and placing a stimulating electrode on the external capsule or cortex, which is close to the recording electrode. The first 5 minutes were recorded for the baseline, and then one of three types of TBS (10Hz or 50Hz or 100Hz) was given. This study then continuted to record for the next 35 minutes (***Figure 10***). The TBS in this study gave continuous 13 stimulation in 10Hz (repeated stimulations with 100ms gap), 50Hz (repeated stimulations with 20ms gap), or 100Hz (repeated stimulations with 10ms gap); this

set of 13 stimulations was repeated 20 times with a 200ms gap. To block the glutamatergic afferents, this study included 200nM of gabazine (SR-95531) for all recordings. This study performed experiments in ACSF (control) and histamine conditions separately. Each condition was analysed for long-term plasticity by comparing each recording's first and last 5 minutes (paired comparison), and analysed whether histamine brought any changes, as compared to controls (ACSF condition), by comparing these two conditions in the last 5 minutes.

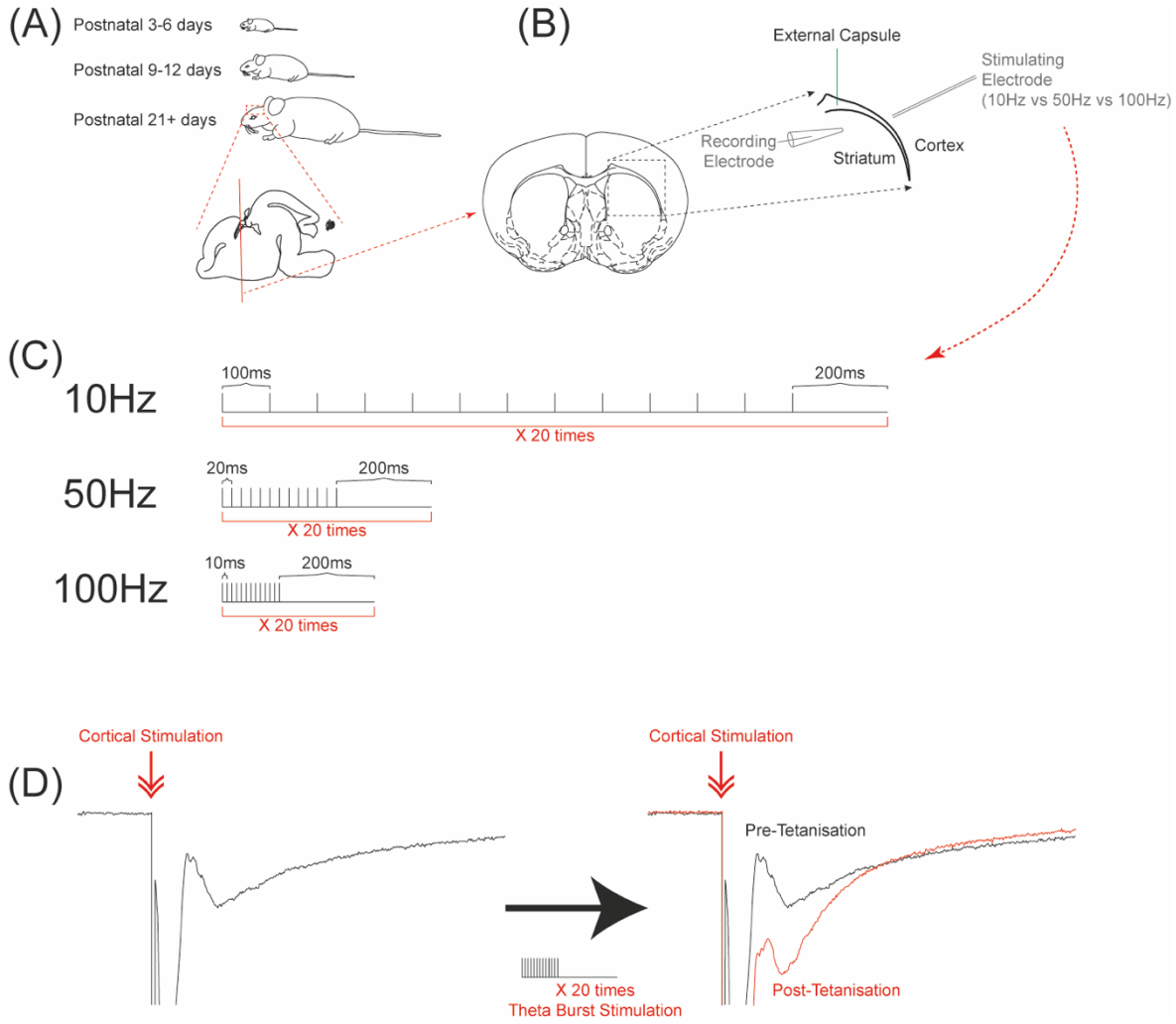


***Figure 10*. Stimulation patterns used for long term plasticity experiments.**

(A) The coronal acute brain slices (350μm) were collected from three developing age groups (P3-6, P9-12 and P21+). **(B)** The stimulation electrode was placed on or near the external capsule from the cortex side, whereas the recording electrode was placed on the striatum. **(C)** The stimulation electrode supplied tetanisation of one of

three frequency patterns (10Hz, 50Hz and 100Hz). One serial set of tetanisation included 13 stimulation, and this was repeated 20 times (total 260 stimulations). **(D)** Example of fEPSP shape before (black colour fEPSP shape) and after (red colour) theta-burst tetanisation.

In 10Hz TBS, none of the six conditions showed a long-term change in normalised fEPSP, and there was no significant difference between ACSF and histamine conditions (normalised change in fEPSP amplitude, P3-6 10Hz ACSF 00-05 min vs P3-6 10Hz ACSF 35-40 min: to 104.41 ± 6.22%, P3-6 10Hz Histamine 00-05 min vs P3-6 10Hz Histamine 35-40 min: 96.25 ± 4.04%, P9-12 10Hz ACSF 00-05 min vs P9-12 10Hz ACSF 35-40 min: to 106.01 ± 4.19%, P9-12 10Hz Histamine 00-05 min vs P9-12 10Hz Histamine 35-40 min: to 94.31 ± 5.48%, P21+ 10Hz ACSF 00-05 min vs P21+ 10Hz ACSF 35-40 min: to 108.54 ± 2.95%, P21+ 10Hz Histamine vs P21+ 10Hz Histamine 35-40 min: to 123.73 ± 14.32%, p=0.510, p=0.406, p=0.189, p=0.358, p=0.068, and p=0.109, paired t-test and Wilcoxon Signed Ranks Test, n=6 / 6 mice, n=5 / 5 mice, n=9 / 8 mice, n=5 / 5 mice, n=4 / 4 mice, and n=3 / 3 mice, ***Figure 11A-C***).

Secondly, this study compared the normalised fEPSP amplitude of ACSF (control) and histamine conditions in the last 5 minutes. As a result, histamine did not cause any significant change in long-term plasticity, as compared to ACSF in the same age conditions (normalised change in fEPSP amplitude, P3-6 10Hz ACSF 35-40 min: 104.41 ± 6.22% vs P3-6 10Hz Histamine 35-40 min: 96.25 ± 4.04%, P9-12 10Hz ACSF 35-40 min: 106.01 ± 4.19% vs P9-12 10Hz Histamine 35-40 min: 94.31 ± 5.48%, P21+ 10Hz ACSF 35-40 min: 108.54 ± 2.95% vs P21+ 10Hz Histamine 35-40 min: 123.73 ± 14.32%, p=0.302, p=0.118, and p=0.629, Independent T-Test and

Mann-Whitney U Test, n=6 / 6 mice, n=5 / 5 mice, n=9 / 8 mice, n=5 / 5 mice, n=4 / 4 mice, and n=3 / 3 mice, ***Figure 11A-C***).

Overall, this study concluded that long-term plasticity was not found in the control condition in the P3-6 age period, and that histamine did not cause any change.

