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A BRAIN PLASTICITY STUDY: FOCUS ON NEURONS AND ASTROCYTES

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Abbreviations

6-OHDA 6-hydroxydopamine hydrobromide

3D three-dimensional

ACM Astrocyte-conditioned médium

ACTH adrenocorticotropic hormone

AgRP Agouti-Related Peptide

aHN adult hippocampal neurogénesis

AKT Protein kinase B

ALC Acetyl-L-carnitine

aNG adult neurogenesis

AMPA alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

APC Antigen-presenting cell

AQP4 Aquaporin 4

ArcN Arcuate Nucleus

ATP Adenosine triphosphate

BA Basal Amygdala

Bad BCL2-associated Agonist of Cell Death

Bax Bcl-2-associated X protein

BBB blood-brain barrier

BDNF Brain-derived neurotrophic factor

C3 central complement factor C3

C4b central complement factor C4b

CA1 Corn of Ammon 1

CA2 Corn of Ammon 2

CA3 Corn of Ammon 3

CaMK Calmodulin-dependent protein kinase

cAMP cyclic Adenosine Monophosphate

CD4 Cluster of Differentiation 4

CD49f Integrin α6

CNS central nervous system

CNTF Ciliary Neurotrophic Factor

CREB cAMP-response element binding protein

CRH Corticotropin-releasing hormone

CTR control

CX30 Connexin 30

CX43 Connexin 43

DA Dopamine

DAB 3,3′-diaminobenzidina

DCX Doublecortin

DG Dentate Gyrus

DNA Deoxyribonucleic Acid

dHP dorsal Hippocampus

DsRed Discosoma red fluorescent protein

EAAT2 Excitatory amino acid transporter 2

EC Enthorinal Cortex

ECM extracellular matrix

ECS extracellular space

ELS early life stress

ERK Extracellular signal-Regulated Kinase

FGF-2 Fibroblast Growth Factor 2

GABA Gamma-Aminobutyric acid

GCL Granular Cell Layer

GDF Growth differentiation factor

GFAP glial fibrillary acidic protein

GFP Green fluorescent protein

GLAST Glutamate Aspartate Transporter

GLT1 Glutamate Synthase

GLUT2 Glucose Transporter 2

GM-CSF Glial-Monocyte Colony-Stimulating Factor

GPCRs G-protein coupled receptors

GS Goat serum

Hes5 Hes Family BHLH Transcription Factor 5

HFD high-fat-diet

HP hippocampus

hNG postnatal hippocampal neurogenesis

HS horse serum

HSD honestly significant difference

IHC immunohistochemical analysis

IL-1β Interleukin-1β

IL-6 Interleukin-6

iPSCs induced-pluripotent stem cells

Kir4.1 inwardly rectifying potassium channel 4.1

LFD low-fat-diet

LTP long-term potentiation

MAP2 microtubule-associated protein 2

MAPK Mitogen-activated protein kinase

MDD major depressive disorder

MERTK MER proto-oncogene tyrosine kinase

mGLUr metabotropic glutamate receptors

MHC major histocompatibility complex

ML molecular layer

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mRNA Messenger Ribonucleic acid

PFA Paraformaldehyde

PFC prefrontal cortex

PLCg Phospholipase C, gamma 1

NeuroD1 Neurogenic differentiation 1

NF-κB nuclear factor kappa-light-chain-enhancer of activated B cells

NLRP3 NLR family pyrin domain containing 3

NMDA N-methyl-D-aspartic acid

NPCs neural progenitor cells

NSCs neural stem cells

NT Neurotrophin

p50 KO p50 knockout

PAPs perisynaptic astrocytic processes

PARK Parkin

PC 1 Protein Convertase 1

PD Parkinson's disease

PGE prostaglandin

PI3K Phosphoinositide 3-kinases

PKC Protein kinase C

PND Post-natal-day

Prox1 Prospero Homeobox 1

PRRs pattern-recognition receptors

PSD post-synaptic density

PVN Paraventricular Nuclei

REM Rapid Eye Movement

RWIS Restraint Water-Immersion Stress

S100β calcium-binding protein B

SF-1 steroidogenic factor-1

SGZ subgranular zone

SIP Sholl Intersection Profile

sLM stratum Lacunosum Moleculare

SN *Substantia Nigra*

SNCA alpha-synuclein

SNpc *Substantia Nigra Pars Compacta*

SNpr *Substantia Nigra Pars Reticulata*

Sox Sex determining region Y-box

SPARC secreted protein acidic and rich in cysteine

SVZ subventricular zone

TBS Tris-buffered saline

TBS-T tris-buffered saline with tween

TLR Toll-like receptor

Thbs1 Thrombospondin 1

TH tyrosine hydroxylase

TNF Tumor necrosis factor

tPA tissue-type plasminogen activator

TRAIL TNF-related apoptosis-inducing ligand

TrkB Tropomyosin receptor kinase B

UCMS unpredictable chronic mild stress

VEGF vascular endothelial growth factor

vHP ventral Hippocampus

vmH ventromedial Hypothalamus

VTA ventral Tegmental Area

Wnt Wingless-related integration

WT wild-type

Abstract

Brain plasticity is the ability of the CNS to functionally and structurally adapt in response to environmental stimuli, aging, and possible pathology. This dynamism requires synergism between different cells of the CNS, and the astrocytes and neurons are significantly involved in all these processes (Nudo, 2006; Theodosis et al., 2008). We focused on studying the plasticity of these neural cells concerning different environmental factors and pathology.

In particular, we studied neuronal plasticity concerning diet change, and in parallel, we studied astrocytes plasticity with Parkinson's disease and major depressive disorder's risk factors.

Adolescence is an important time for the growth of brain areas involved in cognition. Early in childhood, unfavorable eating habits are linked to poorer cognitive outcomes later in life; conversely, a healthy diet is linked to improved cognitive outcomes.

Memory and mood are primarily governed by the hippocampus in the central nervous system: here, the neuroplastic process known as "postnatal hippocampal neurogenesis" (hNG) occurs, allowing newborn neurons to develop, and integrate into hippocampal circuitry. hNG dysregulation is linked to cognitive impairment, and sadness. Persistent overeating has been shown to influence hNG even before considerable body weight increases. These findings imply that excessive food consumption may have a direct effect on the brain, regardless of metabolic abnormalities.

The effects of a brief period of hypercaloric diet on neonatal hippocampus doublecortin+ (DCX) immature neurons in teenage and adult mice were investigated in this work. adolescent (5-week-old) and adult (10-week-old) male mice were fed a high-fat diet (HFD) or a control low-fat diet (LFD) for 1 or 2 weeks, or 1-week HFD followed by 1-week LFD. Following food administration, mice were either perfused for IHC analysis or their hippocampi were dissected for biochemical analyses. In DCX+ cells with immature neuronal characteristics, a detailed morphometric analysis was done. We

found that 1 week of HFD was enough to significantly diminish dendritic tree complexity in DCX+ cells. This impact, in adolescent mice, occurred only in the dorsal hippocampus and was associated with lower BDNF expression levels in the dorsal hippocampus. In adult mice, we saw the same impact but only in the ventral hippocampus. Returning to LFD corrected both structural and metabolic alterations. Overall, our data increase our current knowledge of the consequences of a hypercaloric diet on the brain, suggesting that brief changes in nutritional lifestyle differently affect areas related to cognition or mood in adolescence or adulthood.

The second aspect of brain plasticity that we studied is related to astrocyte plasticity.

Astrocytes are very heterogenous cells, both morphologically and functionally. In recent years, by using morphometric analysis, we discovered a remarkable region/subregion-specificity in the response of astrocytes to aging and stress.

Aging and stress are environmental risk factors involved in many neurodegenerative disorders, such as Parkinson's Disease (PD). At present, little is known about the features of astrocytes in Substantia Nigra pars compacta (SNpc), the region where dopaminergic neurons degenerate in PD, and pars reticulata (SNpr). Herein, we evaluated how aging may affect astrocyte morphology in the SN. To this end, we performed a semi-automated 3D reconstruction of GFAP+ astrocytes of young (6-month-old), middle-aged (14-month-old), and old (20-month-old) C57Bl/6 male mice. On 3D reconstructions, we performed Sholl analysis and quantified various morphology-related parameters for the astrocytic population. With aging, astrocytes underwent a gradual morphological transformation. Indeed, we observed a statistically significant increase in several parameters which correlate with astrocytic morphological complexity in an age-dependent manner, while we saw no difference in SNpr. In addition, we evaluated the impact of 8 weeks of unpredictable chronic mild stress (UCMS) on astrocyte morphology in the SNpc of 8-mo old C57Bl/6 male mice. Unlike aging, exposure to UCMS produced no change in astrocyte morphology in SNpc. Our results suggest that

SNpc astrocytes are affected differently by aging and chronic stress, two risk factors for PD. We are currently extending our morphometric analysis to SN pars reticulata, where astrocytes have distinctive morphological features compared to SNpc. Moreover, we are actively investigating potential molecular and biochemical correlates of aging-associated astrocytic remodeling in SN.

In the future, we plan to dissect, at the molecular level, the distinctive features of astrocytic populations in the SNpc and SNpr, that may underline their different response to aging.

Furthermore, we plan to study the two astrocytic populations during the progression of PD-like neuropathology in relevant animal models of the human disorder.

Another aspect that we investigated is astrocyte plasticity in two hypothalamic regions ArcN and PVN, áreas involved in chronic stress response and the pathogenesis of major depressive disorder (MDD). With the same approach, we performed a semi-automated 3D reconstruction of GFAP+ astrocytes of UCMS-treated C57Bl/6 male mice. On 3D reconstructions, we performed Sholl analysis and quantified various morphology-related parameters for the astrocytic population. We discovered that hypothalamic astrocytes after UCMS underwent a gradual morphological transformation, in both subregions. Indeed, we observed a statistically significant increase in several parameters correlated with astrocytic morphological complexity. These results can increase our knowledge of the involvement of hypothalamic astrocytes in MDD, and put the basis for future pharmacological studies.

Chapter 1

A PECULIAR FORM OF NEURAL PLASTICITY: ADULT AND ADOLESCENT HIPPOCAMPAL NEUROGENESIS

1.1 Adult neurogenesis: the beginning

Neurogenesis refers to the process of the generation of new neurons. The adult brain only generates new neurons in a few areas, including the ventricular–subventricular zone of the forebrain and the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus (Canales Juan J., 2016). Ezra Allen initially described neurogenesis in 1912, demonstrating the presence of mitotic cells in the lateral ventricles of the adult mouse brain (Allen, 1912). Later in the 1960s, Joseph Altman identified the hippocampus as a germinative zone using a tritiated thymidine technique to mark mitotic cells in the adult rat brain (Altman, 1962, 1963). Despite Altman's observations, it took several years for the notion of adult neurogenesis to be accepted. Michael Kaplan conducted pioneering electron microscope studies on neurogenic areas, opposing the widely held belief that new neuronal cells do not form in the adult mammalian brain. He published extensive research on adult neurogenesis in the hippocampus, olfactory bulb, and visual cortex (Kaplan, 1985; Kaplan & Hinds, 1977). At the same time Burd and Nottebohm, pioneered the first functional neurogenesis research, demonstrating the role of neurogenesis in learning in the avian brain. They used electron microscopy to detect synaptic terminals on freshly formed neurons in the forebrain of songbirds. They demonstrated that these new neurons were engaged in learning and integrated functionally into existing circuitry (Burd & Nottebohm, 1985). Then, researchers investigated the regulation of adult hippocampal neurogenesis by hormonal stress and discovered a link between stress and the control of neurogenesis in the hippocampus (Cameron et al., 1993). The convergence of studies with the discovery of neural stem/progenitor cells in the adult striatum (Reynolds & Weiss, 1992) led to the acceptance of adult neurogenesis by the research community. As a result, towards the end of the twentieth century, adult neurogenesis in the hippocampus was widely acknowledged. Neurogenesis in DG has been described in numerous animal species, including humans (Eriksson et al., 1998), and is widely recognized by scientists.

Knoth et al (2010) found evidence of neurogenesis in people aged 0 to 100 years old after finding protein markers for different phases of neurogenesis. The researchers examined postmortem brain tissue samples to identify neurogenesis markers using immunohistochemistry (Knoth et al., 2010) and discovered the rostral migratory stream in the human brain, implying rudimental ongoing olfactory neurogenesis (Sahay, Wilson, et al., 2011). This was demonstrated in the human brain postmortem tissue.

Another group conducted a rigorous study that confirms the validity of the idea of adult human hippocampus neurogenesis. The researchers analyzed hippocampi (dentate gyri) from people aged 14 to 79 years and they discovered a comparable number of intermediate neural progenitors and thousands of immature neurons in the DG, as well as comparable numbers of glia and mature granule neurons and DG volume across ages. Nonetheless, older people have less angiogenesis and neuroplasticity, as well as a smaller pool of quiescent progenitors (Boldrini et al., 2018).

Adult neurogenesis is a phenomenon now widely accepted. Adult-born subventricular zone (SVZ) neurons move along the rostral migratory stream and integrate as interneurons into the olfactory bulb. Adult-born neurons in the SGZ migrate into the granule cell layer (GCL) and integrate as granule cells (C. Zhao et al., 2008). The presence of adult neurogenesis in other parts of the brain is still debatable (Gould, 2007). Although studies have shown neurogenesis in places such as the neocortex and the striatum, further research is needed to prove that adult neurogenesis occurs in these locations. This thesis focuses on adult and adolescent neurogenesis in the hippocampus. The hippocampus is a region in the medial temporal lobe that is essential for learning and memory.

1.2 Hippocampal neurogenesis

1.2.1 The structure of the dentate gyrus

The DG has three layers or laminae: the molecular layer, the granule cell layer, and the hilus (figure 1.1).

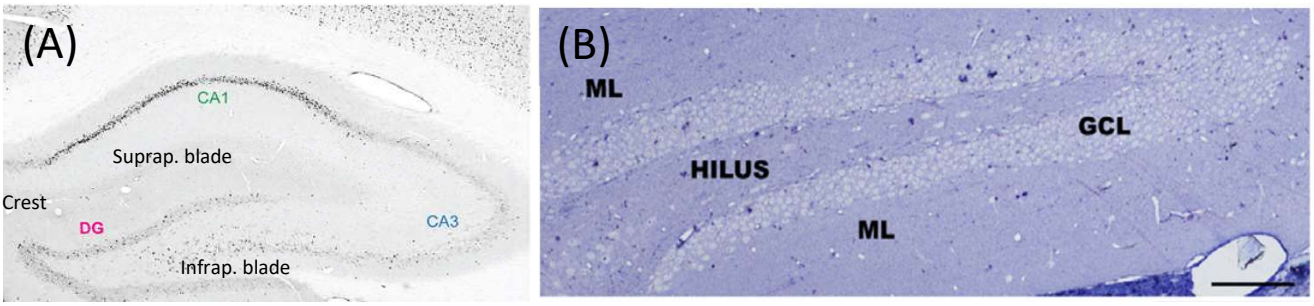

Figure 1.1: The three laminae of the dentate gyrus: The figure depicts the dentate gyrus (DG) with the suprapyramidal blade (Suprap. blade), infrapyramidal blade (Infrap. blade), and crest. Corn of Ammon 1 (CA1) and 3 (CA3) areas are depicted. (**A**) 1.5µm semithin section of mouse DG. (**B**) At a medium level, this figure depicts the granular cell layer (GCL), the molecular layer (ML), and the hilus that is comprised in the DG (Canales J., 2016).

The hippocampus has a trilaminate area with a distinct V or U shape depending on the septotemporal location. The suprapyramidal (or dorsal or higher) blade is the part of the granule cell layer between the CA3 and CA1 fields, whereas the infrapyramidal (or ventral or lower) blade is the opposite side. The crest is the area spanning the two blades at the peak of the V or U form. The subgranular zone is a thin layer of cells between the granule cell layer and the DG's hilus. The SGZ is a germinative matrix for adult neurogenesis thanks to the NPCs, whose neuronal offspring move into the granular cell layer at variable distances, extending their axons and dendrites into the CA3 field and molecular layer, respectively (figure 1.2, Tatu & Vuillier, 2014).