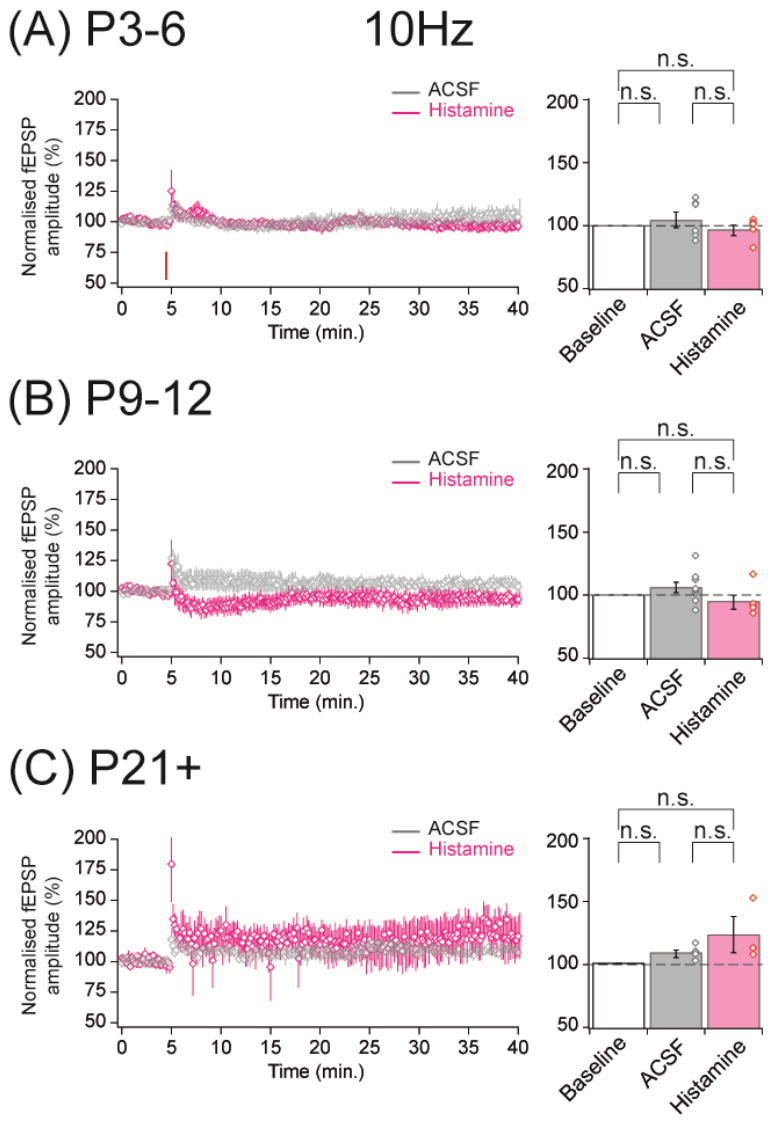


***Figure 11*. Low theta-burst stimulation does not induce long-term plasticity in ACSF and histamine conditions.**

Long-term plasticiy in 3 developing age groups with 10Hz of theta-burst stimulation (TBS) condition. Bar graphs represent mean value of the last 5 minutes (35-40 minutes) of recording in ACSF (grey colour) and histamine (pink colour) conditions. Example traces demonstrate baseline (pre-TBS; 00-05 minutes) and the last 5 minutes (post-TBS; 35-40 minutes). **(A)** P3-6 period: Both ACSF and histamine conditions did not make significant long-term change (10Hz in ACSF 00-05 minutes vs 10Hz in ACSF 35-40 minutes, p=0.510, paired t-test, n=6 / 6 mice; 10Hz in histamine 00-05 minutes vs 10Hz in histamine 35-40 minutes, p=0.406, paired t-test, n=5 / 5 mice). Comparisons of ACSF and histamine in the last 5 minutes were also not significantly different from each other (10Hz in ACSF vs 10Hz histamine, also p=0.302, independent t-test, n=6 / 6 mice vs n=5 / 5 mice). ACSF and histamine conditions in P9-12 (B) and P21+ (C) periods also did not induce long-term plasticity. Paired t-test, independent t-test, Wilcoxon Signed Ranks Test, Mann-Whitney U Test: *p<0.05; n.s.: non-significant.

4. Histamine induces long-term potentiation in P9-12, but blocks it in P21+ period.

Previous studies confirmed that the timing of TBS is critical to producing long-term potentiation, and higher conditions showed that burst timing is critical to long-lasting potentiation (Hawes *et al*., 2013). 50Hz and 100Hz TBS are often used as a protocol to induce plasticity in neural circuits (Larson *et al*., 1986; Artola *et al*., 1990; Lüscher & Malenka, 2012). This study investigated whether any of these frequency options generate long-term plasticity in developing corticostriatal synapses.

In the first postnatal week P3-6, none of the ACSF and histamine conditions showed long-term changes (normalised change in fEPSP amplitude, P3-6 50Hz ACSF 00-05 min vs P3-6 50Hz ACSF 35-40 min: to 106.49 ± 7.46%, P3-6 50Hz Histamine 00-05 min vs P3-6 50Hz Histamine 35-40 min: to 100.20 ± 7.47%, P3-6 100Hz ACSF 00-05 min vs P3-6 100Hz ACSF 35-40 min: to 116.09 ± 7.86%, P3-6 100Hz Histamine 00-05 min vs P3-6 100Hz Histamine 35-40 min: to 110.45 ± 13.30%, p=0.424, p=0.980, p=0.080, p=0.273, paired t-test and Wilcoxon Signed Ranks Test, n=6 / 6 mice, n=5 / 5 mice, n=8 / 8 mice, and n=4 / 4 mice, ***Figure 12A***). There was also no significant gap between control (ACSF) and histamine condtions when this study compared their values in the last 5 minutes (normalised change in fEPSP amplitude, P3-6 50Hz ACSF 35-40 min: 106.49 ± 7.46% vs P3-6 50Hz Histamine 35-40 min: 100.20 ± 7.47%, P3-6 100Hz ACSF 35-40 min: 116.09 ± 7.86% vs P3-6 100Hz Histamine 35-40 min: 110.45 ± 13.30%, p=0.569 and p=0.705, independent t-test and Wilcoxon Signed Ranks Test, n=6 / 6 mice, n=5 / 5 mice, n=8 / 8 mice, and n=4 / 4 mice, ***Figure 12A***).

In the second postnatal week, P9-12, the ACSF condition with both 50Hz and 100Hz TBS did not show a long-term change, whereas histamine showed long-term facilitation with 50Hz, but not with 100Hz (normalised change in fEPSP amplitude, P9-12 50Hz ACSF 00-05 min vs P9-12 50Hz ACSF 35-40 min: to 105.74 ± 10.29%, P9-12 100Hz ACSF 00-05 min vs P9-12 100Hz ACSF 35-40 min: to 107.52 ± 8.53%, P9-12 50Hz Histamine 00-05 min vs P9-12 50Hz Histamine 35-40 min: to 133.64 ± 11.06%, P9-12 100Hz Histamine 00-05 min vs P9-12 100Hz Histamine 35-40 min: to 138.60 ± 22.22%, p=0.589, p=0.401, p=0.029, p=0.157, paired t-test, n=11 / 10 mice, n=10 / 10 mice, n=6 / 4 mice, and n=5 / 5 mice, ***Figure 12B***). As for comparing ACSF and histamine conditions, this study found a significant gap only in the 50Hz condition, but not in 100Hz; Histamine was more facilitated than ACSF in 50Hz (normalised change in fEPSP amplitude, P9-12 50Hz ACSF 35-40 min: 105.74 ± 10.29% vs P9-12 50Hz Histamine 35-40 min: 133.64 ± 11.06%, P9-12 100Hz ACSF 35-40 min: 107.52 ± 8.53% vs P9-12 100Hz Histamine 35-40 min: 138.60 ± 22.22%, p=0.027 and p=0.134, Mann-Whitney U Test and independent t-test, n=11 / 10 mice, n=6 / 4 mice, n=10 / 10 mice, and n=5 / 5 mice, ***Figure 12B***).

In the third postnatal week, P21+, the ACSF condition with both 50Hz and 100Hz TBS showed long-term potentiation, whereas histamine did not show any long-term change with 50Hz TBS (normalised change in fEPSP amplitude, P21+ 50Hz ACSF 00-05 min vs P21+ 50Hz ACSF 35-40 min: to 143.90 ± 9.78%, P21+ 100Hz ACSF 00-05 min vs P21+ 100Hz ACSF 35-40 min: to 126.52 ± 8.06%, P21+ 50Hz Histamine 00-05 min vs P21+ 50Hz Histamine 35-40 min: to 109.60 ± 9.63%, P21+ 100Hz Histamine 00-05 min vs P21+ 100Hz Histamine 35-40 min: to 138.60 ± 22.22%, p=0.006, p=0.011, p=0.375, paired t-test, n=6 / 6 mice, n=9 / 7 mice, n=5 / 5 mice, and n=2 / 2 mice, ***Figure 12C***). Histamine with 100Hz TBS in P21+ was not

tested to confirm statistical difference due to its small sample number (n=2). As for comparing ACSF and histamine conditions in P21+ with 50Hz TBS, ACSF was more facilitated in the last 5 minutes than histamine (normalised change in fEPSP amplitude, P21+ 50Hz ACSF 35-40 min: 143.90 ± 9.78% vs P21+ 50Hz Histamine 35-40 min: 109.60 ± 9.63%, p=0.035, independent t-test, n=11 / 10 mice, n=6 / 4 mice, ***Figure 12C***). As before, histamine with 100Hz TBS in P21+ was not included for statistical test due to its small sample number (n=2).

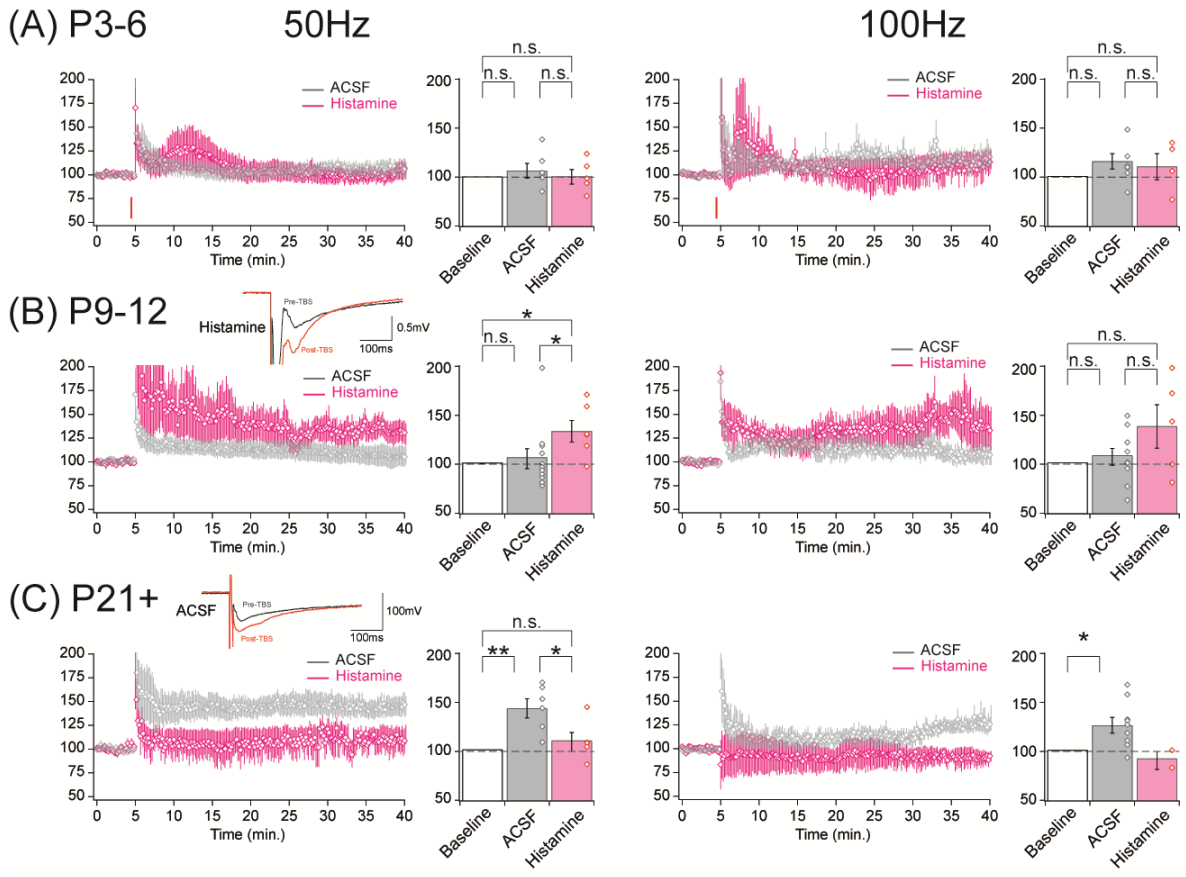


***Figure 12*. Histamine gives opposing effects on the induction of corticostriatal synaptic plasticity depending on postnatal (P)9-12 and P21+ days.**

Long-term plasticity with high frequency theta-burst stimulation, 50Hz (left) and 100Hz (right), in 3 developing age groups. Bar graphs represent the mean value of the last 5 minutes (35-40 min) of recording in ACSF (grey colour) and histamine (pink colour) conditions. Example traces demonstrate the baseline (pre-TBS; 00-05 min) and the last 5 minutes (post-TBS; 35-40 min). **(A)** P3-6 period: Both ACSF and histamine conditions did not induce long-term change in both 50Hz and 100Hz TBS. **(B)** P9-12 period: With 50Hz TBS, Histamine showed a long-term increase (35-40 min), as compared to the baseline (00-05 min) and was significantly more facilitated

than the ACSF condition (35-40 min). However, none of the histamine and ACSF conditions with 100Hz TBS induced long-term plasticity. **(C)** P21+ period: ACSF condition showed long-term facilitation (35-40 min), as compared to its baseline (00-05 min) with both 50Hz and 100Hz TBS. However, histamine condition with 50Hz TBS did not show any long-term change. Histamine condition with 100Hz TBS was not tested for statistics due to its small sample number. Paired t-test, independent t-test, Wilcoxon Signed Ranks Test, Mann-Whitney U Test: *$p<0.05$; n.s.: non-significant.

In conclusion, this study found that histamine induced long-term facilitation of the corticostriatal synapses in the P9-12 period, as compared to the control (ACSF condition), with 50Hz TBS. However, in young adult mice brains (P21+), the control (ACSF condition) showed long-term potentiation with both 50Hz and 100Hz, and histamine blocked this long-term change in 50Hz TBS. These findings suggest that long-term facilitation in the baseline condition can be observed from the P9-12 period through extracellular field recording, and that histamine causes significant changes in synaptic properties from this period, resulting in different outcomes in the P9-12 and P21+ periods.

5. Histamine's long-term facilitation in P9-12 age period is mediated by NMDA and H3 receptors.

Next, this study questioned at which receptors such long-term plasticity facilitation is occuring. Previous studies found that the NMDA receptor is one of the key mediators to induce long-term potentiation (Hebb, 1949), and that increased calcium by the NMDA receptor can elicit both long-term potentiation and long-term depression (Malenka, 1994). This study also considered a recent finding that the amount of the H_3 receptor increases during early developmental periods (Han *et al*., 2020). Therefore, this study added the NMDA and H_3 receptor antagonists to confirm whether the displayed long-term plasticity was dependent upon either of these two receptors. The study used D-(-)-2-Amino-5-phosphonopentanoic acid (D-AP5) (50μM), a potent and selective NMDA antagonist, to block the NMDA receptor, as well as thioperamide (10μM), a H_3 receptor antagonist. As for the TBS condition, the study considered only 50Hz stimulation for the P9-12 and P21+ age periods which showed long-term facilitation with either the presence or absence of histamine (10μM). In order to block the $GABA_A$ receptors, the study included 200nM of gabazine (SR-95531) in all conditions.

In P9-12, the study superfused D-AP5 (50μM) or thioperamide (10μM) with the presence of histamine (10μM) to confirm whether histamine's effect on long-term plasticity is dependent on the NMDA or H_3 receptors. As a result, first, histamine with D-AP5 with 50Hz TBS did not show a long-term change as compared to its baseline (00-05 min) (normalised change in fEPSP amplitude, P9-12 50Hz Histamine+D-AP5 00-05 min vs P9-12 50Hz Histamine+D-AP5 35-40 min: to 83.25 ± 9.45%, p=0.127, paired t-test, n=7 / 3 mice, ***Figure 13A***), and blocked only the histamine condition's

long-term facilitation (normalised change in fEPSP amplitude, P9-12 50Hz Histamine 35-40 min: 133.64 ± 11.06% vs P9-12 50Hz Histamine+D-AP5 35-40 min: 83.25 ± 9.45%, p=0.005 independent t-test, n=6 / 4 mice and n=7 / 3 mice, ***Figure 13A***). Second, histamine with thioperamide with 50Hz TBS did not show a long-term change either as compared to the recording of its first 5 minutes (normalised change in fEPSP amplitude, P9-12 50Hz Histamine+Thioperamide 00-05 min vs P9-12 50Hz Histamine+Thioperamide 35-40 min: to 99.38 ± 17.75%, p=0.973, paired t-test, n=6 / 1 mouse, ***Figure 13A***), and reduced long-term potentiation caused by the histamine condition, but this result was not statistically significant (normalised change in fEPSP amplitude, P9-12 50Hz Histamine 35-40 min: 133.64 ± 11.06% vs P9-12 50Hz Histamine+Thioperamide 35-40 min: 99.38 ± 17.75%, p=0.132 independent t-test, n=6 / 4 mice and n=6 / 1 mouse, ***Figure 13A***). Thus, the study concluded that histamine's modulation on the corticostriatal synaptic long-term potentiation is mediated by the NMDA receptor. Whether the H_3 receptor blocks histamine's long-term facilitation or not could be examined with a bigger sample size, considering the large deviation of the data points in the histamine+thioperamide condtion in this study (***Figure 13A*** right).

In the third postnatal week, the study used data from P21 onwards to secure enough sample numbers. As long-term facilitation was found in the control condition (ACSF condition) but not the histamine condition, the study superfused D-AP5 in the absence of histamine to P21+ mice brain slices. However, the study superfused thioperamide with histamine to P21+ slices to check whether long-term plasticity is recovered or not. As a result, first, D-AP5 with 50Hz TBS did not show a long-term change as compared to its baseline recording (00-05 min) (normalised change in fEPSP amplitude, P21+ 50Hz D-AP5 00-05 min vs P21+ 50Hz D-AP5 35-40 min: to

101.87 ± 9.61%, p=0.850, paired t-test, n=10 / 6 mice, ***Figure 13B***), and blocked the control condition's long-term facilitation in comparison to the last 5 minutes (35-40 min) (normalised change in fEPSP amplitude, P21+ 50Hz ACSF 35-40 min: 139.37 ± 8.74% vs P21+ 50Hz D-AP5 35-40 min: 101.87 ± 9.61%, p=0.012, independent t-test, n=8 / 8 mice, n=10 / 6 mice, ***Figure 13B***). Second, histamine with thioperamide with 50Hz TBS showed long-term potentiation as compared to the first 5 minutes of its recording (normalised change in fEPSP amplitude, P21+ 50Hz Histamine+Thioperamide 00-05 min vs P21+ 50Hz Histamine+Thioperamide 35-40 min: to 137.72 ± 10.30%, p=0.006, paired t-test, n=9 / 3 mice, ***Figure 13B***), and it recovered long-term plasticity that cannot be observed in the histamine condition (normalised change in fEPSP amplitude, P21+ 50Hz Histamine 35-40 min: 108.98 ± 7.89% vs P21+ 50Hz Histamine+Thioperamide 35-40 min: 137.72 ± 10.30%, p=0.045, independent t-test, n=6 / 6 mice, n=9 / 3 mice, ***Figure 13B***). Thus, it is possible to conclude that long-term facilitation of the corticostriatal synapses in young adult mice brains (P21+, control condition) is dependent upon the NMDA receptors, and that histamine blocks this long-term change, which can be recovered by the H_3 receptor. Considering previous findings that the H_3 receptor has various isoforms that demonstrate different signalling properties (Bakker, 2004), it could be concluded that these different H_3 receptor isoforms and constitutively active forms explain the effects seen in ***Figure 13B***.

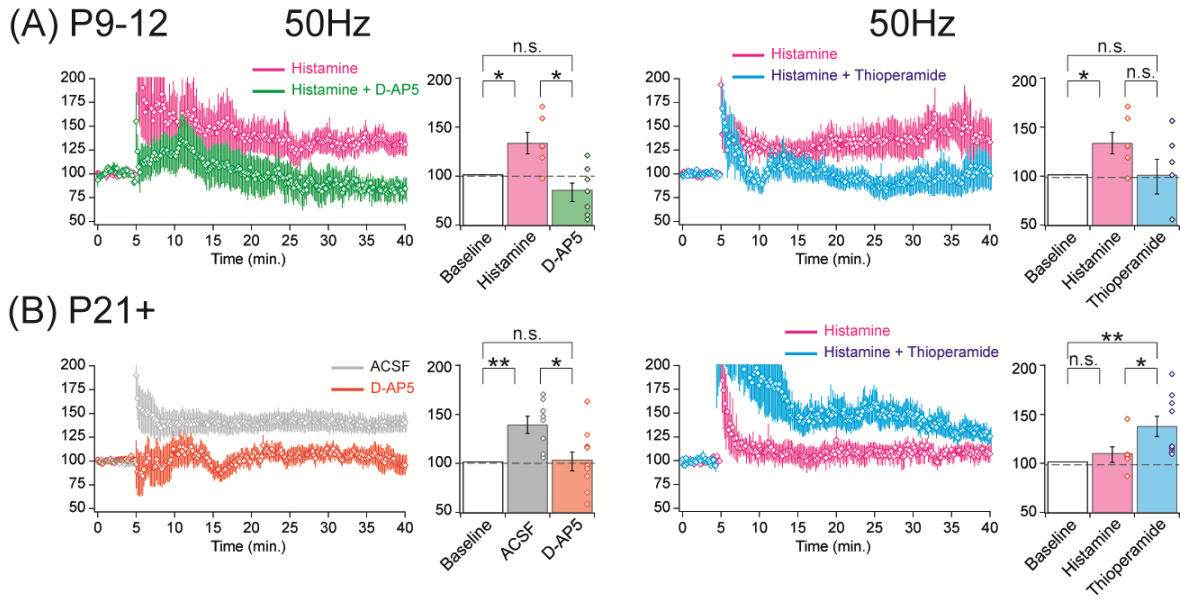


***Figure 13*. Histamine controls NMDA receptor-dependent synaptic plasticity at corticostriatal synapses through the H_3 histamine receptors.**