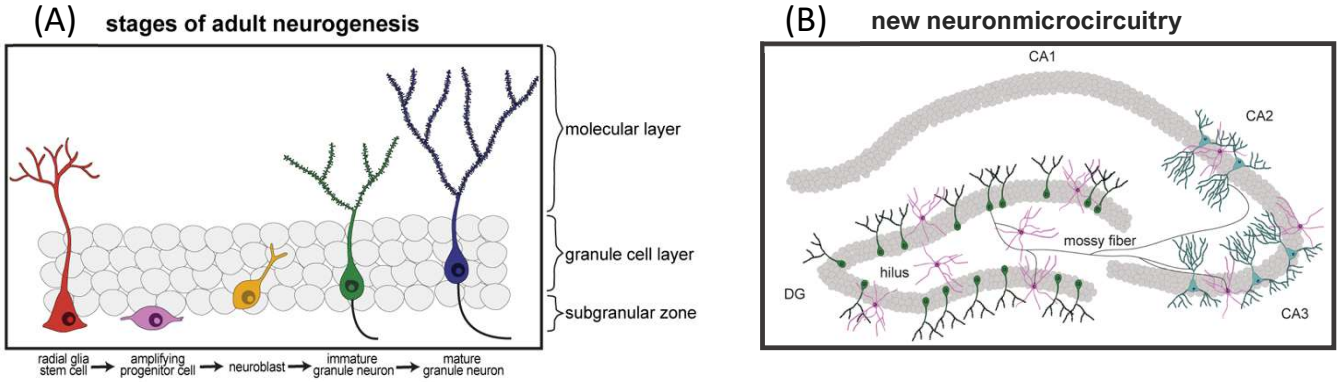

Figure 1.2 Adult neurogenesis in the hippocampus, the circuitry into which the new cells are integrated. (A) Different phases of adult neurogenesis in the hippocampus's dentate gyrus (DG). Radial glial stem cells in the subgranular zone give rise to new granule neurons. These stem cells create multiplying progenitor cells, which form neuroblasts. The neuroblasts migrate into the granule cell layer, where they grow into immature granule neurons with a single dendritic tree extending toward the molecular layer and an axon (mossy fiber, mf) reaching through the hilus to the CA3 and CA2 subfields. (**B**) A schematic depiction of new neuron projections, highlighting the several hippocampus subfields that serve as new neuron targets (DG, CA3, CA2, and CA1). New granule neurons' mossy fibers link to hilar mossy cells, pyramidal cells in the CA3 and CA2, and inhibitory neurons interneurons in the DG, hilus, and CA3 (modified from Cope & Gould, 2019).

Neurogenesis in the adult DG is spatially restricted to a radius of roughly 100 µm from the precursor cell to the mature neuron's ultimate position (Kempermann et al., 2003). Furthermore, unlike in the olfactory bulb, neurogenesis in the DG is cumulative and does not contribute to turnover (Imayoshi et al., 2008). It implies that the DG is constrained by a local restriction and a shortage of new neurons. Despite these spatial constraints, the contribution of these additional cells to hippocampal activities remains significant.

1.2.2 Adult hippocampal neurogenesis: a series of sequential developmental events

Adult hippocampal neurogenesis (aHN) is a complicated process in which neural progenitor cells (NPCs) go through several phases of development (figure 1.3), including cell proliferation, neuronal differentiation, maturation, and integration into the hippocampus' neural network (Gonçalves et al., 2016). Through this process, neural stem cells (NSCs) in the dentate gyrus's SGZ give birth to neurons that eventually integrate into the dentate gyrus' GCL. NSCs are self-renewing cells that may give rise to a variety of cell types depending on their potency and the environment in which they are found (Gage, 2000). Radial glia-like cells (also known as slowly dividing type 1 cells) and quickly

proliferating type 2 neural progenitor cells generate new neurons in the hippocampus. Surviving newly-born neurons go through differentiation and maturation phases before being incorporated into the GCL's neural networks. They transmit axons to cells in the hilus and CA3 by sending dendrites into the molecular layer, allowing them to receive input from perforant route axons (Aimone et al., 2014; Restivo et al., 2015). Various markers can be used to analyze different phases of neurogenesis, as shown in the fig.1.3. In this thesis, we will focus particularly on one: Doublecortin (DCX).

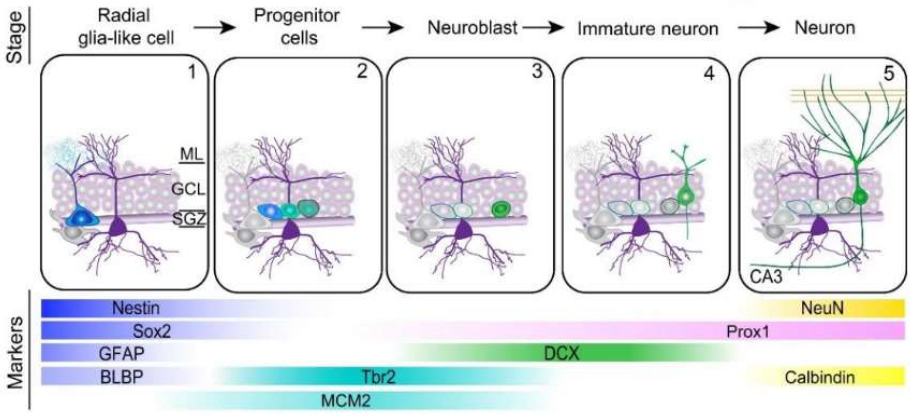

Figure 1.3 Different phases and markers of the adult hippocampal neurogenesis process: (1) activation of dormant radial glia-like cells in the subgranular zone (SGZ); (2) proliferation of non-radial precursor and intermediate progenitors; (3) production of neuroblasts; (4) integration of immature neurons; and (5) maturation of adult-born dentate granule cells. Expression of stage-specific markers, the sequential process of synaptic integration, and key intervals controlling survival and plasticity are also depicted. ML stands for molecular layer; GCL stands for granule cell layer; SGZ stands for the subgranular zone; GFAP stands for glial fibrillary acidic protein; BLBP stands for brain lipid-binding protein; DCX stands for doublecortin; NeuN is for neuronal nuclei (Ming & Song, 2011)

1.2.3 DCX a marker for neurogenesis functional studies

DCX is an endogenous neuroblast and immature neuron marker. It is a microtubule-associated protein that is extensively expressed in the developing brain and is essential for proper neuron migration (Ayanlaja et al., 2017a). Its normal expression occurs within the first two weeks after the birth of a neuron (McDonald & Wojtowicz, 2005). DCX expression is restricted to neurogenic and a few non-neurogenic areas of the adolescent and adult brain (Bonfanti & Nacher, 2012; Dhaliwal et al., 2016; Zare et al., 2019). The role of DCX in the adult brain is unknown.

It has been demonstrated that changing conditions, such as exposure to an enriched environment (Gonçalves et al., 2016) or chronic periods of overnutrition, can affect dendritic growth, connectivity,

and DCX expression during the development phase (T.-K. Han et al., 2019a; Nam et al., 2017). On these bases, we structured the study presented in this thesis: the analysis of the fine structural architecture of DCX + immature neurons in the HP after an exogenous stimulus.

1.2.4 Function of adult hippocampal neurogenesis

DCX+ neurons integrate into the hippocampal circuitry contributing to its functionality. The hippocampus is required for the encoding of new information as well as the development of episodic, spatial, and emotional memory (Deng et al., 2013). To understand the function of adult hippocampal neurogenesis, many studies ablated neurogenesis using genetic, pharmacological, or X-ray irradiation methods, and then examined the effect on cognitive function using hippocampal-dependent behavioral tasks such as the Morris Water Maze and/or contextual fear conditioning (Deng et al., 2013). Adult neurogenesis is required for encoding new information, memory retention, or both learning and memory (Cameron & Glover, 2015). The capacity to discern two comparable situations, also known as pattern separation, is thought to be dependent on neurogenesis (Toda & Gage, 2018). Increasing neurogenesis by inhibiting apoptotic death of adult-generated neurons in adults is enough to improve pattern separation abilities, according to this idea (Sahay, Scobie, et al., 2011). Investigations employing two-photon calcium imaging to monitor the activity of adult-generated cells in awake, acting mice have verified the direct participation of adult-generated neurons in the context of learning and discrimination, which is consistent with their suggested role in pattern separation (Danielson et al., 2016). Neurogenesis, according to computational models and experimental data, should result in the destabilization (or forgetting) of previously acquired memories(Toda & Gage, 2018). According to this hypothesis, as new neurons are recruited to the network, they compete with old neurons, causing a substantial reorganization of the hippocampus circuit. In this sense, cognitive performance in hippocampal-dependent learning and memory tasks of p50−/− and wild-type (WT) mice were examined. p50 is an NF-kappa B family member, whose contribution to controlling cell

death and/or survival is widely demonstrated (Grilli et al., 1996; Mattson & Camandola, 2001; Meffert & Baltimore, 2005). One intriguing possibility is that in p50-/- mice, the minor insertion of new neurons into preexisting circuits is offset by a lower elimination rate of older mature neurons (Denis-Donini et al., 2008). So, there are two plausible methods for how hippocampus adult-born neurons contribute to neurogenesis-dependent hippocampal memory functions: 1. Adult-born neurons inhibit the mature granule cells around them, determining which neurons will be active at any particular time. 2. These neurons are engaged in memory trace encoding (Piatti et al., 2013).

1.2.5 Hippocampal neurogenesis in adolescence

Another aspect that is taken into account in this thesis is the importance of hippocampal neurogenesis in adolescence. The teenage years are a delicate time for neurodevelopment. It is thought to be a crucial stage for the programming of future adult behaviors since it marks the passage from childhood to adulthood and involves major lifestyle changes as well as an increase in independence from caregivers (Arnett, 2000; Sawyer et al., 2012). It has frequently been assumed that the beginning of the biological changes related to puberty in humans marks the beginning of adolescence (Sharma et al., 2013). Although these two developmental phases occur at the same time, adolescence is distinct from the more temporally limited stage of puberty, which relates to the development of sexual maturity. Although there are no clear-cut indicators for the adolescent phase, it is generally accepted that it lasts from ages 12 to 18 in humans and from postnatal day (PND) 21 to 60 in mice and rats (Spear, 2000a). Adolescence in mammals is a crucial time for the formation of the hippocampus circuity and increased neuronal plasticity (Hueston et al., 2017). During adolescence, dentate gyrus neurons undergo structural remodeling (Boldrini et al., 2018). While the volume of a single granule cell nucleus in the DG declines with age, there is a roughly 35–40% linear increase in the overall number of granule cells in the DG in adolescent rats (PND 28) compared to adult (120 PND) rats (Bayer, 1982), suggesting that older rats had smaller neurons and a bigger DG. During adolescence,

granular neurons in the lower blade of the DG also undergo morphological changes. In particular, there is the pruning of the dendrites near the cell body and an increase in the density of the distal dendritic spines in the lower infrapyramidal blade (Hueston et al., 2017). Furthermore, it has been demonstrated that gonadal steroid hormones, which sharply rise throughout adolescence, change the hippocampus's neuronal architecture. Circulating testosterone has been shown to have an impact on the spine synaptic density in the CA1 sector. Likewise, estradiol has been demonstrated to raise the number of dendritic spines in hippocampus neurons (Bettio et al., 2020). In rats and mice, hippocampus neurogenesis levels are up to four times greater during adolescence than they are throughout maturity. Hippocampal neurogenesis involves the generation, differentiation, and integration of new neurons inside the subgranular zone of the GCL of the DG (Curlik et al., 2014). Therefore, it is probable that the teenage brain is more susceptible to environmental variables and experiences because the hippocampus develops much more cells throughout the adolescent period (Curlik et al., 2014). The functional integrity of the hippocampus might suffer significantly as a result of this heightened reaction. Therefore, this developmental stage may be a crucial window during which alterations in hippocampus function may result in organizational changes that endure throughout adulthood given the neurological, hormonal, and behavioral changes that occur during adolescence (Fuhrmann et al., 2015). However, more research has to be done to determine if variations in hippocampus plasticity at this critical stage of growth might affect behavior in adults (O'Leary J. D., 2017).

1.3 Dorsal and ventral hippocampus

The hippocampus appears to be functionally divided into anterior and posterior parts in humans and rodents along its longitudinal axis, according to a growing number of morphological, electrophysiological, molecular, and lesion findings (figure 1.4). In any case, hNG occurs at a varied rate along the entire axis. This thesis furthers the segregation of hNG.

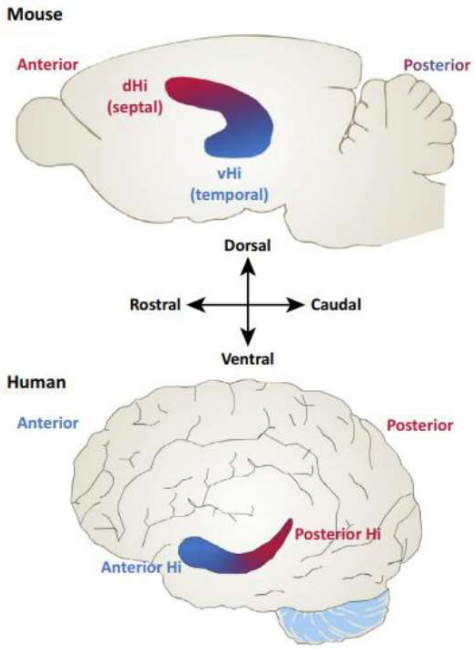

Figure 1.4 Human and mouse hippocampal anatomical division. The human hippocampus is split into anterior (matching to the vHi in rats) and posterior hippocampus, whereas the mouse hippocampus is divided into dorsal (dHi) and ventral (vHi) subregions.

1.3.1 Evidence of segregation along the hippocampal longitudinal axis

According to prior anatomical studies, the hippocampus in rats is physically split along its longitudinal axis (Fanselow & Dong, 2010; Strange et al., 2014). Indeed, in rats, the dorsal Hippocampus (dHP) and ventral Hippocampus (vHP) have separate input and output signals to and from other brain areas. The dHP receives afferents from the retrosplenial cortex and the anterior cingulate cortex(Cenquizca & Swanson, 2007), sending projections to structures involved in the processing of visuospatial information, whereas the vHP connects with the bed nucleus of the stria

terminalis, nucleus accumbens, and hypothalamus, structures that regulate neuroendocrine and behavioral responses to stress, anxiety, motivation, and other stimuli (Fanselow & Dong, 2010; Poppenk et al., 2013). In animals, the first electrical research revealed distinct features in the dorsal and ventral hippocampus. Research in mice (Elul, 1964; Racine et al., 1977) and rats revealed that various electrical features vary along the longitudinal axis of the hippocampus, with different neuronal excitability (Dougherty et al., 2012) and synaptic plasticity (Maggio & Segal, 2007). Also, nonhuman primates and humans both showed electrophysiological variation along the hippocampus axis (Takita et al., 2013). Place cells, often located in the CA1 or CA3, are cells in the hippocampus that activate when an animal moves in a certain region, assisting with spatial discrimination. These place cells are more prevalent in the dHP than the vHP (Cobar et al., 2017). The results show that the dHP is primarily involved in spatial navigation. An electrophysiological study demonstrates that a spatial learning task activates a higher percentage of neurons in the posterior hippocampus than in the anterior hippocampus, supporting the preferential role of the posterior hippocampus (dorsal in rodents) in spatial learning and memory in non-human primates (Takita et al., 2013). Moreover, different hippocampus sub-regions have different gene expression patterns. Studies in rats (Christensen et al., 2010) and mice have shown 48 differential gene expressions in the dorsal DG vs the ventral DG (Cembrowski et al., 2016). The expression of genes linked to serotonergic, cholinergic, and GABAergic neurotransmission is elevated in the vHP (Lee et al., 2017). In summary, the dHP seems to have a more significant role in spatial learning and memory, whereas the vHP seems to have a more significant role in anxiety and stress response (Levone et al., 2021). Lesion studies showed a functional segregation of the hippocampus, with damages of the vHP but not the dHP attenuating anxious behavior in rats in the light-dark box, elevated plus maze, hyponeophagia, and open field tests (McKenzie & Buzsáki, 2016). In rats, however, dHP lesions reduced spatial learning and memory but not vHP lesions (Duda & Węsierska, 2021).

1.3.2 Is adult neurogenesis segregated along the longitudinal axis of the hippocampus?

Adult neurogenesis may be regulated preferentially in the dHP or the vHP, depending on the stimulus (Bond et al., 2020).

Indeed, new neurons in the dHP are required for contextual discrimination and memory tasks in rats, but new neurons in the vHP are required for the antidepressant fluoxetine's anxiolytic effects in mice (Tanti & Belzung, 2013; Wu & Hen, 2014). The dHP exhibits more active neurogenesis than the vHP in mice and it is rich in maturing neuron markers like NeuroD1 and DCX, whereas the vHP is rich in radial glia markers like Sox2 and Hes5 (Zhang et al. 2018).