Long-term plasticity with high frequency theta-burst stimulation (50Hz) in the P9-12 age group (A) and P21+ age group (B) with the NDMA receptor and the H_3 receptor antagonists. **(A)** P9-12 age group: D-AP5 (A, left) and thioperamide (A, right) were superfused to histamine condition to test whether each of these two antagonists block the long-term facilitation that histamine condition made. D-AP5 (A, left) successfully blocked long-term facilitation in histamine condition in P9-12 age period. Thioperamide (A, right) also showed decrease of long-term facilitation that histamine condition showed, but this was not statistically significant. 50Hz - P9-12 in histamine vs histamine+D-AP5, p=0.005, independent t-test, n=6 / 4 mice and 7 / 3 mice. 50Hz - P9-12 in histamine vs histamine+thioperamide, p=0.132, independent t-test, n=6 / 4 mice and 6 / 1 mouse. **(B)** P21+ age group: D-AP5 (B, left) was superfused to ACSF condition, and thioperamide (B, right) was superfused to histamine condition. D-AP5 (B, left) successfully blocked long-term facilitation in ACSF condition, and thioperamide (B, right) recovered long-term facilitation in histamine condition. 50Hz - P21+ in ACSF vs ACSF+D-AP5, p=0.012, independent t-test, n=8 / 8 mice and 10 / 6 mice. 50Hz - P21+ in ACSF+Histamine vs ACSF+Histamine+Thioperamide, p=0.045, independent t-test, n=6 / 6 mice and 9 / 3 mice. Independent t-test: *p<0.05, **p<0.01; n.s.: non-significant.

6. Dorsolateral striatum showed higher level of long-term facilitation of fEPSP than dorsomedial striatum did.

To further investigate the long-term faciliation of normalised fEPSP identified, this study split the data into groups showing long-term faciliation: P9-12 with the presence of histamine and 50Hz TBS, and P21+ without histamine and 50Hz TBS, depending upon the recording position in the dorsolateral striatum (DLS) or the dorsomedial striatum (DMS). Based on the findings of previous studies that the DLS and DMS have differentiating contributions to behaviour from early age periods (see ***Introduction***), the current study set two questions: First, do the DMS and DLS show different long-lasting changes in young adult groups (P21 onwards)? Second, does histamine's effect on long-term plasticity in the P9-12 period differ in these two regions? Due to sample size, this study combined data from two different high frequency TBS (50Hz and 100Hz) before distributing data into the DLS or DMS groups.

In the P9-12 period with histamine, only DLS showed a long-term increase between the first and last 5 minutes, whereas DMS showed post-tetanic potentiation but did not make any significant long-term change (normalised change in fEPSP amplitude, P9-12 50Hz Histamine-DLS 00-05 min vs P9-12 50Hz Histamine-DLS 35-40 min: to 157.32 ± 11.43%, and P9-12 50Hz Histamine-DMS 00-05 min vs P9-12 50Hz Histamine-DMS 35-40 min: to 110.18 ± 13.47%, p=0.004 and p=0.492, paired t-test, n=6 and n=5, ***Figure 14B***). The normalised fEPSP of DLS with histamine was significantly higher in the last 5 minutes than that of DMS with histamine in the last 5 minutes (normalised change in fEPSP amplitude, P9-12 50Hz Histamine-DLS 35-40

min: 157.32 ± 11.43% vs P9-12 50Hz Histamine-DMS 35-40 min: 110.18 ± 13.47%, p=0.025, independent t-test, n=6 and n=5, ***Figure 14B***).

In the P21+ period without histamine, both the DLS and DMS showed long-term faciliation between the first and last 5 minutes (normalised change in fEPSP amplitude, P21+ 50Hz ACSF-DLS 00-05 min vs P21+ 50Hz ACSF-DLS 35-40 min: to 149.49 ± 6.11%, and P21+ 50Hz ACSF-DMS 00-05 min vs P21+ 50Hz ACSF-DMS 35-40 min: to 125.49 ± 6.64%, p=0.001 and p=0.002, paired t-test, n=5 and n=13, ***Figure 14C***). Unlike P9-12, there was no significant gap between the normalised fEPSP of DLS and DMS in P21+ compared to the last 5 minutes (normalised change in fEPSP amplitude, P21+ 50Hz ACSF-DLS 35-40 min: 149.49 ± 6.11% vs P21+ 50Hz ACSF-DMS 35-40 min: 125.49 ± 6.64%, p=0.053, independent t-test, n=5 and n=13, ***Figure 14C***).

Overall, long-term facilitation was only found in the DLS with histamine in the P9-12 period with high frequency TBS, whereas data in the DMS showed no long-term change. Long-term facilitation was found in both the DLS and DMS without histamine in the P21+ period with high frequency TBS, with no significant gap.

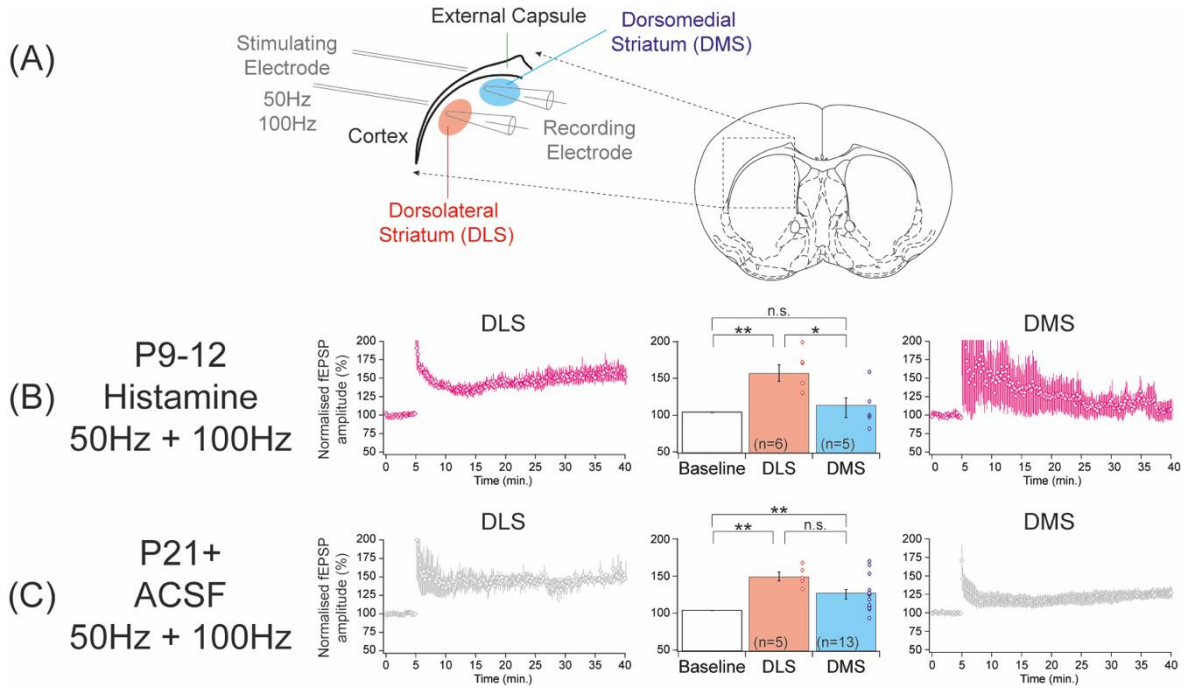


***Figure 14*. The dorsolateral striatum showed bigger amount of long-term facilitation than the dorsomedial striatum did.**

The long-term plasticity outcome in the P9-12 and P21+ age groups with high frequency (50Hz and 100Hz) theta-burst stimulation in the dorsolateral striatum (DLS) and dorsomedial striatum (DMS). **(A)** To investigate whether the observed long-term plasticity in previous figures varied by the specific region, data was split into the DLS or DMS. **(B)** Long-term plasticity in P9-12 induced by histamine in high frequency showed difference in the DLS and DMS: The DLS showed significant long-term facilitation, whereas the DMS did not. **(C)** Long-term plasticity in P21+ in the control (ACSF) condition was found in both the DLS and DMS. The DLS showed higher long-term plasticity than the DMS, but the gap between them was not significant (p=0.053). Paired t-test and independent t-test: *p<0.05, **p<001; n.s.: non-significant.

7. Inhibition of the HDC enzyme seems to affect striatal size.

Previous studies with rats found that the peak of neurogenesis and histamine level coincide around embryonic day (E)14 during the prenatal period (Molina-Hernández & Velasco, 2008; Rodríguez-Martínez *et al*., 2012; Molina-Hernández *et al*., 2012). This would suggest a possible role in prenatal brain development. To determine if this is true in mice brains, the study used small injections of 5μg/μL of α-FMH, an irreversible HDC inhibitor which decreases histamine synthesis (Kollonitsch *et al*., 1978) into the ventricle of embryonic mice at either E12.5 or E15.5. The study then collected brains 2-3 days later (E15.5 and E17.5 days) to compare the size of the striatum and proliferative zones in control and α-FMH conditions. Specifically, the study compared the “lateral ganglionic eminence (LGE), ventricular & subventricular zones (striatal neuroepithelium) (LGE+V)”, which correspond to the proliferative zone, and “caudate-putamen (CP)” which corresponds to the striatum as defined in the embryonic mouse brain atlas. As this study has not obtained enough sample data, it could not test statistical significance in all conditions, but has instead compared mean value and tested Wilcoxon Signed Ranks Test only for the medial section of E15.5 days (***Figure 15***).