As a result, dHP neural progenitor cells have been demonstrated to develop more quickly, which is linked to increased basal network activity (Bond et al., 2020).

Furthermore, stress has been shown to alter multiple phases of adult neurogenesis, with a preference for the vHP over the dHP. Antidepressant-induced increases in cytogenesis and neurogenesis occur preferentially in the vHP but not the dHP (Felice et al., 2012; O'Leary & Cryan, 2014).

Chronic stress has been shown to reduce cell proliferation, neuronal differentiation, maturation, and survival, with a preference for the vHP of rats (Hueston et al., 2017b).

In this thesis we studied the modulation of murine adult and adolescent neurogenesis within hippocampal subregions in response to dietary change, high-fat-diet (HFD).

1.4 Factors affecting levels of neurogenesis

Adult neurogenesis is characterized by its sensitivity to physiological and pathological stimuli at nearly every stage, from neural precursor proliferation to the development, maturation, integration, and survival of newborn neurons. Over the last decade, a considerable body of literature proving the impact of these factors has developed (Babcock et al., 2021; Marx et al., 2021).

Many physiological stimuli affect postnatal neurogenesis. Physical exercise, for example, increases cell proliferation in the adult SGZ, whereas an enriched environment promotes new neuron survival (Ma et al., 2017). These elements promoting neurogenesis have also been related to improved performance in hippocampus-dependent activities.

In adult SGZ and SVZ, however, factors can cause a significant reduction in cell proliferation, such as aging (Babcock et al., 2021b), stress (Levone et al., 2015), chemotherapy (Winocur et al., 2015) and social isolation (Cinini et al., 2014).

It is obvious that different stimuli can govern distinct phases of postnatal neurogenesis, and that one stimulus can have many targets. Different stimuli also interact with one another, affecting the eventual outcome of adult neurogenesis. In general, the effect of external stimuli on adult neurogenesis is complex, and it depends on timing, dose/duration, specific paradigms, animal models (age, sex, genetic background), and research methods. The biggest challenge is figuring out what cellular and molecular pathways are at work when it comes to adult neurogenesis regulation (Kuhn et al., 2018).

Diet is another significant component in controlling aHN, and the consequences of dietary alterations are the major emphasis of this thesis.

1.4.1 Diet and neurogenesis

Diet can affect aHN. aHN can be influenced by diet on four levels: calorie intake, meal frequency, meal texture, and meal content. These four characteristics not only modulate aHN in rodents (Poulose

et al., 2017), but they also modulate cognitive performance and mood in humans, according to independent rodent studies and intervention or epidemiological research (Zainuddin & Thuret, 2012).

Calorie restriction can increase lifespan, improve behavioral results in several neurodegenerative disease rodent models, and improve spatial learning (Hooijmans et al., 2009; Rich et al., 2010). It was discovered that a 30–40% reduction in calorie consumption promotes aHN in rodents and that this effect is partly mediated by Brain-derived neurotropic factor (BDNF, J. Lee et al., 2002; Poulose et al., 2017). Calorie restriction has been linked to improvements in age-related learning and memory deficits, in addition to neuroprotective benefits in animal models of neurodegenerative diseases like Alzheimer's, Huntington's, and Parkinson's disease (J. Lee et al., 2000; Park & Lee, 2011). Human longitudinal studies have also discovered a link between lower calorie consumption and a reduced risk of Alzheimer's and Parkinson's disease (J. Lee et al., 2000; Logroscino et al., 1996; Luchsinger et al., 2002; Park & Lee, 2011).

Also, meal frequency has an important role in aHN modulation. Longer time between meals boosts aHN without reducing calorie consumption. It also affects hippocampal gene expression linked to hippocampus-dependent tasks and mood in mice (Stangl & Thuret, 2009).

Food texture also affects aHN; rats fed with a soft diet rather than a solid/hard diet have lower hippocampus progenitor cell proliferation. It is hypothesized that chewing, which is linked to corticosterone levels, causes cell growth (Aoki et al., 2005).

Interestingly, research has found that similar soft diets decrease learning and memory ability in rats (Kushida et al., 2008). If chewing plays a role in aHN, these findings could be useful for the elderly with cognitive decline, as tooth deterioration may impede chewing abilities.

Dietary composition is also a critical element in controlling aHN (Stangl & Thuret, 2009).

Because a range of nutrients has been identified as possible modulators of aHN, meal content gives great flexibility in regulating aHN (Poulose et al., 2017; Zainuddin & Thuret, 2012). Some research highlighted the effect of diet on hippocampus neurogenesis and cognition in adults. Low-calorie diets have been found to improve memory performance in elderly people (Witte et al., 2014a; Zainuddin & Thuret, 2012). Low-calorie diets (Fontan-Lozano et al., 2007) or diets with increased flavonoids (W. Wang et al., 2011), omega-3 fatty acids (Dyall et al., 2010), polyphenols (Sarubbo et al., 2018), magnesium (Abumaria et al., 2013) or zinc (Levenson & Morris, 2011) can increase proliferation and survival of newly born neurons in the DG, as well as performance on hippocampal-related tasks (W. Wang et al., 2011). There is also evidence that nutritionally advantageous diets can protect against stress-induced impairment in hippocampus neurogenesis and cognitive impairments. The treatment of neuronal cultures with omega-3 fatty acid, for example, restored the corticosterone-induced inhibition of neuronal development (Pusceddu et al., 2015). Furthermore, flavonoid-rich diets given to rats (unspecified gender) exposed to prolonged unpredictable stress restored the stress-induced reduction in proliferating new neurons inside the DG (An et al., 2008). Similarly, male and female mice treated with calorie restriction for 10 days demonstrate a reduction in chronic social stress-induced depressive-like behavior (Lutter et al., 2008).

1.4.2 Dietary changes: focus on teenage nutrition

An increasing amount of data suggests that teenage nutrition is important for overall well-being, including brain health (C. O. Bondi et al., 2014). Obesity, diabetes and cognitive and emotional issues could be consequences of a Western diet rich in processed foods, fats, and sweets (Ruiz et al., 2019). Healthy diets, on the other hand, such as a Mediterranean diet rich in vegetables, seafood, fruits, and nuts, include a variety of macronutrients such as omega-3 fatty acids, omega-6 polyunsaturated fatty acids, and flavonoids, which support both brain and body health (Siervo et al., 2021). Thus, current research shows that not only is nutritional status essential for adolescent brain health, but so is total diet composition, which includes macronutrients, fatty acids, and vitamin levels. To date, most

research on the influence of food on cognition and neurogenesis throughout adolescence has concentrated on the negative effects of high-fat diets (HFD) or high-sugar diets. In animal studies, for example, male mice fed an HFD during adolescence (beginning at PND21) had worse cognitive performance in the radial arm maze and fewer new neurons in the DG, but none of these alterations were found when the diet was provided during maturity (Boitard et al., 2012a). Similarly, an HFD administered to male rats throughout adolescence (beginning at PND21) reduced long-term memory performance in the Morris water maze, but an HFD fed during maturity had no effect. Furthermore, human teenagers who consume Western diets score worse on visual-spatial learning and memory tasks, both of which are linked to hippocampus function, lending evidence to the connection between nutritional status and hippocampal function. (Nyaradi et al., 2014)

These findings suggest that better food treatments may play a significant role in controlling hippocampus function.

However, as with exercise, it has to be established whether nutrition has a distinct influence on stress-induced alterations in hippocampus neurogenesis and cognition throughout adolescence versus adulthood.

Recent experimental findings in mouse models demonstrated that continuous periods of overnutrition decrease the expression of DCX+ cells (T.-K. Han et al., 2019a; Nam et al., 2017). These detrimental effects are more pronounced at younger ages (Ferreira et al., 2018) and may be location-specific according to hippocampal functional segregation (Vinuesa et al., 2016). Additionally, some of these changes take place before a large weight gain (Snyder et al., 2012a). These findings imply that, regardless of metabolic disturbances, overeating may have a direct impact on brain structures. Based on these findings and in consideration of their possible pathophysiological importance, we looked at how a brief HFD affected the delicate anatomical architecture of hippocampus DCX+ immature neurons in teenage and adult mice.

Dietary adjustments made throughout adolescence may have a longer-lasting effect than dietary changes made during maturity. It should also be emphasized that food is the most important element in causing changes in gut microbiota composition (McAllan et al., 2014) and that the detrimental effects of stress on the microbiome in childhood (Tremblay et al., 2021), and adulthood (Gupta et al., 2020) may be reversed by dietary modifications. The influence of stress and nutrition on the microbiome in adolescence has not yet been explored, however, it is well known that during adolescence, the structure and balance of the gut microbiota change. However, other lifestyle modifications that start in adolescence, including as stress, nutrition, alcohol, and drug use, have an influence on the microbiota, and this may be a key mechanism behind the control of hippocampus neurogenesis and related cognitive performance during this period of life (McVey Neufeld et al., 2016). These results suggest that while stress may have a more significant and long-lasting impact on hippocampal neurogenesis and cognitive function during adolescence, it may also be a time when making healthy lifestyle changes, such as eating a healthier diet and exercising more, can not only offset these negative effects but also produce positive effects in their own right (Hueston et al., 2017). Future study into the possible synergistic effects of food, exercise, and stress is thus required and will aid in determining which treatments during adolescence create substantial benefits on cognition later in life (Marosi & Mattson, 2014).

1.4.3 Mechanisms underlying diet-induced changes to hippocampal neurogenesis

Hippocampal neurogenesis is thought to be, at least partly, mediated by corticosterone and neurotrophins which are modulated by diet.

Corticosterone may potentially play a role in modulating the effects of HFD. Lindqvist et al. (2006) examined corticosterone levels in rats fed a high-fat diet for four weeks. In addition to a reduction in hippocampus neurogenesis, HFD rats had higher corticosterone levels. They postulated that HFD's effects on hippocampus neurogenesis were mediated, at least in part, by increased serum

corticosterone levels. Continuous exposure to high amounts of corticosterone has been demonstrated to reduce aHN (Foroozan et al., 2021)

Neurotrophin-3 is a neurotrophin factor that has been demonstrated to be influenced by dietary restriction (NT-3). Neurogenesis can be aided by NT-3 by enhancing neuronal differentiation (Arcego et al., 2018; Park & Lee, 2011).

Another neurotrophin involved in aHN is BDNF, which is required by adult hippocampal neurons for cell growth and survival. BDNF levels were increased in rats that were on a restricted diet (Park & Lee, 2011). BDNF levels have also been found to be lower in the hippocampus of rats fed a high-fat, high-sugar diet (Zhao et al., 2021).

1.4.3.1 BDNF

BDNF is broadly expressed in most brain areas, with the hippocampus having the greatest amounts, followed by the cerebral cortex (Hofer et al., 1990). According to cell type analyses, BDNF is mostly expressed by primary glutamatergic neurons and is lacking in interneurons (Marty et al., 1997). The pre-mRNA sequence drives BDNF gene translation to the endoplasmic reticulum (Lessmann et al., 2003). This process happens largely at the soma level, while BDNF production can occur in the dendrite under specific conditions (Heerssen and Segal, 2002). Translation produces the dimeric pro-BDNF protein, which is cleaved to become mature BDNF (figure 1.5).

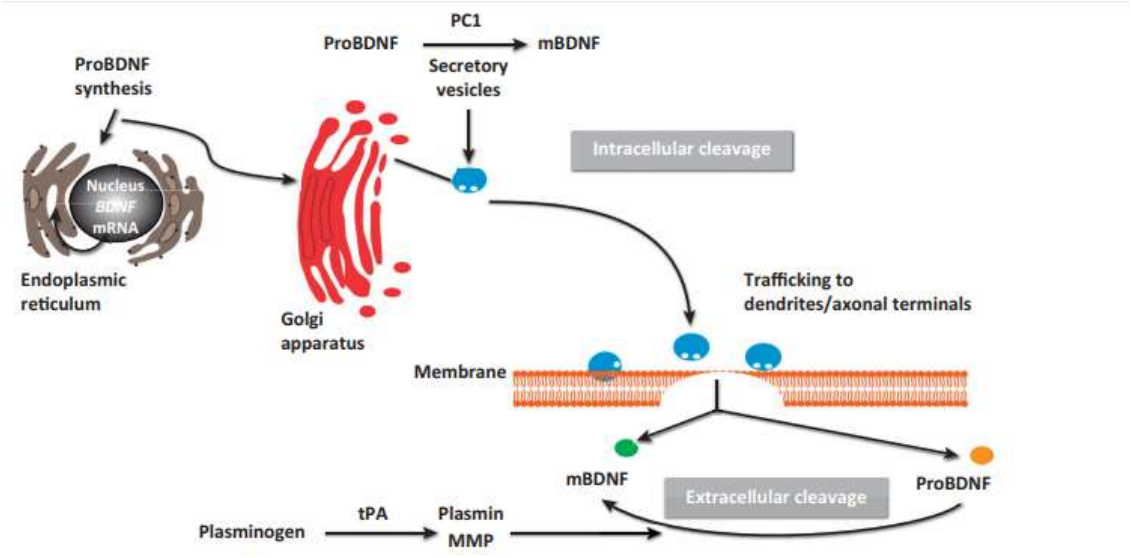

Figure 1.5: Mechanisms for Brain-Derived Neurotrophic Factor Production and Release (BDNF). The endoplasmic reticulum translates the BDNF mRNA into the proBDNF protein. ProBDNF is carried into the Golgi and converted by extracellular protein convertase 1 (PC1) within the vesicles to the mature form of BDNF (mBDNF). The axonal or dendritic terminals serve as the sites of release for the secretory granules. ProBDNF and mBDNF are both secreted by neurons in an activity-dependent way (Marosi & Mattson, 2014).

The prodomain is crucial in sorting BDNF into one of two secretion pathways: the regulated pathway and the constitutive pathway (Mowla et al., 1999). The controlled secretion mechanism involves BDNF packed in large-diameter vesicles that fuse with the plasma membrane in response to an intracellular Ca^{2+} elevation. Distal neural processes initiate this secretion. The constitutive mechanism includes BDNF packed in smaller granules and released constantly via a Ca^{2+}-independent fusion process. In the absence of a specified triggering event, this secretion takes place mostly at the soma and proximal processes (figure 1.6 Kuczewski et al., 2009)

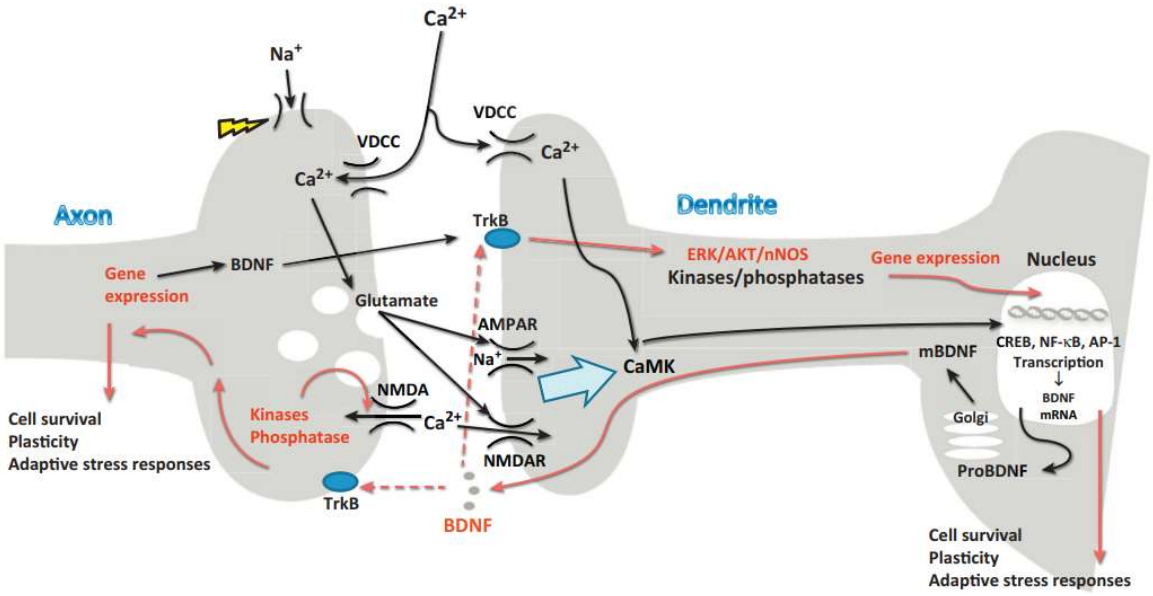

Figure 1.6: **Activity of BDNF**. Na+ inflow depolarizes the plasma membrane when an axon potential reaches its presynaptic terminal, which then causes Ca^{2+} influx and the release of the excitatory neurotransmitter glutamate into the synaptic cleft. At the postsynaptic membrane, glutamate binds to NMDA and AMPA receptors. When the AMPA receptors are activated, the membrane depolarizes and Ca^{2+} influx occurs via NMDA and VDCC. When Ca^{2+} activates CaMKs, CREB and NF-κB are also activated, which leads to the transcription of the Bdnf gene. The production of genes essential for the survival and plasticity of neurons is triggered by the release of mBDNF at synapses, which also activates TrkB receptors, which in turn activate downstream signaling cascades such PLCg, PI3K, and MAPKs. By changing the NMDA receptors' activation kinetics and raising the quantity of docked synaptic vesicles at the presynaptic terminal, BDNF signaling also causes fast changes in membrane excitability and synaptic transmission. Abbreviations: AMPA(R) stands for a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (receptor); BDNF stands for brain-derived neurotrophic factor; CaMK stands for Ca^{2+}/calmodulin-dependent kinase; CREB stands for cAMP response element-binding protein; MAPK stands for mitogen-activated protein kinase (Marosi & Mattson, 2014).

For the growth, upkeep, and flexibility of the central and peripheral neural systems, the neurotrophin-family protein BDNF is crucial (Chao et al., 2006). In addition to promoting neurite outgrowth and synaptogenesis and inhibiting programmed cell death/apoptosis, BDNF aids neurons in differentiating from stem cells. Picomolar concentrations of BDNF cause biological responses in neurons throughout the developing and adult mammalian nervous system. The maturation of GABAergic inhibitory networks in the cortex and the development of neurons in the hippocampus are both influenced by BDNF (Waterhouse & Xu, 2009). Further studies showed that exogenous BDNF injection increased neurogenesis whereas BDNF knockdown decreased it in adult DG (Deltheil et al., 2008; Taliaz et al., 2010). Proliferation increased in BDNF heterozygous knockout mice (Colucci-D'Amato et al., 2020; Sairanen, 2005). Additionally, recent research indicates that BDNF is a crucial regulator of energy metabolism, with action locations and mechanisms very different from those of hormones like leptin and insulin (Podyma et al., 2021).

1.5 Outline of the study

Consumption of hypercaloric and fat-rich meals is linked to an elevated risk of metabolic disorders (Wali et al., 2020), and is generating an increase in these diseases worldwide (Saklayen, 2018). Furthermore, poor diets marked by caloric intake that considerably surpasses bodily energy expenditure have been linked to an increased risk of developing neurodegenerative (Cordner & Tamashiro, 2015a) or mental diseases (Chatterjee et al., 2016). A third of all clinical instances of neurodegenerative disease are thought to be attributable to modifiable lifestyle risk factors including nutrition (Scarmeas et al., 2018). A negative nutritional lifestyle has a greater influence at earlier ages, such as in childhood and adolescence. The adolescent years are a time of fast cognitive growth, but also tremendous vulnerability (Tandon et al., 2016). A thorough evaluation of clinical literature revealed that poor food habits early in life are connected with poor cognitive results later in life. A healthy diet, on the other hand, is linked to superior cognitive outcomes (Tandon et al., 2016). Consumption of normal-caloric and fresh components at a young age has been linked to improved cognitive function during growth (von Stumm, 2012). On the contrary, a diet heavy in processed components and added sugar has been linked to worse adolescent school success, language, and nonverbal reasoning (Nyaradi et al., 2013). Interestingly, multiple investigations, both in human and preclinical animals, have found a link between excessive food consumption and brain volume loss (Hooshmand et al., 2016a; Luciano et al., 2017a). Memory and learning processes are governed by numerous brain regions in the CNS, but the hippocampus plays a major role. This area is distinguished by the physical segregation of its activities along the dorsoventral axis: the dorsal hippocampus appears to be related largely to cognition, whereas the ventral hippocampus appears to be associated with stress, emotion, and affect (reviewed in Ref. Fanselow & Dong, 2010). hNG occurs in the DG of both the dorsal and ventral hippocampus, allowing newborn neurons to develop and, over time, integrate into the hippocampal circuitry and contribute to its functionality (Toda & Gage, 2018). A

vast body of evidence demonstrates that when hNG is dysregulated, it leads to cognitive impairment and mood changes (Bortolotto et al., 2014; Oomen et al., 2014). Chronic malnutrition is known to impair this kind of neuroplasticity by reducing the amount of proliferating cells and newborn adult hippocampus neurons (Lindqvist et al., 2006b). The development of cells expressing DCX, a protein required for neuronal differentiation and migration, is a critical stage in the hNG process (Ayanlaja et al., 2017b). Recent experimental findings in mouse models demonstrated that protracted periods of overnutrition lower the number of DCX+ cells (T.-K. Han et al., 2019a; Nam et al., 2017) and that these negative effects are greater at younger ages (Ferreira et al., 2018) and may be region-specific (Vinuesa et al., 2016). Furthermore, some of these changes occur before major weight gain (Snyder et al., 2012b). These findings imply that, regardless of metabolic abnormalities, overnutrition may have a direct effect on brain structures, herein we investigated the effects of a short period of an HFD on the fine structural architecture of hippocampal DCX $^{+}$ immature neurons in adolescent and adult mice. In this study, we looked at how a brief term of HFD affected the fine anatomical architecture of hippocampus DCX + immature neurons in adolescent and adult mice.

1.6 Materials and methods

Animals. Male C57BL/6J mice of 4 weeks of age (adolescents) and 5 months of age (adults) were utilized in two different studies each. Mice kept 3–5/ cage with access to water and food ad libitum, were housed in a light- (12 h light, 12 h dark) and temperature- (22–24 °C) controlled room in high-efficiency particulate air (HEPA)-filtered Thoren units (Thoren Caging Systems) at the University of Piemonte Orientale animal facility. Animal care and handling were performed by the Italian law on animal care (D.L. 26/2014), as well as European Directive (2010/63/UE) and ARRIVE guidelines, and approved by the Organismo Preposto al Benessere Animale (OPBA) of University of Piemonte Orientale, Novara, Italy (DB064.61).

Diet administration protocol. A timeline representation of the experimental design can be found in figure 1.7 A and B together with the composition of the low-fat diet (LFD) and HFD (figure 1.7 C, D)

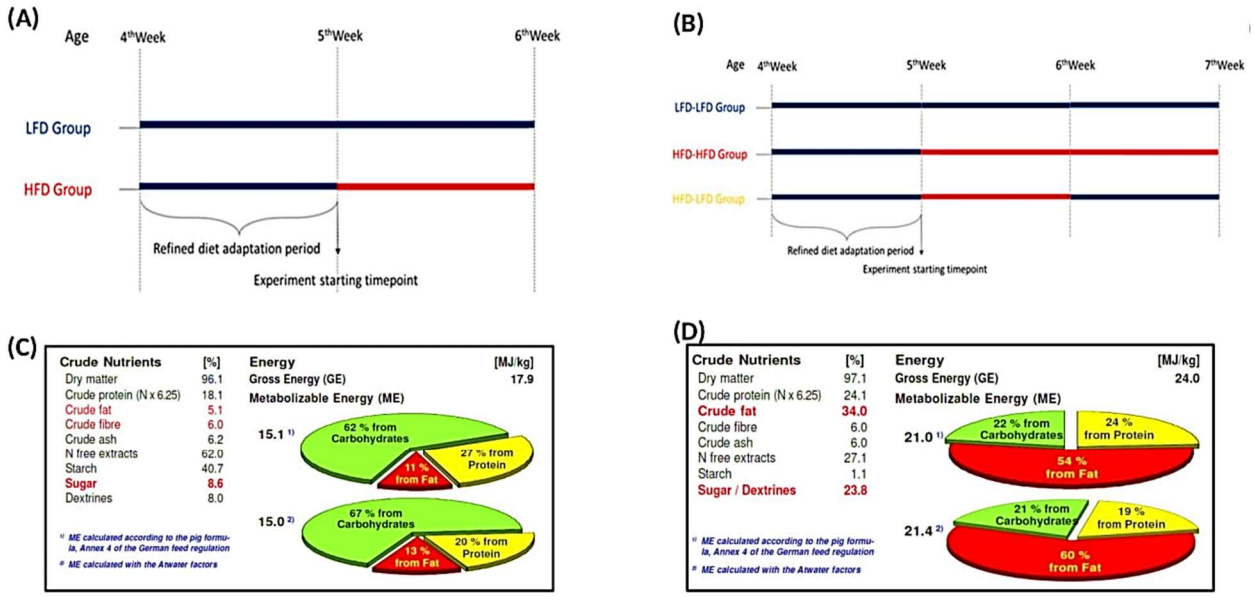

Figure 1.7: Design of the study (A, B) Schematic experimental design and diet composition LFD (**C**), HFD (**D**) (Laboratori Piccioni, https://totofood.it/)

Study 1: eight animals (4 weeks of age) started receiving a LFD (13% kcal from fat, 67% kcal from carbohydrates, 20% kcal from proteins, Laboratori Piccioni), instead of the normal chow diet provided by the animal facility, starting from the fourth week of age so to get used to a refined diet (Pellizzon & Ricci, 2018, 2020). After 1 week (5 weeks of age), animals were randomly divided into 2 groups: the first group continued to be fed with LFD (LFD group, n = 4), while the second group of animals was fed with an HFD (60% kcal from fat, 21% kcal from carbohydrates, 19% kcal from proteins, Laboratori Piccioni) (HFD group, n = 4). Both groups received LFD or HFD for 1 week. The same handling was done with eight adult animals (10 weeks of age).

Study 2: Thirty-four 4-week-old mice underwent LFD as previously described. After 1-week of LFD, animals were randomly divided into 3 groups: the first group continued to be fed with LFD, while the second and third groups of animals were fed with an HFD. After another week, only the third group of animals reverted to an LFD for another week (HFD-LFD group, n = 12), while the first (LFD-LFD, n = 11) and the second (HFD-HFD, n = 11) groups continued with their diet regiment (LFD and HFD respectively). The same handling was done with adult animals (10 weeks of age) with the same number of animals for each group of diet.

In all the studies all experimental groups switched from the chow diet to LFD 1 week before the beginning of the experimental protocol, so to ensure comparable basal conditions. The use of a refined diet (LFD) for the control groups, and not of a chow diet, is required not only for better matching of fiber and nutrient composition but also for texture between LFD and HFD (Utsugi et al., 2014).

In all the studies, animal body weight, and mean values of food/caloric intake per mouse per day were recorded weekly. Briefly, to evaluate food and caloric intake, food was weighed at the beginning of the week and after 7 days (at the same time). The overall consumed food/cage was calculated by subtracting food weight after 1 week from the initial amount of provided diet. This

value was divided by the number of days (7) and by the number of mice per cage to obtain a mean of food intake.

Tissue preparation for immunohistochemical analysis (IHC). At the end of the diet regimen, 8 animals from study 1 and 12 mice from study 2 (n = 4 per each experimental group) were deeply anesthetized with a mix of Zoletil (Zolazepam, 60 mg/kg) and Xylazine (20 mg/kg) i.p. and transcardially perfused with saline and then with paraformaldehyde (PFA) 4% in 0.1 M phosphate buffer pH 7.4, as previously described (Bondi et al., 2021). After PFA-perfusion, brains were rapidly removed, post-fixed in 4% PFA for 24 h, dehydrated in 15% sucrose for 24 h, and then transferred in sucrose 30% for at least 24 h. Then, 40 μm-thick coronal sections were cut with cryostat and collected in cryoprotectant solution at − 20 °C until use.

Tissue preparation for western blot analysis. At the end of the diet regimen, the remaining animals from study 2 (LFD-LFD group n = 7, HFD-HFD group n = 7, HFD-LFD group n = 8) were euthanized by cervical dislocation, and brains were rapidly removed and dissected using a mouse brain matrix (designed for the slicing of coronal sections through the brain at intervals of 1 mm) to isolate separately dorsal and ventral hippocampus. Once isolated, dorsal and ventral hippocampi were snap-frozen and stocked at − 80 °C until use.

Immunohistochemistry and image acquisition. Dorsal and ventral hippocampus areas included in the analysis were delineated according to the Paxinos Mouse Brain Atlas (Paxinos & Franklin, 2004). From a complete series of one in eight brain sections throughout the dentate gyrus, four corresponding sections for each mouse were selected from Bregma − 0.94 to − 2.46 mm (dorsal hippocampus) or from Bregma − 2.54 to − 4.04 mm (ventral hippocampus). Staining was performed on free-floating sections as previously described (Denis-Donini et al., 2008). Endogenous peroxidase activity was blocked with 0.3% H_2O_2 in 0.1 M TBS for 10 min. Sections were subsequently treated at 4 °C for 1 h in a blocking solution containing 10% goat serum (GS) and

0.3% Triton X-100 in 0.1 M TBS, pH 7.4, and incubated with guinea pig anti-DCX antibody (1:15,000, Millipore, Ab2253) in 5% GS, 0.1% Triton X-100 in 0.1 M TBS, for 36 h at 4 °C. Then, sections were incubated with biotinylated goat anti-G. Pig secondary antibody (1:150, Vector Laboratories, BA-7000) in 5% GS in 0.1 M TBS for 2 h at 4 °C. Labelled cells were visualized using the ABC system (Vectastain Elite, Vector Laboratories, PK-6100) with 3,3′-diaminobenzidine as chromogen (Sigma-Aldrich, D3939). Images were acquired using an LSM700 laser-scanning confocal microscope (Carl Zeiss, Le Pecq, France), with 20× magnification (objective: EC Plan-Neofluar 20×/0.5 M27) with an image matrix of 1024 × 1024 pixel, a pixel scaling of 0.313 × 0.313 µm and a depth of 8 bit. Confocal images were collected in Z-stacks with a slice distance of 0.4 µm.

3D DCX^+ cell selection, reconstruction, and quantitative morphometry. The image stacks were imported into ImageJ FIJI software (version 1.52), where 3D reconstructions were performed by an investigator blinded to animal groups using the Simple Neurite Tracer plugin (Longair et al., 2011) which allows semi-automatic and unbiased reconstruction of cell arborizations, as previously described (Bortolotto et al., 2019; Saraiva et al., 2019). DCX^+ immature neurons to be reconstructed were selected based on the following criteria: (i) located in the suprapyramidal blade of DG, (ii) with their dendritic tree growing perpendicular to GCL, (iii) with soma located in the inner third of GCL and (iv) with dendrites entering the molecular layer. Cells whose dendrites/tips were detected in the first or the last scan plan of the z-stack were excluded from analysis because their tree may be cut during sectioning. Examples of cells that, based on the abovementioned criteria, were included or excluded from the analysis are shown in figure 1.8 A and B respectively.

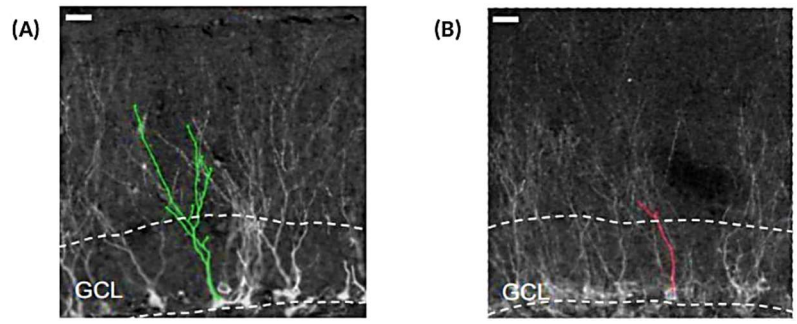

Figure 1.8: Z-projection of the 3D reconstruction (in green) of a DCX+ cell included (**A**) and (in red) excluded (**B**) in our analysis

30–40 cells per animal (corresponding to 120–160 cells per experimental group), in the dorsal and ventral hippocampus, were chosen. Morphological analysis was performed on a 3D reconstruction of the DCX^+ cell with the Sholl analysis plugin (Ferreira et al., 2014), using default settings (enclosing radius cutoff = 1 intersection, Sholl method = linear) with radii increasing by 5 μm. The Sholl Intersection Profile (SIP) counts the number of intersections between cell dendrites and concentric spheres emanating from the center of cell soma. Moreover, 3D reconstructions were exported as SWC files and analyzed with the L-measure tool to evaluate additional morphometric features (Scorcioni et al., 2008).