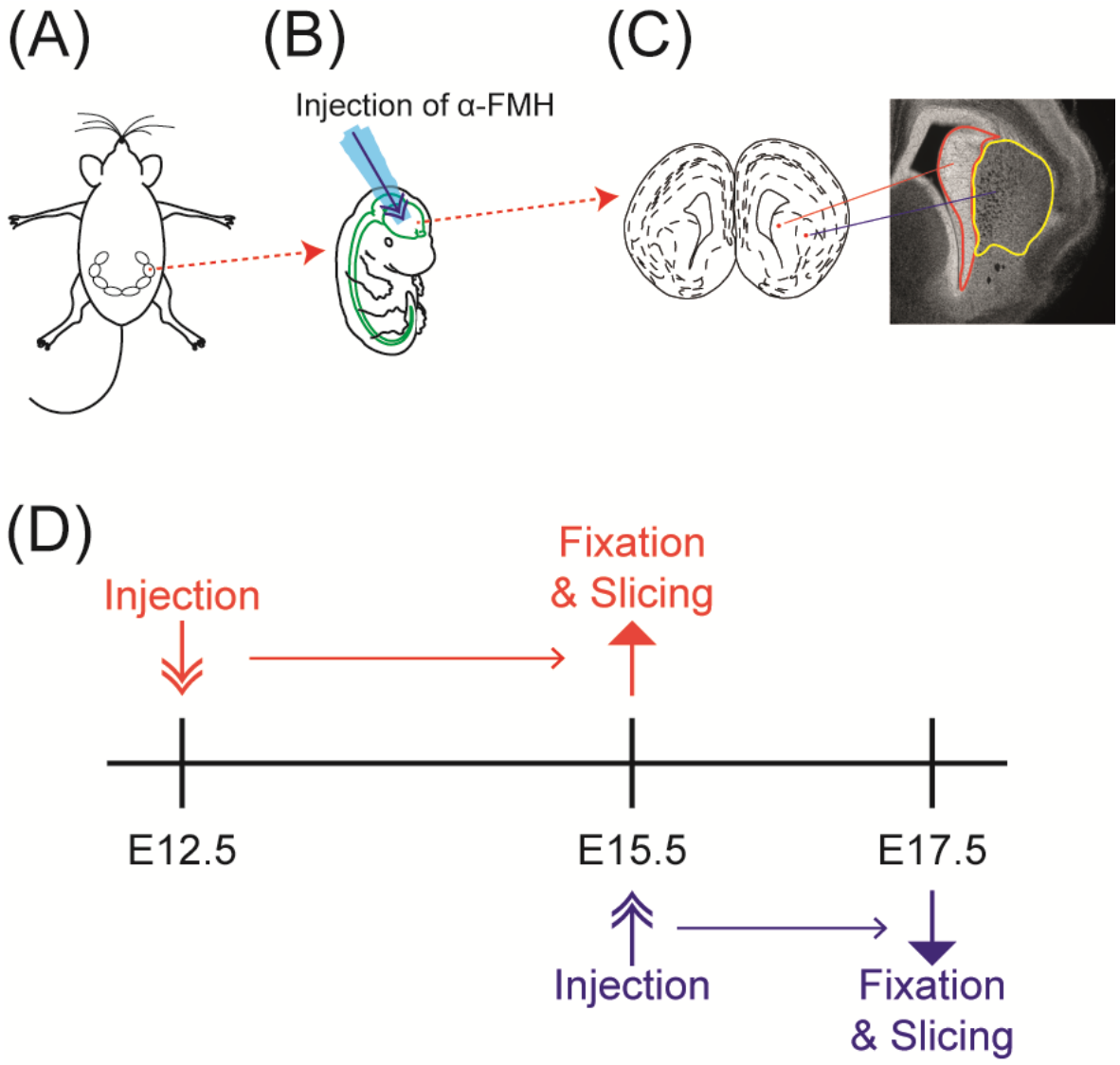


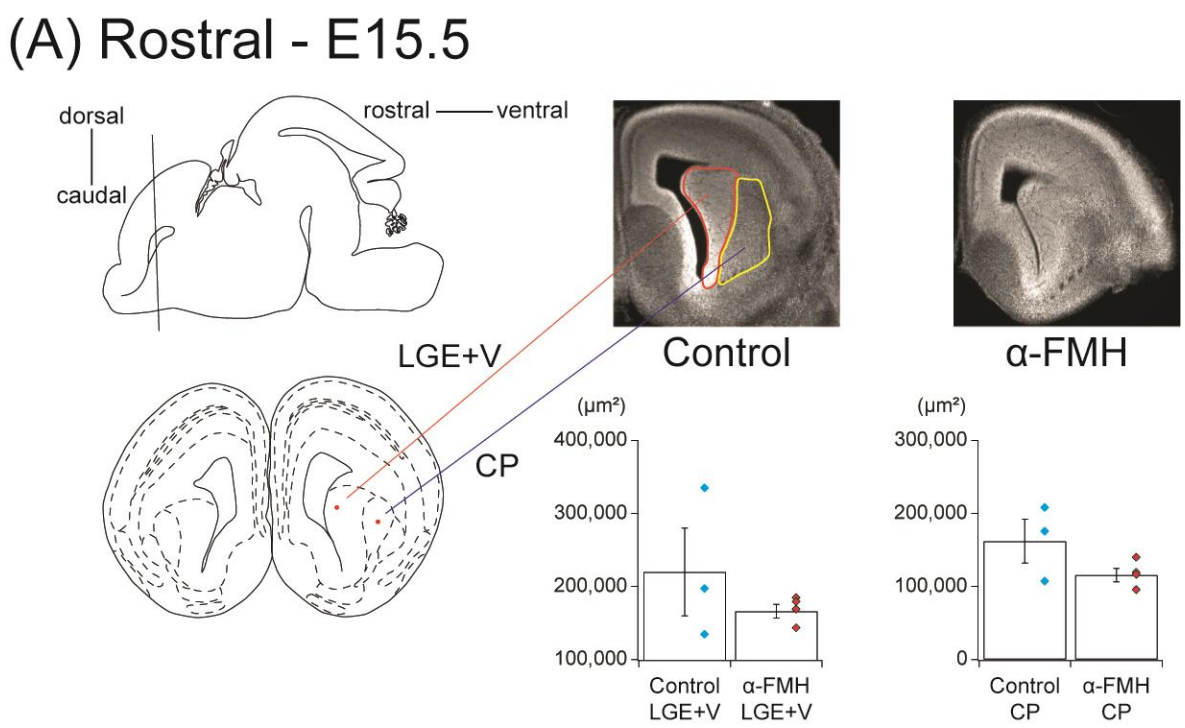
***Figure 15*. Procedure of α-fluoromethylhistidine (α-FMH) injection and slicing.**

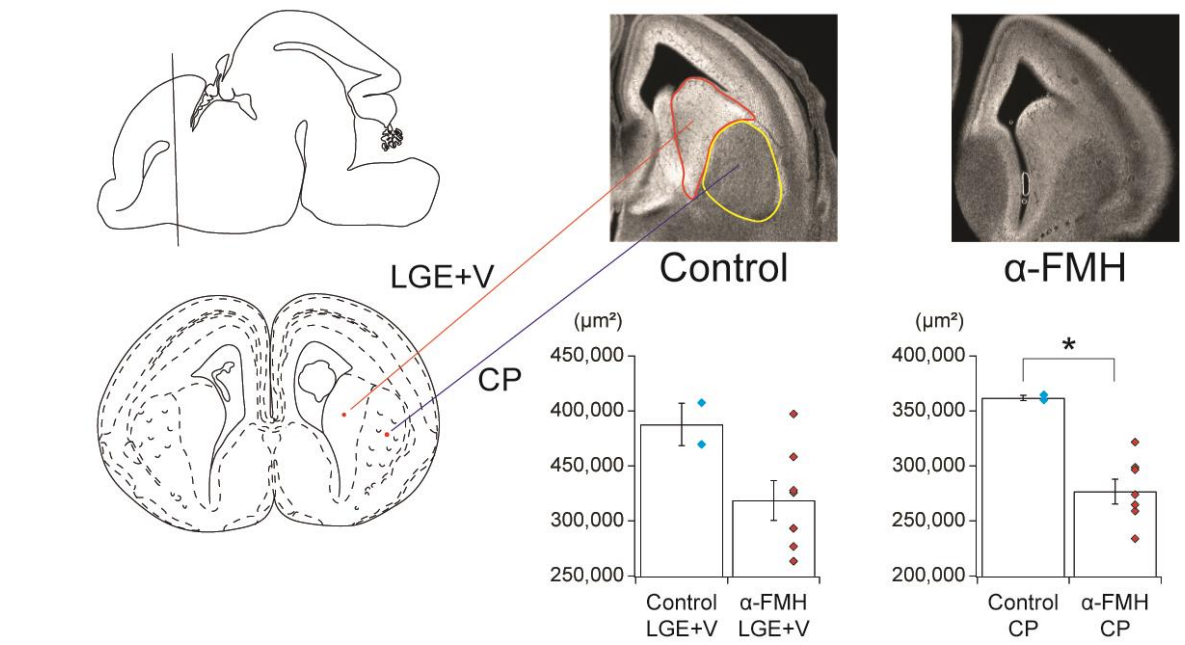
Procedure of neurogenesis experiment with α-FMH. **(A)** Pregnant mouse (wild type). **(B)** α-FMH was injected to the brain of each embryo in embryonic (E)12.5 or 15.5 day. (C) After fixation and slicing, the striatum size was divided into two groups for measuring size: lateral ganglionic eminence, ventricular + subventricular zones (striatal neuroepithelium) (red colour), and caudate-putamen (yellow colour). **(D)** The embryos were collected and their brains were sliced in E15.5 or E17.5 day.

In the medial section on E15.5, the study observed that the striatum was smaller in the α-FMH condition than in control conditions. The values were not statistically significant in the proliferative zone (lateral ganglionic eminence, ventricular and subventricular zones) (LGE+V Control Medial: 388 x 103 ± 19 x 103 μm² and LGE+V α-FMH Medial: 319 x 103 ± 18 x 103 μm², p=0.079, Wilcoxon Signed Ranks Test, n=2 and n=7, ***Figure 16***), but showed a significant difference in the caudate-putamen (CP Control Medial: 362 x 103 ± 2 x 103 μm² and CP α-FMH Medial: 277 x 103 ± 11 x 103 μm², p=0.040, Wilcoxon Signed Ranks Test, n=2 and n=7, ***Figure 16***).

In the rostral section on E15.5, the size of the striatum in the α-FMH condition was smaller than in control conditions, but these values were not statistically significant in both the proliferative zone (LGE+V Control Rostral: 220 x 103 ± 60 x 103 μm² and LGE+V α-FMH Rostral: 166 x103 ± 9 x103 μm², n=3 and n=4, ***Figure 16***) and the caudate-putamen (CP) (CP Control Rostral: 162 x 103 ± 30 x 103 μm² and CP α-FMH Rostral: 115 x 103 ± 9 x 103 μm², n=3 and n=4, ***Figure 16***).

In the caudal section on E15.5, this study did not see a significant difference in striatum size with α-FMH in both the proliferative zone (LGE+V Control Caudal: 327 x 103 ± 61 x 103 μm² and LGE+V α-FMH Caudal: 363 x 103 ± 24 x 103 μm², ***Figure 16***) and the caudate-putamen (CP Control Caudal: 320 x 103 ± 3 x 103 μm² and CP α-FMH Caudal: 345 x 103 ± 31 x 103 μm², n=2 and n=6, ***Figure 16***); if anything, they were slightly larger, but these values were not statistically significant.


(A) Rostral - E15.5
dorsal
caudal
rostral
ventral
LGE+V
CP
Control
α-FMH
(μm²)
400,000
300,000
200,000
100,000
Control
LGE+V
α-FMH
LGE+V
(μm²)
300,000
200,000
100,000
0
Control
CP
α-FMH
CP


(B) Medial - E15.5
LGE+V
CP
Control
α-FMH
(μm²)
450,000
400,000
450,000
300,000
250,000
Control
LGE+V
α-FMH
LGE+V
(μm²)
*
400,000
350,000
300,000
250,000
200,000
Control
CP
α-FMH
CP

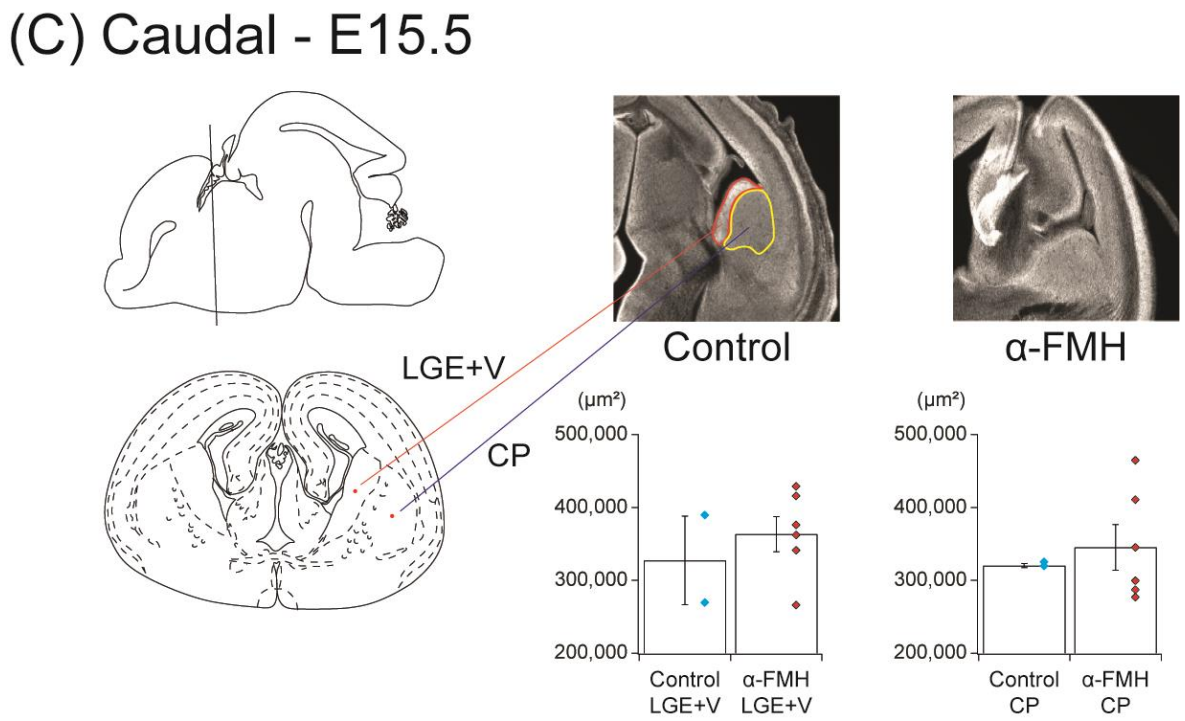


***Figure 16*. Histamine reduces the size of striatum in developing embryo brain (E15.5)**

Comparison of size of the striatum in control and α-FMH conditions in **(A)** rostral, **(B)** medial and **(C)** caudal slices. α-FMH (5μg/μL) was injected on E12.5 and then the brain was sliced on E15.5. Sagittal view of the embryonic brain (up-left), sliced brain with the striatum part (down-left), example microscopic photos of control and α-FMH conditions (up-right), and bar graphs of size of specified striatal parts (down-right). LGE+V: Lateral ganglionic eminence, ventricular and subventricular zones (striatal neuroepithelium). CP: Caudate-Putamen. Rostral control: n=3, Rostral α-FMH: n=4, Medial control: n=2, Medial α-FMH: n=7, Caudal control: n=2, Caudal α-FMH: n=6. Note that the sample numbers are not sufficient to draw statistical conclusions.

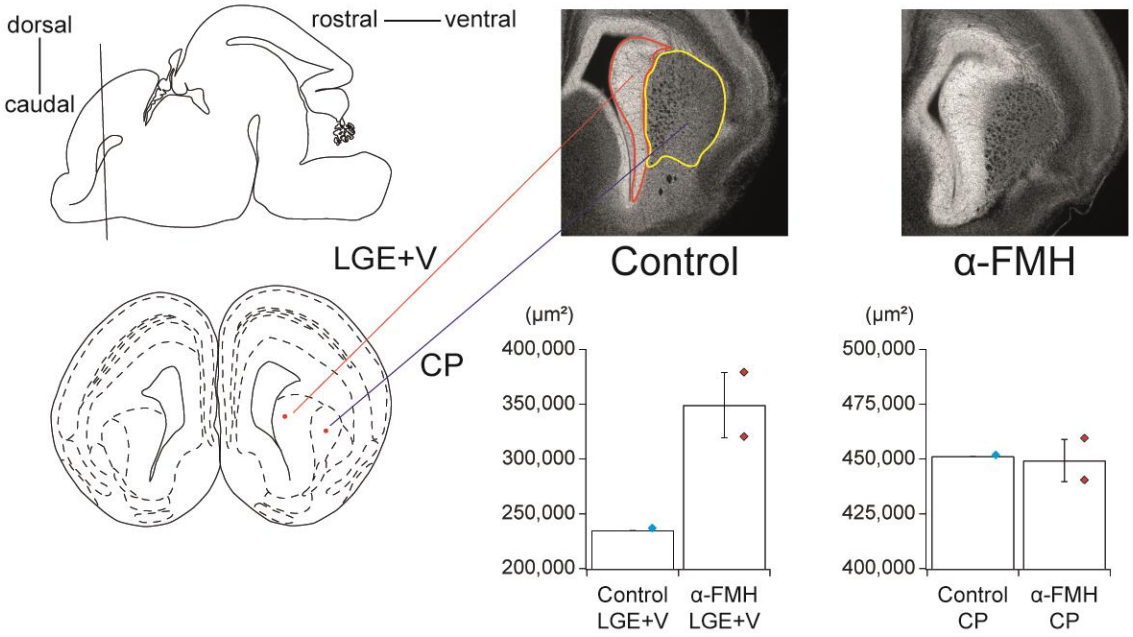
In the rostral section in E17.5, the size of the caudate-putamen in the α-FMH condition is almost the same as in the control (CP Control Rostral: 451 x 103 μm² and CP α-FMH Rostral: 449 x 103± 10 x 103 μm², n=1 and n=2, ***Figure 17***), but the size of the proliferative zone in α-FMH was larger than in the control (LGE+V Control Rostral: 235 x 103 μm² and LGE+V α-FMH Rostral: 349 x103 ± 30 x103 μm², n=1 and n=2, ***Figure 17***).

In the medial section on E17.5, the size of the striatum in the α-FMH condition was bigger than the control in both the proliferative zone and the caudate-putamen (LGE+V Control Medial: 264 x 103 μm² and LGE+V α-FMH Medial: 341 x 103 ± 45 x 103 μm², n=1 and n=3, ***Figure 17***; CP Control Medial: 656 x 103 μm² and CP α-FMH Medial: 797 x 103 ± 96 x 103 μm², n=1 and n=3, ***Figure 17***).