Western blot analysis. Briefly, dorsal and ventral hippocampi were homogenized in RIPA buffer (Tris 50 mM, NaCl 100 mM, EGTA 5 mM, Nonidet NP-40 1%, Dithiothreitol 5 mM, Protease inhibitor cocktail [P8340, Sigma Aldrich] 10 μl/ml, PMSF 1 mM, NaF 25 mM, $NaVO_4$ 1 mM) in ice and incubated at 4 °C for 2 h under constant agitation. Samples were then centrifuged at 20,000*g* for 30 min at 4 °C and supernatants were collected. Protein concentration was evaluated with Bradford assay. Forty micrograms of proteins for each sample were separated onto 8% acrylamide gel and then transferred to a nitrocellulose membrane. After blocking (2 h in 5% non-fat dry milk in TBS 1X), membranes were incubated with rabbit anti-DCX (1:1000, Cell Signaling, 4604), rabbit anti-βIII tubulin (1:5000, Abcam, ab18207), rabbit anti-BDNF (1:2000, Abcam, ab108319), rabbit antiNLRP3 inflammasome (1:1000, Cell Signaling, 15101), mouse anti-Caspase 1 (1:1000,

Adipogen, AG-20B-0044) and mouse anti-GFAP (1:1000, Millipore, MAB3402) overnight at 4 °C and then incubated with corresponding HRP conjugated secondary antibody (R&D systems, 1:10,000) for 1 h at room temperature. Proteins were detected with an ECL detection system (SuperSignal West Pico PLUS Chemiluminescent Substrate, Thermo) and quantified by densitometry using analytic software (ImageLab software, Biorad). Results were normalized concerning the β-actin densitometric value.

Statistical analysis. All statistical analysis and data visualizations were performed in GraphPad Prism 8. For statistical analysis of body weight and food and caloric intake, Two-way ANOVA with Tukey's post hoc test was used. For statistical analysis of morphological parameters, a linear mixed effects model was used to model the data of each parameter, with the animal as a random effect. Using this approach, it is possible to overcome the dependency of repeated observations within each animal[27]. The presence of significant differences was tested using a Nested t-test or one-way ANOVA. SIPs were analyzed by mixed-effects nested ANOVA approach with the individual animal as a random effect. Western blot results were analyzed with one-way ANOVA with Tukey's post hoc test. For all analyses, significance was defined as $p < 0.05$.

1.7 Results

Seven days of HFD affects the cellular complexity of DCX immunolabeled cells in the dorsal hippocampus of adolescent mice. 5-week-old C57Bl/6 male mice were exposed to a short period (7 days) of HFD (n = 4) or LFD (n = 4) (figure 1.9A). As shown in figure 1.9B, a statistically significant increase in body weight was observed in both HFD and LFD mice at the end of the diet regimens when compared to day 1 for each experimental group, without differences between the two dietary protocols. Food intake (g/mouse/day) and caloric intake (kcal/mouse/day) were higher in HFD than in the LFD group, and data are reported in Table 1.

	Food intake (g/mouse/day)	Caloric intake (kcal/mouse/day)
LFD	2.60 ± 0.23	11.11 ± 1.00
HFD	3.09 ± 0.18$^{\#}$	17.69 ± 1.02$^{\#\#\#}$

Table 1. Food and Caloric intake of mice fed 7 days with LFD or HFD. $^{\#}$ p < 0.05, $^{\#\#\#}$p < 0.001 vs. LFD.

At the end of the diet period, mice were perfused, and their brains were removed for immunolocalization studies of the doublecortin protein in the dentate gyrus of the hippocampal formation. In the suprapyramidal blade of the DG, we selected thirty DCX^+ immature neurons with their cell body located in the inner third of the GCL and a dendritic tree reaching the molecular layer. Sholl analysis allows resolving a one-dimensional representation (Sholl Intersection Profile, SIP) of the complexity of any given three-dimensional cellular structure (figure 1.9C). For this reason, we used it to evaluate the complexity of dendritic arborizations of DCX^+ cells (Sholl DA, 1953). We initially evaluated the effects of LFD and HFD on DCX^+ immature neurons in the dorsal DG (from Bregma − 0.94 to − 2.46 mm). In this region, DCX^+ cells of HFD animals displayed a remarkable reduction in SIP compared to LFD mice, with a statistical difference observed at 80–220 μm distance from the soma (Figure 1.9D). This difference was further confirmed by a reduction in additional dendritic morphometric parameters, namely the total number of bifurcations, branches, and tips (figure 1.9E–G, $p < 0.01$ for all parameters) as well as by a decrease in the length of the longest dendrite referred to as path distance (figure 1.9H, $p < 0.05$).

Based on these results, in 5-week-old male mice, 7 days of HFD are sufficient to produce a dramatic reduction in the complexity and length of the dendritic tree of DCX^+ immature neurons in the GCL of dorsal DG.

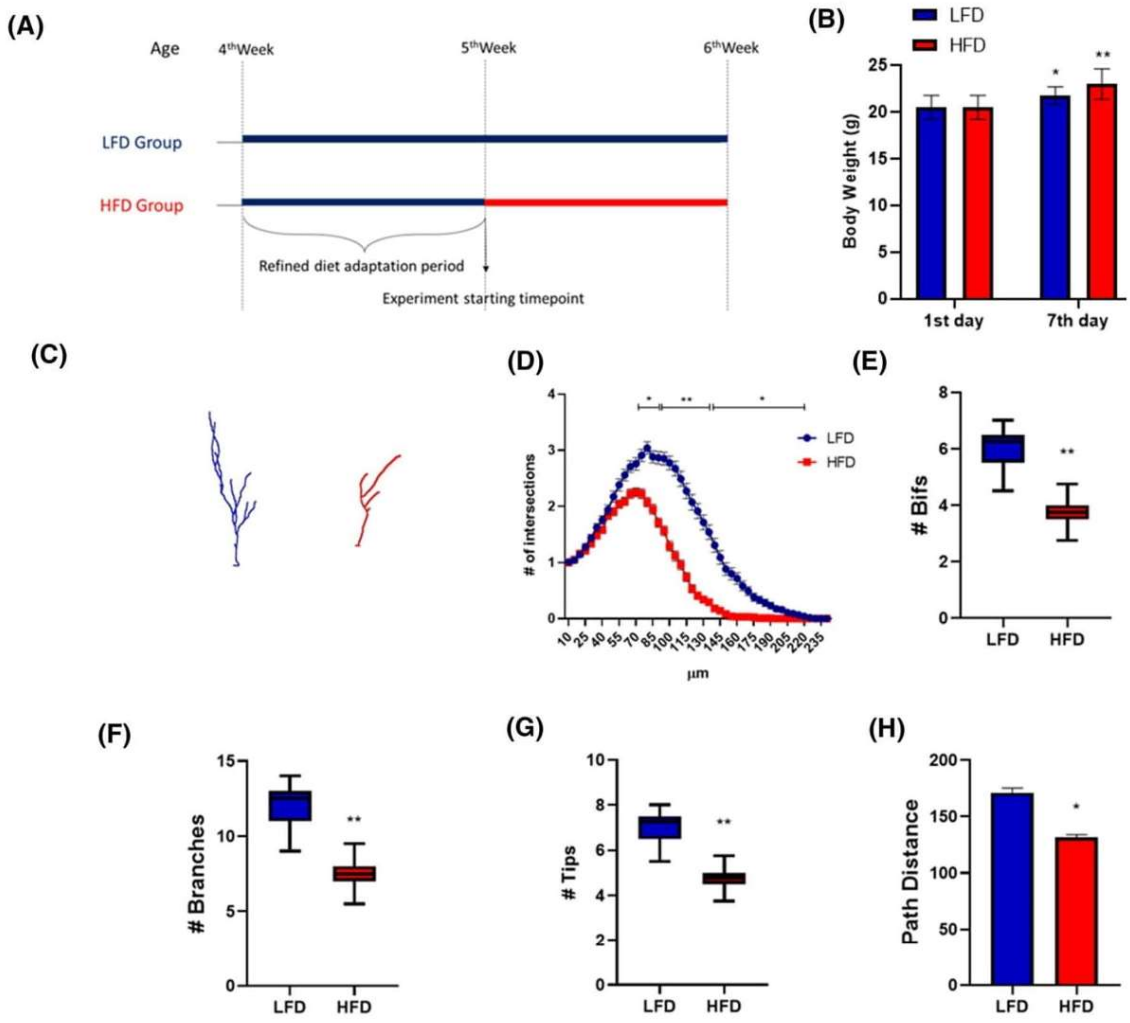

Figure 1.9. 7-day HFD affects the cellular complexity of DCX immunolabeled cells in the dorsal hippocampus. Schematic experimental design (**A**). Animal body weight at the beginning of the experiment (1st day of diet, 5 weeks of age) and after 7 days of relative diet (**B**). Data are represented as mean ± SEM. *p < 0.05, **p < 0.01 vs. 1st day corresponding group value. Two-way ANOVA with Tukey's multiple comparisons test. Representative DCX+ cell 3D morphological reconstruction in the dorsal hippocampus of animals fed with a LFD (Blue) or HFD (Red) for 1 week (C). Sholl intersections profiles of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of animals fed for 7 days with HFD (Red) or LFD (Blue) starting from the fifth week of age (n=4 animals per group) (D). Data are presented as mean±SEM.* p < 0.05, **p < 0.01 vs. LFD, nested ANOVA on the linear mixed-effect model, with an animal as a random effect. Summary of morphometric parameters illustrating the total number of bifurcations (**E**), the total number of branches (**F**), the total number of terminal tips (**G**), and the path distance (**H**) of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of animals fed for 7 days with HFD (Red) or LFD (Blue) starting from the fifth week of age (n=4 animals per group). Data are represented as Box and Wiskers graph (E–G) or bar graph (mean±SEM) (H). *p<0.05, **p<0.01 vs. LFD, ANOVA on linear mixed-effect model, with animal as a random effect. ImageJ FIJI software (version 1.52) (https://imagej.nih.gov/ij/) was used to produce cell 3D morphological reconstruction. GraphPad Prism 8 (https://www.graphpad.com/) and PowerPoint were used to generate the figure.

HFD effects on the morphological complexity of DCX$^+$ immature neurons are transient and reversible in adolescent mice. Since a 7 day-period of HFD results in remarkable morphological changes in adult-born DCX$^+$ cells, we then tested whether this effect may be reversible. The second group of 5-week-old mice (n = 12) was subjected to a 7-day-long HFD supply followed by a return to LFD for 7 days (HFD-LFD group). Animals fed for 14 days with LFD (LFD-LFD group, n = 11) or HFD (HFD-HFD group, n = 11) were used as controls (experimental design summarized in figure 1.10A). As shown in Fig. 1.10B, we observed a weekly increase in body weight in all diet regimens if compared to day 1. At the end of the study (14 days timepoint), a statistical difference in body weight between the HFD-HFD group and the animals subjected to other diet regimens was present (LFD-LFD and HFDLFD, $p < 0.05$). Food and caloric intake were also calculated in all experimental groups, as reported in Table 2.

	Food intake (g/mouse/ day)		Caloric intake (kcal/mouse/ day)	
	1st week	2nd week	1st week	2nd week
LFD-LFD	2.83 ± 0.19	2.99 ± 0.11	12.11 ± 0.83	12.79 ± 0.47
HFD-HFD	3.26 ± 0.32$^{\#}$	3.54 ± 0.36$^{\#}$	18.68 ± 1.82$^{\#\#\#}$	19.07 ± 1.02$^{\#\#\#}$
HFD-LFD	3.20 ± 0.12$^{\#}$	2.77 ± 0.10	18.33 ± 0.71$^{\#\#\#}$	12.63 ± 1.69

Table 2. Food and Caloric intake of mice fed 14 days with LFD or HFD or 7 days with HFD followed by 7 days with LFD. $^{\#}$ $p < 0.05$, $^{\#\#\#}p < 0.001$ vs. LFD-LFD.

After DCX immunostaining of brain sections, morphometric analysis was performed as previously described (n = 4 animals per group) (figure 1.10C). Compared to the LFD-LFD mice, 14 days of HFD led to a marked reduction of the complexity of DCX$^+$ immature neurons, with a statistical difference between 65 and 140 μm from the soma (figure 1.10D), and a significant reduction in the total number of bifurcations, branches, tips, and path distance (figure 1.10E–H). Conversely, in the HFD-LFD group, we observed no significant difference in cellular complexity compared to LFD-LFD mice (figure 10D). Once again, our results were corroborated by L-measure software analysis. Indeed, the total number of bifurcations, branches, tips (figure 1.10E–G) as well as path distance (figure 1.10H) were not different in HFD-LFD and LFD-LFD mice. Altogether these data suggest

that the impairment in the dendritic tree complexity of DCX$^+$ cells associated with a short period of HFD is a transient event and it can be fully reversed by returning to a normal-caloric diet.

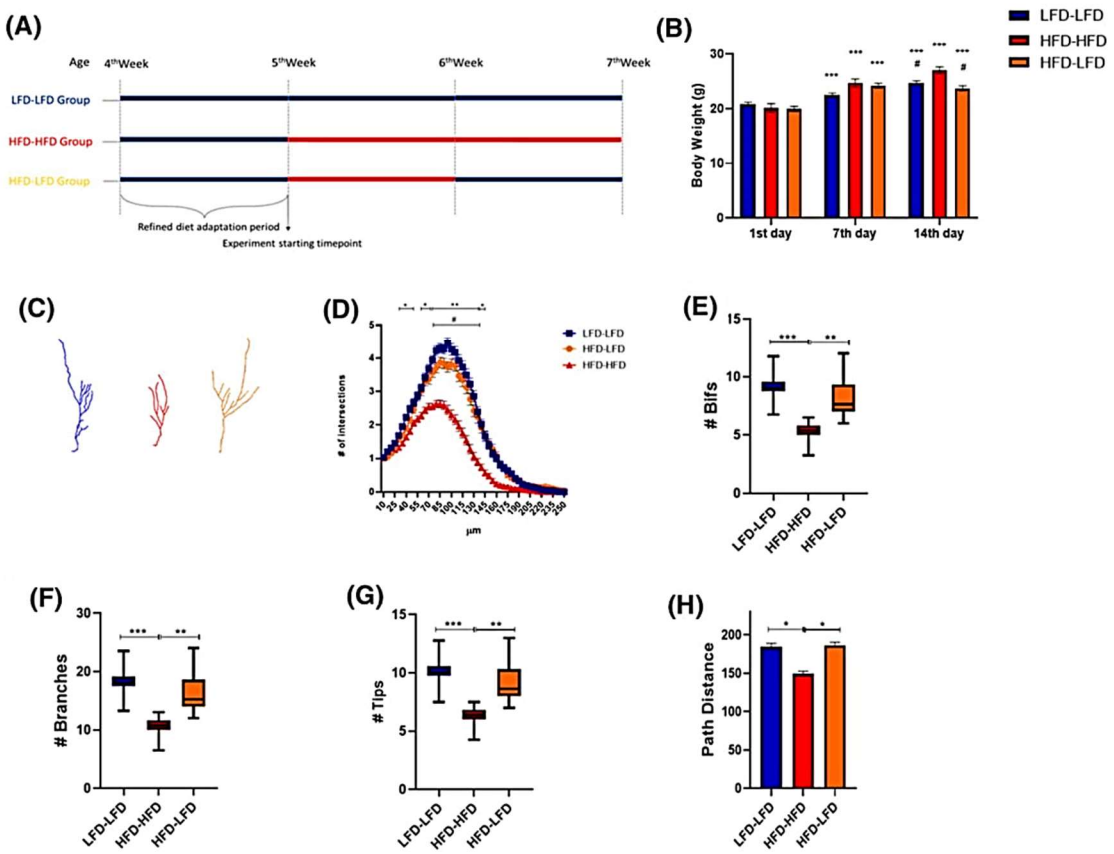

Figure 1.10. 7-day HFD effects on the morphological complexity of DCX$^+$ cells are reversible. Experimental design (**A**). Animal body weight at the beginning of the experiment (1st day of diet, 5 weeks of age) and after 7 and 14 days of relative diet (**B**). Data are represented as mean ± SEM. ***p < 0.001 vs. 1st-day corresponding group value. $^{\#}$p < 0.05 vs. HFD-HFD at the same time point. Two-way ANOVA with Tukey's multiple comparisons test. Representative DCX$^+$ cell 3D morphological reconstruction in the dorsal hippocampus of animals fed with a LFD (Blue) or HFD (Red) for 2 weeks or HFD for 1 week followed by LFD for another week (Orange) (**C**). Sholl intersections profiles of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of animals fed for 14 days with HFD (Red) or LFD (Blue) or for 7 days with HFD followed by 7 days with LFD (Orange) starting from the fifth week of age (n = 4 animals per group) (**D**). Data are presented as mean ± SEM. *p < 0.05, **p < 0.01 LFD-LFD vs. HFD-HFD; $^{\#}$p < 0.05 HFD-LFD vs. HFD-HFD, nested ANOVA on the linear mixed-effect model, with an animal as a random effect. Summary of morphometric parameters illustrating the total number of bifurcations (**E**), the total number of branches (**F**), the total number of terminal tips (**G**), and the path distance (**H**) of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of animals fed for 14 days with HFD (Red) or LFD (Blue) or for 7 days with HFD followed by 7 days with LFD (Orange) starting from the fifth week of age (n = 4 animals per group). Data are represented as Box and Wiskers graph (**E–G**) or bar graph (mean ± SEM) (**H**). *p < 0.05, **p < 0.01, ***p < 0.001, ANOVA on the linear mixed-effect model, with an animal as a random effect. ImageJ FIJI software (version 1.52) (https:// ImageJ. nih. gov/ ij/) was used to produce cell 3D morphological reconstruction. GraphPad Prism 8 (https:// www. graph pad. com/) and PowerPoint were used to generate the figure.

To complement our analysis, we compared the dendritic complexity of DCX$^+$ cells in mice receiving the same dietary regimen for 1 or 2 weeks. Compared to 1 week of diet administration, both LFD and HFD-fed animals showed a statistical increase in DCX$^+$ cells SIP after 2 weeks of relative diet supply (figure 1.11A, F). Except for path distance (figure 1.11E, J), additional

morphometric parameters, i.e. the number of bifurcations, branches, and tips (figure 1.11B–D, G–I) confirmed data from Sholl analysis. Although in both LFD- and HFD-fed animals we observed an increase in the SIP after 2 weeks compared to 1 week of diet supply, in HFD mice this increase was significantly reduced compared to LFD mice, as demonstrated by comparing AUC differences (figure 1.11K).

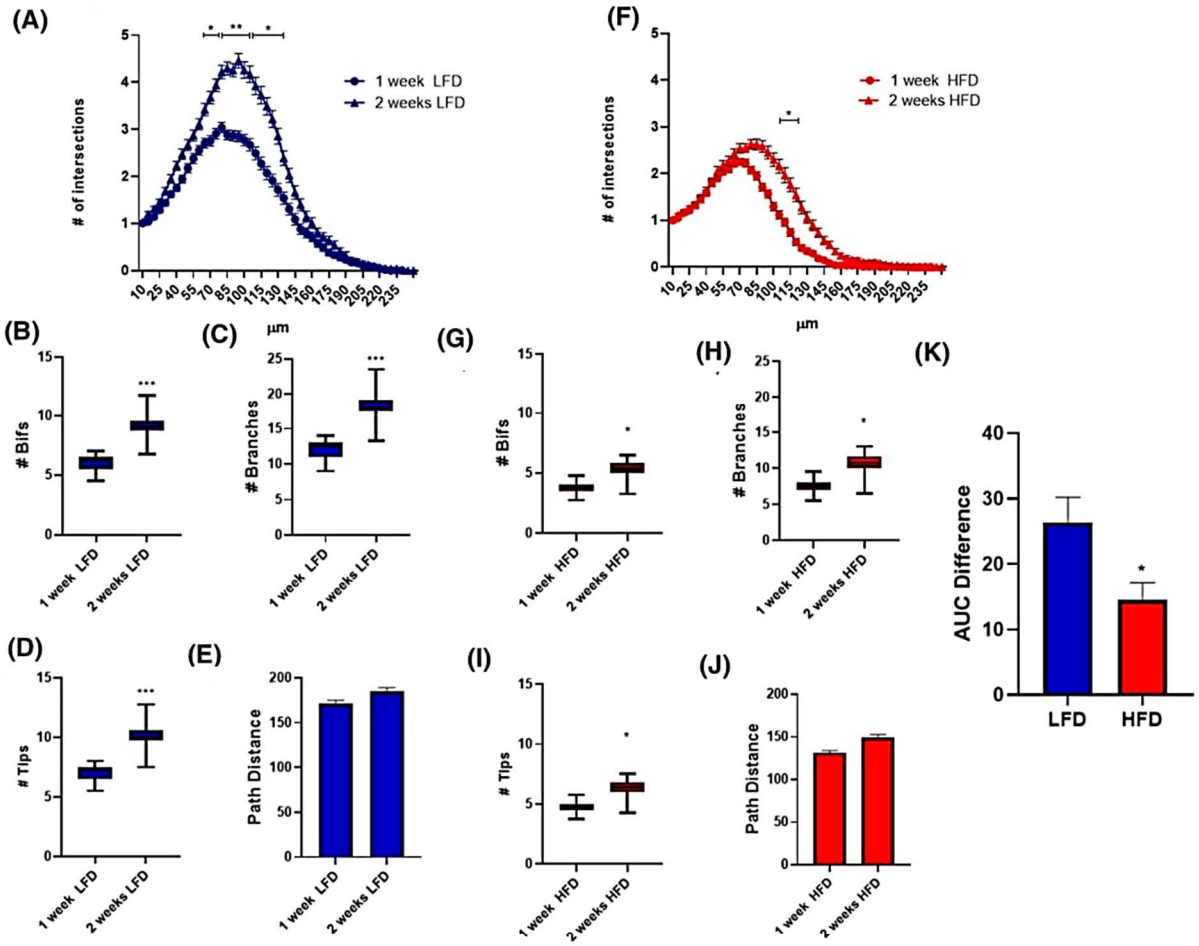

Figure 1.11. Dendritic complexity of DCX⁺ cells in mice receiving the same dietary regimen for 7 or 14 days. Sholl intersections profiles of DCX immunolabeled cells in the suprapyramidal blade of the dentate gyrus of the dorsal hippocampus of animals fed for 7 or 14 days with LFD (**A**) or HFD (**F**) starting from the fifth week of age (n = 4 animals per group). Data are presented as mean ± SEM. *p < 0.05, **p < 0.01vs. 1 week, nested ANOVA on the linear mixed-effect model, with an animal as a random effect. Summary of morphometric parameters illustrating the total number of bifurcations (**B**, **G**), the total number of branches (**C**, **H**), the total number of terminal tips (**D**, **I**), and the path distance (**E**, **J**) of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of animals fed for 7 or 14 days with LFD or HFD starting from the fifth week of age (n = 4 animals per group). Data are represented as Box and Wiskers graph (**B–D**, **G–I**) or bar graph (mean ± SEM) (**E**, **J**). *p < 0.05, ***p < 0.001 vs. 1 week, ANOVA on the linear mixed-effect model, with an animal as a random effect. The difference in the area under the curve (AUC) of the SIP of DCX⁺ cells in dHP of animals fed for 2 or 1 week with LFD or HFD (**K**). Data are represented as a bar graph (mean ± SEM). *p < 0.05 vs. LFD. GraphPad Prism 8 (https:// www. graph pad. com/) and PowerPoint were used to generate the figure.

Short HFD does not affect the cellular complexity of DCX$^+$ immature neurons in the ventral hippocampus of adolescent mice. Our initial analysis was performed in the dorsal DG due to the involvement of this hippocampal subregion in cognitive functions. We then extended our analysis to the complexity of the dendritic tree of immature DCX$^+$ cells in the ventral DG (from Bregma − 2.54 to − 4.04 mm).

Previous studies suggested differences in DCX$^+$ cells' maturation rate along the dorsoventral axis of the hippocampus (Snyder et al., 2012). We first analyzed potential differences in dendritic tree complexity of DCX$^+$ cells in dorsal and ventral DG of animals fed with either LFD or HFD for 1 week. As described in figure 1.12, in LFD animals DCX$^+$ cells displayed a more complex dendritic tree in the dorsal hippocampus if compared to the corresponding cell population in the ventral DG, as shown by SIP (figure 1.12A). In addition, a statistically significant increased number of bifurcations, branches, and tips (figure 1.12B–D) as well as in path distance (figure 1.12E) was present in dorsal compared to ventral immature neurons. Conversely, in HFD-fed mice, differences were observed neither in SIP (figure 1.12F) nor in the number of bifurcations, branches, and tips in dorsal vs ventral DCX$^+$ cells (figure 1.12G–I). Only path distance was decreased ($p < 0.05$) in DCX$^+$ cells in ventral compared to dorsal DG of HFD mice.

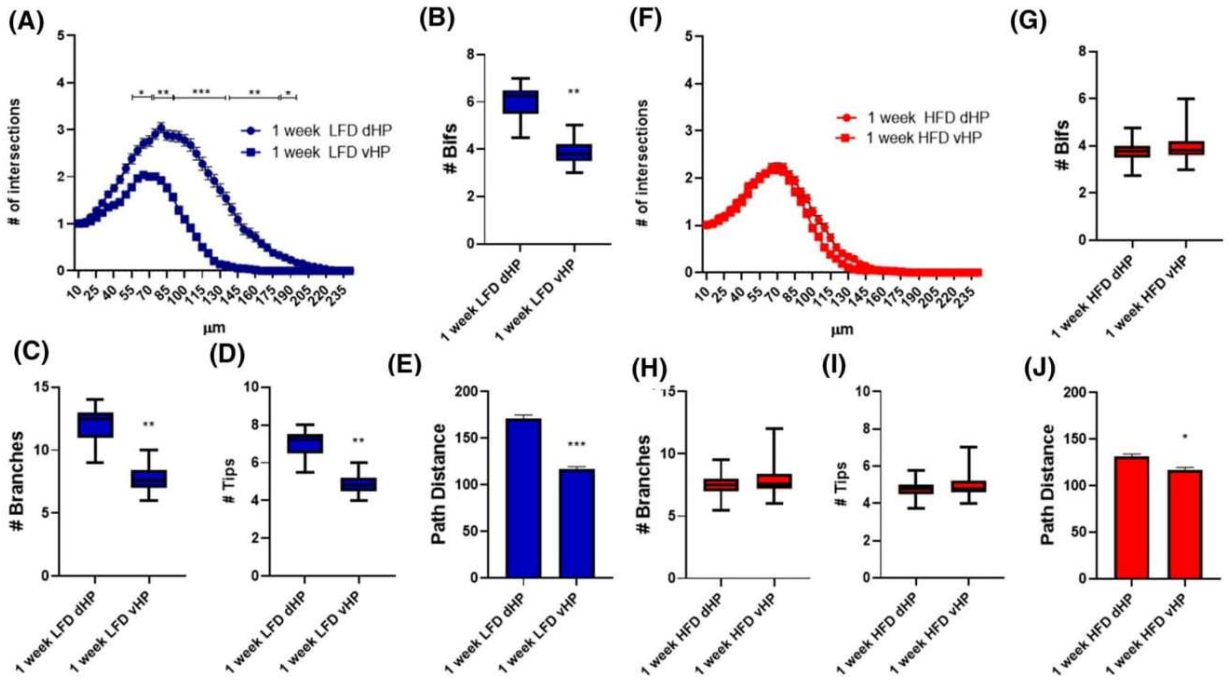

Figure 1.12. Dendritic complexity of DCX⁺ immature neurons in the dorsal and ventral hippocampus of mice receiving the same dietary regimen for 7 days. Sholl intersections profiles of DCX immunolabeled cells in the suprapyramidal blade of the dentate gyrus of the dorsal or ventral hippocampus of animals fed for 7 days with LFD (**A**) or HFD (**F**) starting from the fifth week of age (n = 4 animals per group). Data are presented as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001 vs. dHP, nested ANOVA on a linear mixed-effect model, with an animal as a random effect. Summary of morphometric parameters illustrating the total number of bifurcations (**B**, **G**), the total number of branches (**C**, **H**), the total number of terminal tips (**D**, **I**), and the path distance (**E**, **J**) of DCX immunolabeled cells of the dentate gyrus of the dorsal or ventral hippocampus of animals fed for 7 days with LFD or HFD starting from the fifth week of age (n = 4 animals per group). Data are represented as Box and Wiskers graph (**B–D**, **G–I**) or bar graph (mean ± SEM) (**E**, **J**). * p < 0.05, ** p < 0.01 vs. dHP, ANOVA on the linear mixed-effect model, with an animal as a random effect. GraphPad Prism 8 (https:// www. graph pad. com/) and PowerPoint were used to generate the figure.

Finally, we compared morphometric parameters of immature neurons in the ventral DG of animals fed 1 week with LFD or HFD (figure 1.13A). No statistically significant difference was displayed in the two experimental groups, as demonstrated by both the Sholl analysis (figure 1.13B) and L-measure software analysis (figure 1.13C–F). These findings suggest that: (I) in juvenile mice dorsal DG immature neurons display more complex and longer dendritic trees than corresponding ventral cells; (II) 7 days HFD reduces the complexity of DCX⁺ cells in dorsal and not in ventral DG; (III) HFD mice have DCX⁺ immature neurons with similar complexity in dorsal and ventral DG.

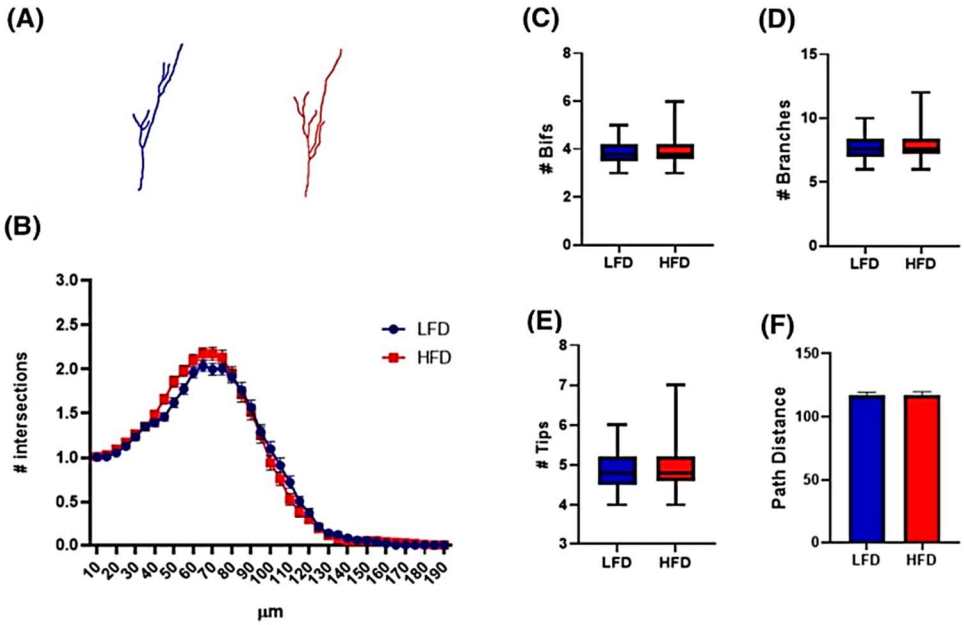

Figure 1.13. No effect of 7-day HFD on cellular complexity of DCX⁺ cells in the ventral hippocampus. Representative DCX⁺ cell 3D morphological reconstruction in the ventral hippocampus of animals fed with an LFD (Blue) or HFD (Red) for 1 week (**A**). Sholl intersections profiles of DCX immunolabeled cells of the dentate gyrus of the ventral hippocampus of animals fed for 7 days with HFD (Red) or LFD (Blue) starting from the fifth week of age (n = 4 animals per group) (**B**). Data are presented as mean ± SEM. Summary of morphometric parameters illustrating the total number of bifurcations (**C**), the total number of branches (**D**), the total number of terminal tips (**E**), and the maximum reached extension from the soma (**F**) of DCX immunolabeled cells of the dentate gyrus of the ventral hippocampus of animals fed for 7 days with HFD (Red) or LFD (Blue) starting from the fifth week of age (n = 4 animals per group). Data are represented as Box and Wiskers graph (**C–E**) or bar graph (mean ± SEM) (**F**). ImageJ FIJI software (version 1.52) (https:// ImageJ. nih. gov/ ij/) was used to produce cell 3D morphological reconstruction. GraphPad Prism 8 (https:// www. graph pad. com/) and PowerPoint were used to generate the figure.

BDNF expression changes correlate with HFD-associated impairment of DCX⁺ cells in the dorsal hippocampus of adolescent mice. We decided to correlate changes in DCX⁺ cell dendritic tree complexity in response to HFD with alterations in the expression levels of several proteins which are relevant in the neuroplasticity of the postnatal and adult hippocampus. Previous studies reported that HFD may impact the number of DCX⁺ cells (Hwang et al., 2008) and/or the expression levels of this protein which is often used as a marker of adult-born neuroblasts (Bortolotto et al., 2019). We performed a western blot analysis of DCX expression in the dorsal hippocampus of animals subjected to HFD and relative controls. Although there was a trend for reduction in the HFD-HFD experimental group, no statistically significant change in DCX protein levels was observed in the dorsal hippocampus of these mice compared to LFD-LFD and HFD-LFD (LFD-LFD vs. HFD-HFD, $p = 0.07$; HFD-LFD vs. HFD-HFD $p = 0.08$) (figure 1.14A).