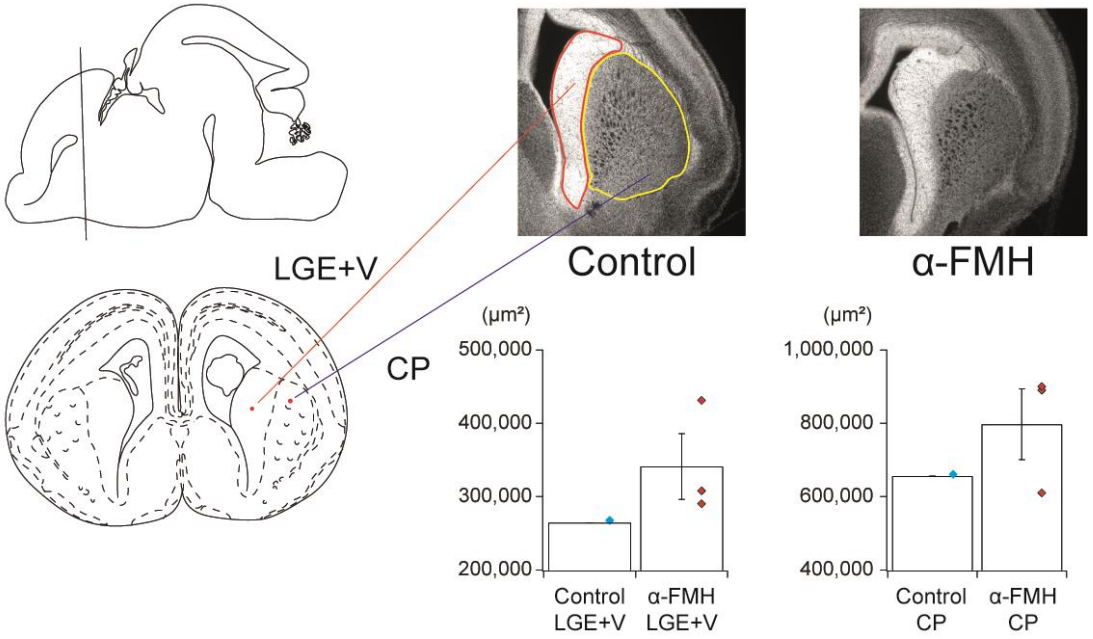
In the caudal section on E17.5, the size of the proliferative zone in the α-FMH condition was smaller than the control (LGE+V Control Caudal: 253 x 103 ± 42 x 103 μm² and LGE+V α-FMH Caudal: 164 x 103 ± 14 x 103 μm², n=2 and n=3, ***Figure 17***) but bigger in the caudate-putamen (CP Control Caudal: 719 x 103 ± 24 x 103 μm² and CP α-FMH Caudal: 736 x 103 ± 41 x 103 μm², n=2 and n=3, ***Figure 17***).

In considering the statistics of the E15.5 samples, the smaller size of the caudate-putamen in medial sections of the brain make it plausible that a reduction in the levels of histamine, caused by α-FMH in this experiment, negatively affects the development of the striatum, though this implication is based on interim data with a small sample size.

(A) Rostral - E17.5



(B) Medial - E17.5



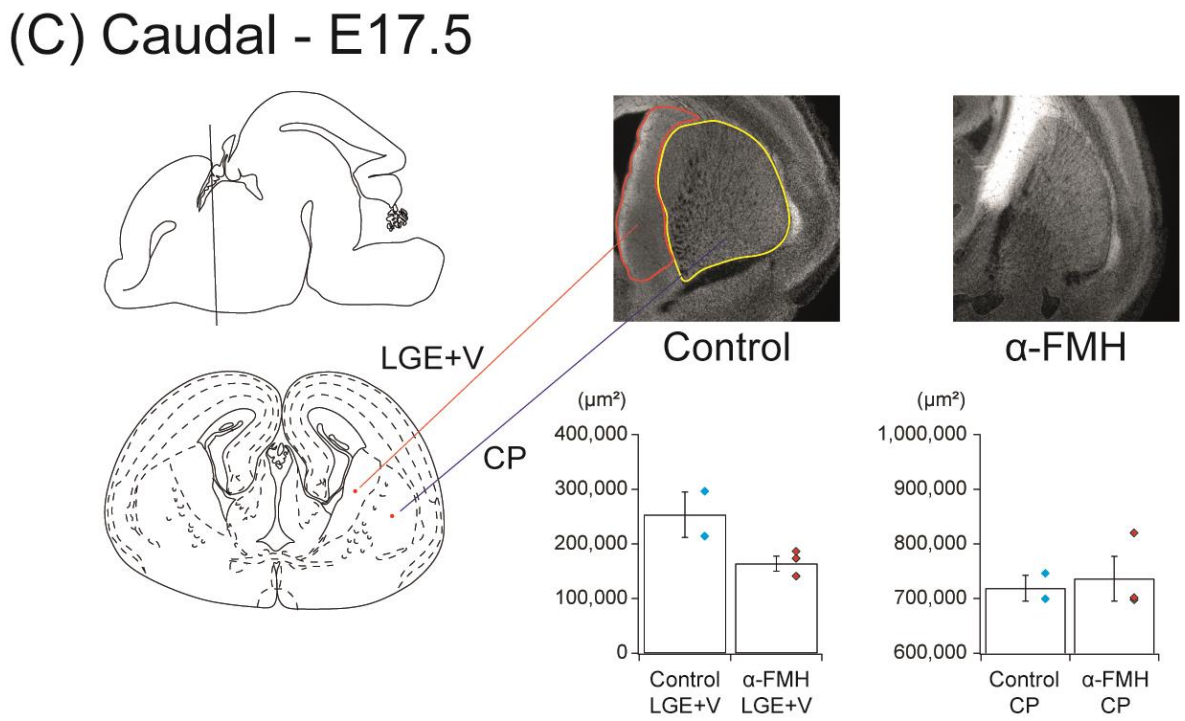


***Figure 17*. Histamine reduces the size of striatum in developing embryo brain (E17.5)**

Comparison of size of the striatum in control and α-FMH conditions in **(A)** rostral, **(B)** medial and **(C)** caudal slices. α-FMH (5μg/μL) was injected on E15.5 and then the brain was sliced on E17.5. Sagittal view of the embryonic brain (up-left), sliced brain with the striatum part (down-left), example microscopic photos of control and α-FMH conditions (up-right), and bar graphs of size of specified striatal parts (down-right). LGE+V: Lateral ganglionic eminence, ventricular and subventricular zones (striatal neuroepithelium). CP: Caudate-Putamen. Rostral control: n=1, Rostral α-FMH: n=2, Medial control: n=1, Medial α-FMH: n=3, Caudal control: n=2, Caudal α-FMH: n=3. Note that the sample numbers are not sufficient to draw statistical conclusions.

Ⅳ. Discussion

1. Discussion and implication

This study of the role of histamine in the development of the striatum has led to several observations. The observations on the role of histamine in early postnatal synaptic transmission have shown that histamine is able to modulate the corticostriatal fEPSPs in each of the three developmental age groups.

Firstly, this study's data indicates that the negative modulation of histamine also occurs in early age periods. This matches a previous finding in adult mice brains (Ellender *et al*., 2011). Pharmacological study of the receptor subtypes involved in this negative modulation of corticostriatal transmission also suggests that histamine is acting predominantly at the H_3 receptor. Indeed, using the selective H_3 receptor antagonist thioperamide, the study was able to block most of the actions of histamine on the evoked fEPSP.

Secondly, this study could not identify a significant change in the corticostriatal short-term plasticity caused by histamine. This study did not show any significant gap between control (ACSF) and histamine conditions in the continuous pulses' ratios. This result is contrary to the previous findings of Ellender *et al*. (2011), which showed a significant increase in the paired pulse ratio (the first two pulses) in adult mice brains, which means that histamine acts on the presynaptic site of the synapse. It is necessary to consider if the type of recording might affect this ratio. The research in Ellender *et al*. (2011) employed whole-cell patching whereas this study used field recordings. As fEPSPs cover more than one cell, the proportion might be different from that of whole cell patching recording. In addition, it is possible that the

point of recording in the striatum as well as that of stimulation in the external capsule also influenced the paired pulse ratio. Given previous findings that the striatum can be subdivided depending upon different compositions of nuclei and each part's corticostriatal or/and thalamostriatal projections (Voorn *et al*., 2004), the EPSP can vary depending upon where the recording is taken as those points could have different proportions of compositions. Indeed, the study by Ellender *et al*. (2011) only showed significant increase in the paired pulse ratio in the D_2 SPNs, not the D_1 SPNs. This study interprets that the inconclusive outcome may be based on the combination of D_1 and D_2 SPNs. However, this study found that the P3-6 age group showed facilitation in fEPSP, whereas the other age groups showed slight levels of depression. This study also found that histamine causes an increase in the trend level of this in the P3-6 age group, implying that histamine's impact on transmission is larger in ages before the young adult period.

Thirdly, to start investigating possible roles for histamine during early stages of striatal development, this study decided to investigate whether histamine affects the properties of long-term potentiation at the corticostriatal synapses. This study showed that long-term facilitation in control conditions was found in only the young adult group (P21+) with 50Hz and 100Hz TBS, not 10Hz TBS. Interestingly, histamine induced long-lasting potentiation in the earlier period (P9-12) with 50Hz TBS, and blocked this long-term plasticity in P21+ with 50Hz TBS. It is also noted that histamine's effect did not lead plasticity to long-term depression. This suggests several important implications. First, long-term plasticity exists in the control condition in the young adult period, not only the mature age periods. Second, histamine causes the opposite effect in the P9-12 (inducing long-term facilitation) and P21+ (blocking long-term facilitation) periods. These results imply that histamine has a

critical impact on synaptic properties from at least P9 onwards. Further, more detailed investigations are needed to seek other variables and properties of synapses to identify exactly where and how histamine has an impact. The electrophysiological properties of long-term plasticity in the presence of histamine also need to be analysed.