Similarly, we did not observe changes in the expression levels of βIII tubulin, another established marker for newly born neuroblasts (figure.1.14B; von Bohlen und Halbach, 2011)

Since long and short-term HFD is associated with neuroinflammation (Moraes et al., 2009; Nakandakari et al., 2019) which may result in negative effects in adult-born neurons/neuroblasts (Covacu & Brundin, 2017), we also evaluated if a short period of HFD is sufficient to activate an astrocyte-associated response via changes in glial fibrillary acidic protein (GFAP) expression. As shown in figure 1.14C, neither 14-day-HFD nor 7-day-HFD followed by 7 days of LFD significantly affected GFAP expression in the dorsal hippocampus. Similarly, the NLRP3 inflammasome pathway is increased in association with HFD in several tissues including the brain (Sobesky et al., 2016). Western blot analysis demonstrated that, in our experimental setting, both NLRP3 and Pro-Caspase 1 protein expression levels were not different in the dorsal hippocampal region of HFD and LFD mice (figure 1.14 D, E). Finally, we analyzed the expression of Brain-Derived Neurotrophic Factor (BDNF), a signaling molecule that is strongly associated with neuronal tropism and with neuroplasticity/neurogénesis (Moya-Alvarado et al., 2018). When the HFD-HFD group was compared to LFD-LFD mice, we observed a statistically significant decrease in the expression of both its active dimeric and precursor forms in the dorsal (figure 14F, $p < 0.05$) but not in the ventral (figure 1.14G) hippocampus. Although in the dorsal hippocampus both pre- and dimeric BDNF protein levels in the HFD-LFD group are higher than in the HFD-HFD group, this difference was not statistically significant ($p = 0.20$ for the precursor form and $p = 0.18$ for the active dimeric form HFD-LFD vs HFD-HFD group).

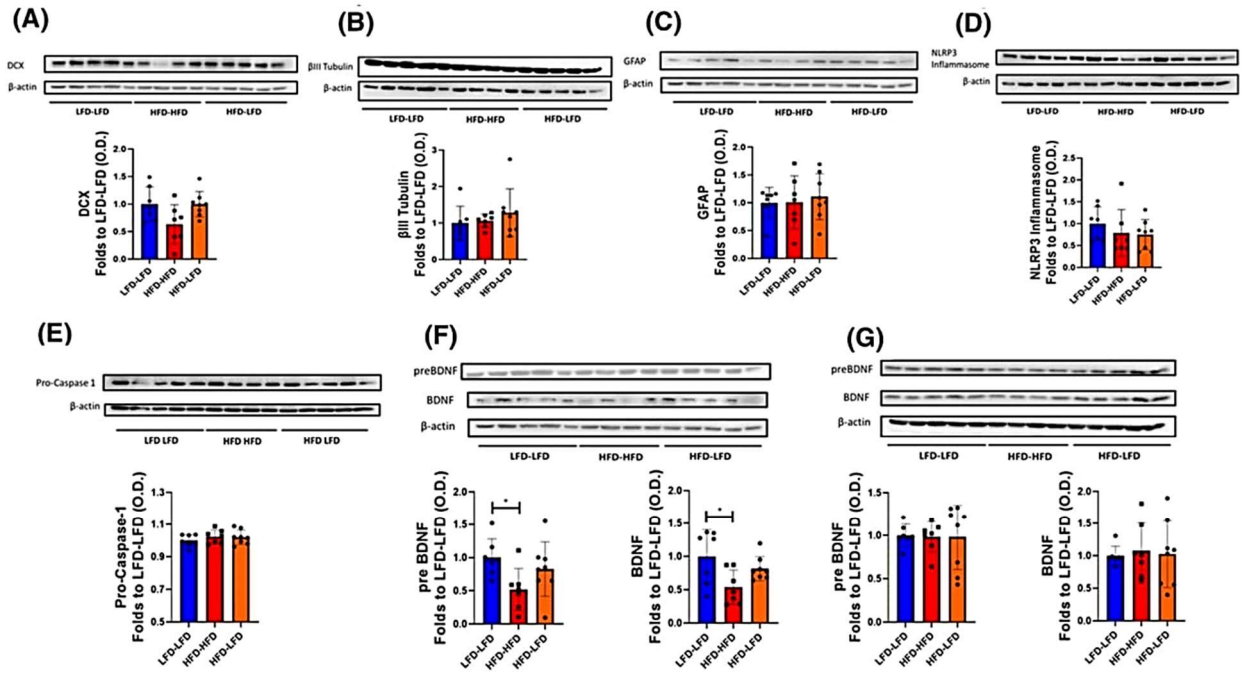

Figure 1.14. Biochemical changes associated with HFD in the dorsal and ventral hippocampus. DCX (**A**), β III Tubulin (**B**), GFAP (**C**), NLRP3 Inflammasome (**D**), Pro-Caspase 1 (**E**), and BDNF (**F**) western blot analysis of the dorsal hippocampus of animals fed for 14 days with HFD (Red) or LFD (Blue) or for 7 days with HFD followed by 7 days with LFD (Orange) starting from the fifth week of age (n = 7 LFD-LFD, n = 7 HFD-HFD, n = 8 HFD-LFD). BDNF (**G**) western blot analysis of the ventral hippocampus of animals fed for 14 days with HFD (Red) or LFD (Blue) or for 7 days with HFD followed by 7 days with LFD (Orange) starting from the fifth week of age (n = 7 LFD-LFD, n = 7 HFD-HFD, n = 8 HFD-LFD). The bands shown are representative. Data are presented as mean ± SD and a single dot represents the result from one animal. *p < 0.05, One-way ANOVA with Tukey's post-hoc test.

With the same approach (Chiazza et al., 2021) we repeated the experiments with adult male mice (10-week-old).

Short HFD does not affect the cellular complexity of DCX$^+$ immature neurons in the dorsal hippocampus of adult mice. 10-week-old C57Bl/6 male mice were subjected to either HFD (n = 4) or LFD (n = 4). At the end of the diet period, mice were perfused and their brains were taken for immunolocalization investigations of the doublecortin protein in the hippocampus formation's dentate gyrus. We chose thirty DCX+ immature neurons with cell bodies in the inner third of the granular cell layer and a dendritic tree reaching the molecular layer from the suprapyramidal blade of the DG and performed Sholl analysis to evaluate the complexity of dendritic arborizations of DCX+ cells (SHOLL, 1953). We first looked at how LFD and HFD affected DCX+ immature

neurons in the dorsal DG (from −0.94 to −2.46 mm). We evaluated the morphometric characteristics of immature neurons in the dorsal DG of mice given either LFD or HFD for one week.

Sholl analysis revealed no statistically significant difference between the two experimental groups (figure 1.15).

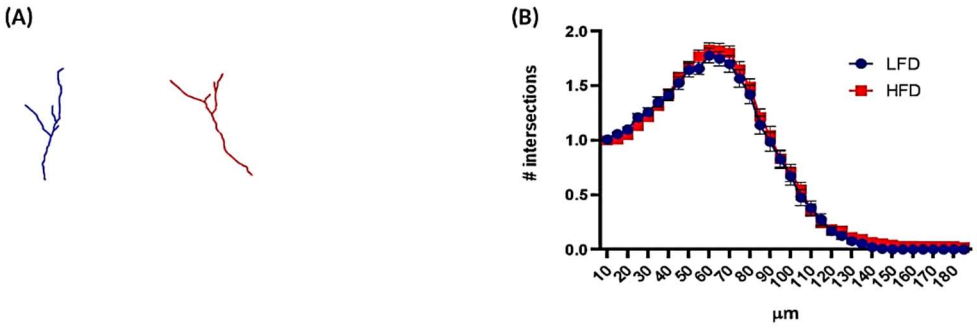

Figure 1.15 No effect of 7-day HFD on cellular complexity of DCX+ cells in the dorsal hippocampus of adult mice Representative DCX$^+$ cell 3D morphological reconstruction (**A**) and Sholl intersections profiles (**B**) of DCX immunolabeled cells of the dentate gyrus of the dorsal hippocampus of adult animals fed for seven days with HFD (Red) or LFD (Blue) starting from the tenth week of age (n = 4 animals per group). Data are presented as mean ± SEM.

Seven days of HFD affects the cellular complexity of DCX immunolabeled cells in the ventral hippocampus of adult mice.

The complexity of the dendritic tree of immature DCX+ cells in the ventral DG (from Bregma 2.54 to 4.04 mm) was then investigated.

Previous research has found variations in the maturation rate of DCX+ cells along the dorsoventral axis of the hippocampus (Snyder et al., 2012).

In the vHP region, DCX$^+$ cells of HFD animals displayed a reduction in SIP compared to LFD mice statistically different (figure 1.16).

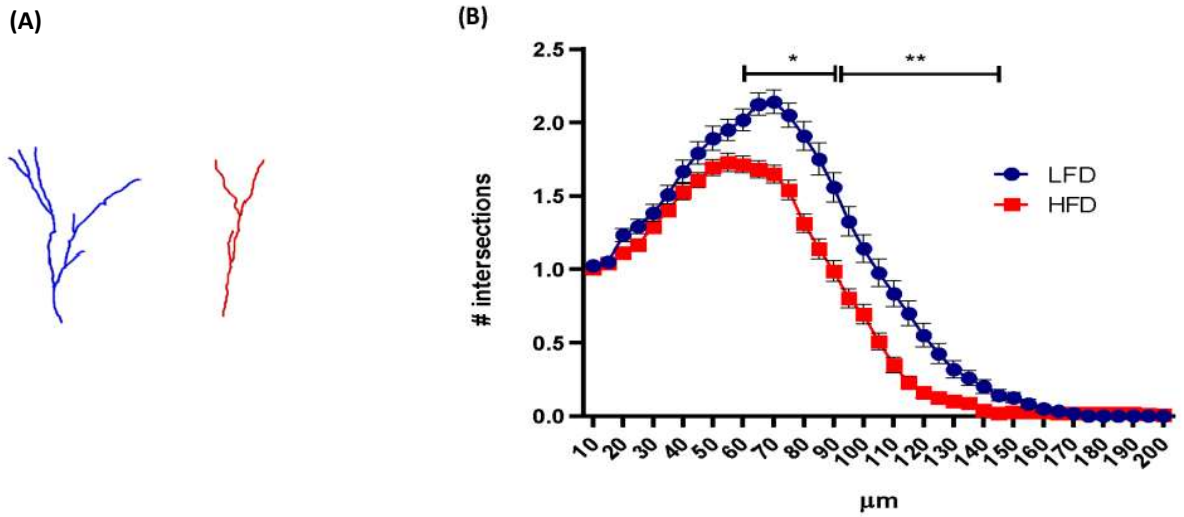

Figure 1.16: 7-day HFD affects cellular complexity of DCX immunolabeled cells in ventral hippocampus Representative DCX+ cell 3D morphological reconstruction (**A**) and Sholl intersections profiles (**B**) of DCX immunolabeled cells of the dentate gyrus of the ventral (B) hippocampus of adult animals fed for seven days with HFD (Red) or LFD (Blue) starting from the tenth week of age (n = 4 animals per group). Data are presented as mean ± SEM. * $p<0.05$, **$p<0.01$ vs. LFD; nested ANOVA on the linear mixed-effect model, with an animal as a random effect.

Based on these findings, 7 days of HFD in 10-week-old male mice resulted in a significant decrease in the complexity of the dendritic tree of DCX+ immature neurons in the GCL of ventral DG.

HFD effects on the morphological complexity of DCX$^+$ immature neurons are transient and reversible in the ventral hippocampus of adult mice

Because a 7-day HFD period leads to dramatic morphological alterations in adult-born DCX+ cells, we investigated whether this impact is reversible. The second set of four 10-week-old mice (n = 4) was fed HFD for seven days before returning to LFD for seven days (HFD-LFD group). Animals fed LFD (LFD-LFD group, n = 4) or HFD (HFD-HFD group, n = 4) for 14 days served as controls. At the end of the trial (14 days), there was a significant difference in body weight between the HFD-HFD group and the animals on the other feeding regimens (LFD-LFD and HFD-LFD, $p <0.05$).

Morphometric analysis was done on brain slices after DCX immunostaining (n=4 mice per group) as previously reported (figure 1.17 A). When compared to LFD-LFD mice, 14 days of HFD resulted in a significant reduction in the complexity of DCX+ immature neurons (figure 1.17 B), as well as a

significant reduction in the total number of bifurcations, branches, tips, and path distance (figure 1.17C- F).

In contrast, we found no significant change in cellular complexity between HFD-LFD mice and LFD-LFD mice in the HFD-LFD group.

Overall, our findings imply that the decrease in dendritic tree complexity of DCX+ cells caused by a brief period of HFD is a temporary event that is completely corrected by returning to a normal-caloric diet.

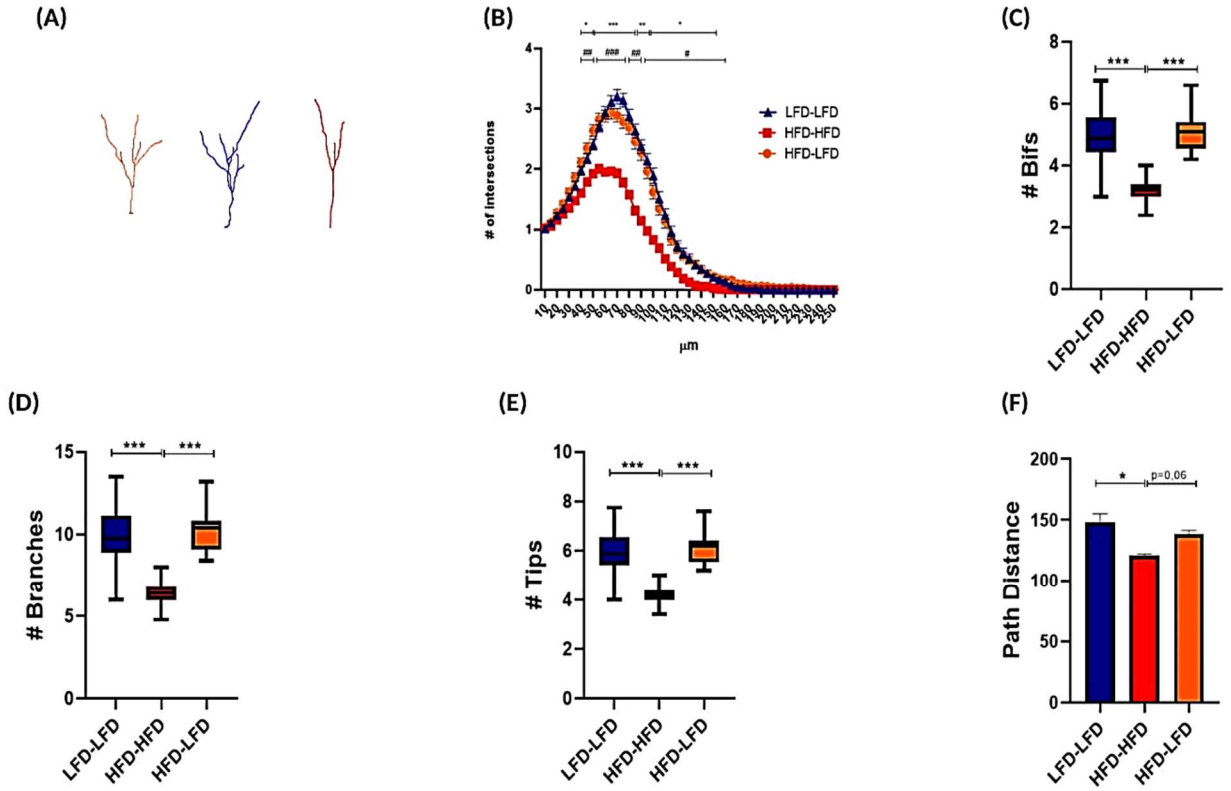

Figure 1.17: 7-day HFD effects on the morphological complexity of DCX+ cells are reversible: Representative DCX$^+$ cell 3D morphological reconstruction in the ventral hippocampus of animals fed with an LFD (Blue) or HFD (Red) for two weeks or HFD for one week followed by LFD for another week (Orange) (**A**). Sholl intersections profiles (**B**) and summary of morphometric parameters illustrating the total number of bifurcations (**C**), the total number of branches (**D**), the total number of terminal tips (**E**), and the path distance (**F**) of DCX immunolabeled cells of the dentate gyrus of the ventral hippocampus of adult animals fed for fourteen days with HFD (Red) or LFD (Blue) or for seven days with HFD followed by seven days with LFD (orange) starting from the tenth week of age (n = 4 animals per group). Data are presented as mean ± SEM. * p<0.05, **p<0.01 LFD-LFD vs. HFD-HFD; # p<0.05, ## p<0.01, ### p<0.001 HFD-LFD vs. HFD-HFD, nested ANOVA on a linear mixed-effect model, with an animal as a random

effect (B). Data are represented as Box and Wiskers graph (C-E) or bar graph (mean ± SEM) (F). * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ANOVA on a linear mixed-effect model, with an animal as a random effect

These data imply that 7 days of HFD lowers the complexity of DCX+ cells in the ventral DG but not in the dorsal DG.