Fourthly, this study questioned whether such long-term changes can be changed based on the location on the striatum. This study split data of long-term plasticity experiments into two groups depending upon the location of recording and stimulating electrodes. This study found that long-term facilitation with histamine in P9-12 was found in the DLS, but not in the DMS. Long-term facilitation in the control (ACSF) condition in P21+ in the DLS was also bigger than in the DMS, though both showed significant, long-lasting potentiation. These findings suggest several important implications. First, histamine's effect on long-term plasticity was found in the DLS, which is associated with stimulus-driven behaviour, instead of the DMS, which is associated with goal-driven behaviour. This preferential effect of histamine on the DLS through the H_3 receptor can be investigated further with the stereotypical symptoms of Tourette's syndrome. Assuming that this study's results are confirmed with a sufficient sample size, a behavioural investigation could specifically determine whether histamine and/or the H_3 receptor on the DLS reduced or increased the symptoms of Tourette's syndrome.

Second, the DLS showed a larger impact of the long-term increase than the DMS did in the control condition data in P21+. This implies that we can expect to observe long-term corticostriatal synaptic plasticity in the young adult mouse brain, and that long-term plasticity is stronger in the DLS than in the DMS.

Fifthly, this study questioned which receptors mediate long-term plasticity in P9-12 and P21+ periods. This study found that the NMDA and H_3 receptors mediate long-term facilitation in both age groups in ACSF and histamine conditions. This information will be important background for further studies of synaptic properties.

Lastly, this study confirmed that histamine also affects the prenatal development of the brain in embryo periods by showing α-FMH's negative impact on the size of the striatum. Importantly, this suggests that histamine's effect is present not only at synapses but potentially also during periods of neurogenesis. However, the data in this study contains two to seven samples from each group, which is a low sample number. Assuming that the finding that α-FMH causes a negative effect on the development of the striatum is true, this outcome can be part of the H_3 receptor's effect during neurogenesis. For example, a previous study showed that the H_3 receptor inhibited development and expansion of the proliferation of neural stem cells via 'cAMP-response element binding (CREB)' – 'brain-derived neurotrophic factor (BDNF)' pathways (Wang *et al*., 2020).

2. Study limitations

There are several limitations to this study. First, the conclusion showing a discrepancy of plasticity in the DLS and DMS is based on combined data of 50Hz TBS and 100Hz TBS, not a single TBS condition. Second, the findings on neurogenesis with the α-FMH experiment are drawn from a small sample size. Third, it was found that histamine's effect on the corticostriatal long-term plasticity is mediated by both the NMDA and H_3 receptors in P9-12, but only the NMDA receptor was not tested for the young adult age period (P21+).

3. Future work

The results discussed above imply several future directions to investigate the effects of histamine on the corticostriatal circuit of prenatal and postnatal mice.

Firstly, histamine's negative modulation of corticostriatal synaptic transmission needs to be investigated more specifically. This study showed that histamine's negative modulation of corticostriatal synaptic transmission in early ages started from the P3 age period. However, as the field recording captured signals from more than 100 neurons, it cannot yet be reported whether this histamine modulation is neuron-specific or not. The application of whole-cell patching recording, for example, would be able to confirm whether histamine causes different outcomes depending upon the D_1 or D_2 SPNs. Assuming that the individual recording causes differential histaminergic modulation, we can move on to analyse which layer of the cortex is associated.

Secondly, long-term plasticity in the DMS and DLS needs to be studied in further detail to identify specific circuit location and synaptic properties. This study's results are based on stimulating cortex layers 4-6 and recording the dorsal striatum near the external capsule. Given that the DLS is more likely to be linked to sensorimotor cortices whereas the DMS is more likely to be linked to limbic cortices (Perrin & Venance, 2019), it is necessary to identify which type of SPN and which layer in the cortex cause long-term corticostriatal plasticity in the DMS and DLS. This study also investigated only two receptors, the NMDA and H_3 receptors, with regards to the long-term increase, whereas there are other receptors related to long-term potentiation such as D_1/A2A and mACh (Lovinger, 2010). As previous studies reported that different receptors are activated in the DLS by different types of learning,

a more detailed understanding of these receptors will offer a more accurate description of the mechanism of long-term plasticity in the corticostriatal circuits. For example, it is known that CB1 and D_2 are the main receptors for the DLS in skill learning, whereas CB1, D_2 and A2A are the main receptors for the same region in instrumental/response learning (Lovinger, 2010). We can investigate various aspects of striatal plasticity in rodents under learning conditions by employing extracellular recording (i.e.: firing rate & coherence), two-photon imaging (neuronal maps & structural plasticity), GRIN lens imaging (fiber photometry), and patch-clamp (intrinsic membrane properties, the ratio of AMPA receptor and NMDA receptor, and plasticity saturation/occlusion) (Perrin & Venance, 2019).

There are both harmonious and tensions when these results are compared to previous research. A study of long-term plasticity in the dorsal striatal adult brain slice reported that 50Hz TBS showed more facilitation than 100Hz TBS did, which concurred with this study's findings; that study, however, found that the DMS showed more facilitation than the DLS, which is the opposite (Hawes *et al*., 2013). It is necessary to consider the discrepancy in the animals' ages and the recording technology employed, but it is believed that further details about the receptors and learning stage will offer a clearer understanding.

Thirdly, assuming that detailed knowledge of differential long-term plasticity in the DMS and DLS is found and that histamine causes changes compared to control conditions, we can utilise this information (first, ACSF vs histamine; second, age period, and third, TBS condition) to update behavioural models. One hypothesis is that the DLS, which corresponds to the motor cortex (MC), is activated in both early training (goal-directed learning) and late training (habit), whereas the DMS, which corresponds to the prefrontal cortex (PFC), is mainly activated in early training (goal-

directed learning) (Thorn *et al*., 2010), though another previous study reported that the DMS and DLS was distinct from one another in early training but not in extended training (Vandaele *et al*., 2019). If histamine's preferential impact on either the DMS or DLS in particular age periods is confirmed, we can use that information to form at least two conditions of rodents and then assign them behavioural tasks. For example, supposing that histamine induces preferential strengthening of the DLS in P9-12, we can test whether mice show significant changes in habitual learning in the presence or absence of histamine on the DLS in P9-12. This can be measured with behavioural experiments in a variable-ratio schedule or a fixed-ratio schedule of reinforcement. In a variable-ratio schedule, rewards are given to subjects after a varying set of responses. Therefore, this reinforcement stimulates the motivation of subjects as they should show a steady and high rate of responses in order to obtain benefits. In contrast, in a fixed-ratio schedule, rewards are given to subjects after a set number of responses. Therefore, this reinforcement does not motivate subjects as subjects can predict the schedule of benefits, and subjects become more likely to rely on their habits. Based on this idea, if mice show any significant difference in any of these reinforcement schedules in the presence or absence of histamine (or histaminergic neurons) in the DLS in P9-12, as compared to mice in control conditions, it can be concluded that histamine plays an important role in either the habit or motivation of brain functions through the DLS (or the DMS).

If this approach results in any positive outcomes, it may offer a more detailed explanation of why this study observed conflicting outcomes to previous research on the contribution of the DMS and DLS throughout learning stages.

Fourthly, a neurogenesis study using α-FMH needs to be conducted with more quantitative measurements of brain volume and biochemical identification of

neurons. The results of this study are limited not only due to a low sample number, but also due to the accuracy of the methodology. Therefore, more accurate methods such as MRI scanning will answer whether α-FMH is a good inhibitor of histamine synthesis during prenatal periods, and whether and how much histamine is important for the development of the striatum. If these two questions offer a positive result, further conclusions can be drawn. Given that histaminergic cells are projected to most parts of the brain from the TMN (Watanabe *et al*., 1983; Panula *et al*., 1984; Wada *et al*., 1991; Nieto-Alamilla *et al*., 2016), it is necessary to identify which part of the brain (i.e.: the striatum, the cortex and the thalamus) showed differences due to the effect of histamine. If any part of the brain shows a significant change, then it is necessary to understand why and how it happened. For example, if the size of the striatum is reduced due to a lack of histamine during the prenatal period, it is necessary to determine the reason the size decreased, such as a change in neuronal properties or the early death of neurons. Further detail about the location is also necessary (i.e.: D_1 → SNr/GPi or D_2 → GPe etc.). Considering that people with Tourette's syndrome have been shown to have a significantly smaller striatal volume than normal people (Peterson *et al*., 2003) and a significant decrease in the density of the parvalbumin and choline acetyltransferase cholinergic interneurons in the striatum (Kataoka *et al*., 2010), further investigation of histamine's impact on prenatal neurogenesis will be meaningful no matter the result to understand both the role of histamine in the brain and brain disease characterized by deficits of the striatum. The effect of inhabitation by α-FMH can also be measured by counting not only histaminergic neurons, but also glutamate decarboxylase (or glutamic acid decarboxylase; GAD) neurons. The TMN neurons contain not only histaminergic neurons, but also GAD enzymes and GABA (Vincent *et al*., 1983; Takeda *et al*., 1984;

Senba *et al*., 1985; Airaksinen *et al*., 1992; Trottier *et al*., 2002). Therefore, investigating quantitative and qualitative changes in GAD neurons can be a way to measure the effect of α-FMH.

Fifthly, future studies need to confirm whether this study (injection of α-FMH) has depleted histamine to validate the anatomical results (***Figure 16*** & ***Figure 17***). To measure this, HPLC-flourometry (Yamatodani *et al.*, 1985; Munari *et al*., 2013) can be used to test the amount of histamine in the brain dialysates. To label histamine, a polyclonal rabbit anti-histamine antibody 19 C (RRID:AB_2314639; Panula *et al*., 1990) can be used as a primary antibody at a dilution of 1:10,000, and a commercial Alexa 488 conjugated monoclonal goat anti-rabbit antibody (RRID:AB_2576217, ThermoFisher A11034; Puttonen *et al*., 2018) can be used as secondary antibody at a dilution of 1:1,000. If this future study employs a sufficient sample size and confirms that histamine is fully depleted, the role of histamine in prenatal periods could be concluded in further detail.

4. Conclusion

In conclusion, the current study provided evidence that histamine negatively modulates corticostriatal synaptic transmission and has differential impacts on synaptic plasticity in the P9-12 and P21+ age groups. As this study's investigation focused on several aspects of the background, such as working receptors, further studies on other synaptic properties and behavioural measurements are necessary.

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