BDNF expression changes correlate with HFD-associated impairment of DCX^+ cells in the ventral hippocampus of adult mice.

Also with adult mice, we decided to correlate changes in DCX^+ cell dendritic tree complexity in response to HFD with alterations in the expression levels of several proteins which are relevant in the neuroplasticity of the postnatal and adult hippocampus.

We looked at the expression of Brain-Derived Neurotrophic Factor (BDNF), a signaling protein linked to neuronal tropism and neuroplasticity/neurogenesis. When we compared the HFD-HFD mice to the LFD-LFD animals, we found a statistically significant reduction in the expression of both its active dimeric and precursor forms in the ventral (figure 1.18, $p<0.05$) but not the dorsal hippocampus.

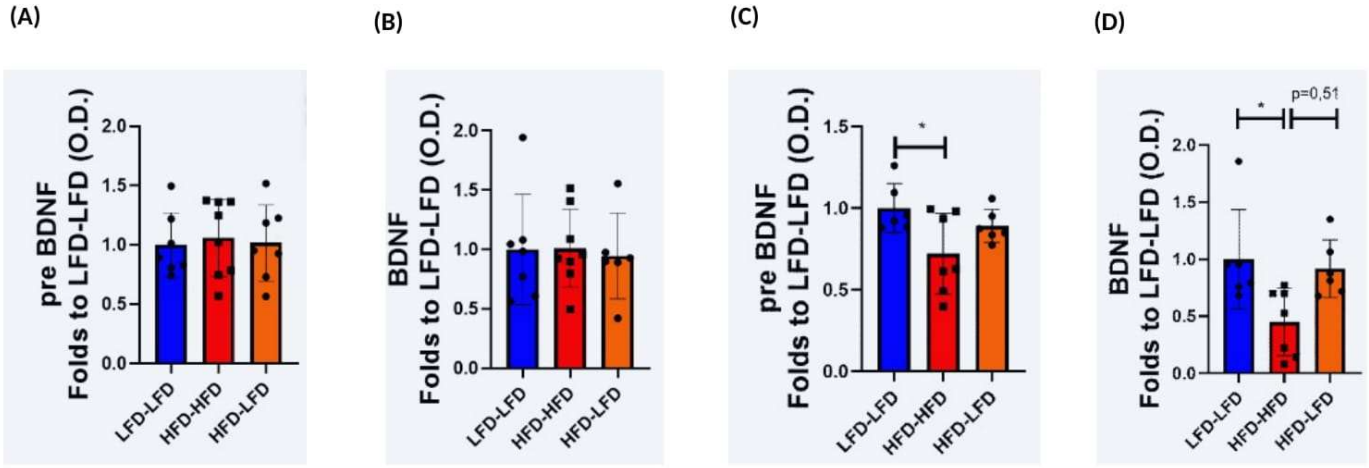

Figure 1.18: BDNF changes associated with HFD in the dorsal and ventral hippocampus: BDNF western blot analysis of the dorsal (**A-B**) or ventral (**C-D**) hippocampus of adult animals fed for fourteen days with HFD (Red) or LFD (Blue) or for seven days with HFD followed by seven days with LFD (orange) starting from the fifth week of age (n = 7 LFD-LFD, n=8 HFD-HFD, n=7HFD-LFD). Data are presented as mean ± SD and a single dot represents the result from one animal. * p<0.05, One-way ANOVA with Tukey's post-hoc test.

1.8 Conclusions

Neuronal cells change to functionally and structurally adapt in response to environmental stimuli such as diet and we demonstrated that those changes are area-specific. We focused on neuroblast complexity concerning diet.

Using Sholl analysis and other morphometric measures such as branch length and the number of terminal tips and bifurcations, we investigated minor structural changes in the cytoarchitecture of the dendritic tree of DCX+ immature neurons. We show for the first time that a 7-day HFD period is sufficient to reduce the dendritic complexity and length of DCX+ immature neurons in teenage and adult male mice area-specifically. Surprisingly, these effects were only seen in the dorsal DG, not the ventral DG for teenage mice, while we see effects on ventral and not in dorsal DG in adult mice.

It has been widely demonstrated that diet has a significant impact on adult memory (Nilsson & Nilsson, 2009). In particular, longitudinal human studies have shown that better adherence to healthy diets is connected with a lower incidence of dementia. These studies point to the possibility that diets high in antioxidants, healthy fats, low to moderate consumption of red meat, and low consumption of refined sugars, carbohydrates, and unhealthy fats may guard against dementia preserving brain integrity and volume (Hooshmand et al., 2016).

Observational studies demonstrate that the Mediterranean Diet improves general cognitive performance, memory, and executive function (Rodrigues et al., 2020).

Adherence to a Western-style diet heavy in saturated fat, refined carbohydrates, and high caloric density, along with overeating behavior, which leads to lifestyle disorders, is a risk factor for affecting brain function and health (Stevenson et al., 2020).

Metabolic illnesses such as obesity and type 2 diabetes have an impact on brain function in adults (T2D) (Reichelt et al., 2018).

According to the present trend of mid-life obesity, dementia will grow more than projected in the future, according to the findings of Australian cohort research based on demographic data (Nepal et al., 2014).

Diabetes raises the risk of Alzheimer's disease (Cheng et al., 2012), and obesity, linked to mood and cognitive impairments (Agustí et al., 2018). Recent meta-analyses support the link between nutritional quality, mental health (eg, depression, cognitive function, (Jacka, 2017), and appetite control (Ekstrand et al., 2021).

Overweight and obesity in children have grown significantly over the last two decades, prompting worries about their psychosocial and cognitive repercussions. In a nationally representative sample of children, the links between academic achievement, cognitive functioning, and increasing BMI are shown: children and adolescents who are overweight have cognitive problems and lower academic performance (Li et al., 2008).

Adolescence is a critical era for the growth of brain areas involved in cognition (Spear, 2000b). Reichelt et al (2015) suggest the relationship between HFD and decreased learning and memory function (Reichelt et al., 2015).

Furthermore, the rodent studies reviewed by Cordner & Tamashiro (2015) provide evidence that consumption of of HFD for any length of time at any point in the lifespan can potentially result in impaired performance on a variety of behavioral learning and memory tests, including the Morris Water Maze (J. Wang et al., 2015), Barnes Maze (Ohland et al., 2013), Radial Arm Maze (Alzoubi et al., 2013), T-Maze, Y-Maze (Kosari et al., 2012), Novel Object Recognition test, and conditioned inhibition (Cordner & Tamashiro, 2015).

The hippocampus is important in cognition. Many studies showing a deleterious influence on hippocampus structure and functions give evidence that HFD might disrupt neuron development (Z. Wang et al., 2016).

Adult rats on a high-fat/high-sugar diet showed reduced hippocampus-specific spatial memory in the radial maze paradigm after 3-5 days, but no effect was shown in hippocampus-independent memory tests (Kanoski & Davidson, 2010). Many researchers have examined the influence of HFD on hippocampus-dependent learning and memory during the particularly sensitive juvenile age, revealing that these diets impair both relational and spatial memory (Valladolid-Acebes et al., 2011, Boitard et al., 2012; Kaczmarczyk et al., 2013, del Rio et al., 2016, Del Olmo & Ruiz-Gayo, 2018).

In rats, HFD at this age has been linked to poor relational and spatial memory ability (as discussed in del Olmo & Ruiz-Gayo, 2018) and lower hNG (Boitard et al., 2012).

Previous research has shown that long-term HFD (2-6 months) in adult rats reduces not only aHN but also the number of neuroblasts and immature neurons expressing the marker DCX in the dentate gyrus (Denoth-Lippuner & Jessberger, 2021; Han et al., 2019; Llorens-Martín et al., 2016). In other words, the DG's DCX+ cell population's morphological traits reflect their maturity status. We focused on a DCX+ population of 3-week-old immature neurons based on their soma location within the GCL and dendritic tree reaching the ML. This cell population, whose architectural features have previously been shown to be influenced by environmental stimuli (Dioli et al., 2019), appeared suitable for investigating the potential effects of short periods of LFD or HFD on their late maturation phase in 5-week-old mice or 10-week-old mice, an age roughly corresponding to adolescence and adulthood respectively in humans (Dutta & Sengupta, 2016).

We showed that a 7-day HFD period is enough to negatively affect the dendritic branching and length of DCX+ juvenile neurons in adolescent and adult male mice. Surprisingly, these effects only

occurred in the dorsal DG and not in the ventral DG in adolescent mice and viceversa in adult mice. Because the hippocampus is a complex structure with morphological and functional segregation along the dorso-ventral axis, our findings are important. The dHP is related with cognition, the vHP is involved with emotional behavior and stress response. Adult-born neurons' functional contribution differs along the dorsoventral axis as well (Kheirbek & Hen, 2011). For example, in a contextual discriminating test, ablation of aHN exclusively in the dorsal, but not the ventral, murine DG resulted in delayed discrimination acquisition (Wu & Hen, 2014). Chronic stress, on the other hand, has a detrimental effect on adult-born neurons in the ventral DG but not the dorsal DG.

Finally, some therapeutically important medications, including antidepressants, have been shown to particularly enhance hNG in the ventral hippocampus (Tanti & Belzung, 2013).

Although one study indicated that HFD can alter synaptic plasticity process in female mice's ventral hippocampus (Krishna et al., 2015), the effect of HFD on memory appears to affect predominantly dorsal hippocampal-dependent learning while protecting other forms of learning (Stouffer et al., 2015). This might be due to the specific impairment of the dorsal hippocampus produced by these diets' oxidative stress, inflammation, and/or altered neurotransmission. In this regard, HFD consumption has a detrimental effect on the hippocampus in terms of both spatial learning and memory, and it has been discussed that HFD appears to contribute to obesity in part by interfering with the suppression of hippocampal-dependent memory, which is essential for adjusting energy intake to meet energy requirements (Davidson et al., 2007; del Olmo & Ruiz-Gayo, 2018). Most of the studies agree that HFD impairs hippocampal function.

The discovery that we observed in adolescent mice, structural alterations of DCX+ cells predominantly in the dorsal hippocampus in our experimental environment might imply that a brief period of a high-caloric diet may preferentially influence dorsal hippocampal- and neurogenesis-dependent processes, including cognition. On the other hand, the alterations of DCX + cells that we

see in adult mice may preferentially influence ventral hippocampal- and neurogenesis-dependent processes, including emotional and stress behavior.

Our findings revealed a significant difference in the complexity of immature neurons between the dorsal and ventral hippocampus. Cells from the dorsal hippocampus's DG had much higher dendritic complexity than those from the ventral hippocampus. Despite the tight inclusion criteria mentioned in the materials and methods section and shown in figure 1.8, we are not able to exclude the possibility that some tips/dendrites of cells included in our study were removed because to sectioning. This might result in a bias, especially when comparing the dorsal vs. ventral hippocampus. On the one hand, it is plausible that some non-intact cells were included in our study by mistake.

These several cells may look less sophisticated in the ventral DG (vs. dorsal) due to coronal sectioning rather than their actual maturation stage. However, we may have limited our research to cells with less complicated arborization since more mature DCX+ cells were severed by coronal sectioning in ventral DG and hence eliminated from our analysis. Nonetheless, the differences in morphological complexity of DCX+ cells revealed herein between dorsal and ventral DG are consistent with prior studies that showed a slower maturation of newborn neurons in the ventral DG compared to the dorsal DG in young 9 week-old rats.

We also found that returning to a 1-week LFD restored the effects of brief HFD on the complexity of DCX+ immature neurons in both areas and age. Our *in vivo* findings are consistent with recent proteomic investigations in 12-week-old C57Bl/6J male mice (McLean et al., 2019). Rapid alterations in protein expression profile were seen in the hippocampus area following 3 or 7 days of an HFD diet. Surprisingly, returning to a low-fat diet corrected these changes (McLean et al., 2019). In rats who endured 3 months of HFD beginning in adolescence, the change over to a normal-caloric diet was likewise linked with recovered levels of hNG (Boitard et al., 2016). Interestingly, we discovered that DCX+ immature neurons in mice receiving 2 weeks vs. 1 week of LFD had a considerably more

complicated dendritic tree. One possible conclusion is that 2 weeks of LFD, as opposed to 1 week of LFD, may increase cellular maturation. The complexity of DCX+ cells is also considerably increased after 2 weeks of HFD compared to 1 week in the same regimen. Interestingly, the difference in morphological complexity between two and one week of HFD is much smaller than the difference between two and one weeks of LFD. Overall, we feel that this finding supports the notion that brief periods of HFD alter the development of immature DCX+ neurons differently than similar periods of LFD. Our findings show that, in contrast to LFD, brief HFD may prevent and/or slow down the late physiological maturation of DCX+ immature neurons.

One limitation of the research is that all mice were shifted from chow to low fat diet 1 week before the start of the experimental protocol to adapt to a refined nutrition and guarantee comparable basal conditions among LFD/HFD groups, such as food texture, which may differ slightly between chow and refined diets. It is probable that 1 week of diet adaptation, converting from a chow (hard-diet) to a low-fat diet (softer-diet), will have an effect on DCX+ cell complexity since this modification occurs around 1 week before they reach the immature stage, during their differentiation process. We cannot rule out the possibility that the reduction in complexity of DCX+ immature neurons in the HFD group is due to the interaction of food texture and high fat content rather than diet alone because a chow group was not part of the experimental design for direct comparison with the HFD and LFD groups.

We aimed to connect structural alterations in the DCX population with biochemical processes induced by HFD in a region-specific manner in our study. We examined DCX expression levels as well as βIII tubulin, another hallmark of immature neurons, and found no significant differences in both proteins in the dorsal hippocampus of HFD- vs LFD-fed animals (for adult animals are still ongoing). This finding emphasizes the importance of morphometric investigations like ours in detecting tiny structural changes in newborn cells that are maturing.

HFD has also been associated to changes in glial number, shape, and/or function in many brain areas (Gzielo et al., 2017; S.-F. Tsai et al., 2018). For 30 weeks, middle-aged 37-week-old male Wistar-Kyoto rats were given either a normal diet or a 45% HFD (i.e., until 67 weeks of age). They found that rats were given an HFD had fewer astrocytes and tyrosine hydroxylase-containing neurons in the substantia nigra and locus coeruleus than rats fed a normal diet. Hippocampal pyramidal neurons, on the other hand, were unaffected. The reduction in astrocytes may result in decreased brain protection and impair the survival of tyrosine hydroxylase-containing neurons but not pyramidal neurons in the hippocampus (del Olmo & Ruiz-Gayo, 2018).

Long-term HFD compromises duodenal barrier function and induces glial-dependent signaling throughout the gut-brain axis, which involves the GFAP/TLR4 network. This is accompanied by a drop in BDNF expression that spreads throughout the nervous system, a reduction in the number of dendritic spines in enteric and central neurons, and behavioral changes. Despite ongoing intestinal barrier malfunction, the impacts on the nervous system and consequent behavioral abnormalities were minimized by disrupting glial function with the gliotoxin. These findings imply that glial-mediated communication is critical for transmitting neuropathological signals throughout the nervous system and causing psychiatric co-morbidity during metabolic diseases (Chou et al., 2022).

In our study, no alterations in the expression levels of the astrocytic marker GFAP, the NLRP3 inflammasome, and Pro-caspase 1 in the dorsal hippocampus of HFD adolescent mice were found. However, due to the relatively short duration of the food supply, we cannot rule out that changes in the (Numakawa et al., 2017) mRNA for these inflammatory markers happened in the absence of protein alterations in our experimental settings.

Extrinsic and intrinsic molecular pathways allow for temporal and geographical regulation of dendritic arborizations in newly formed neurons. Brain-derived neurotrophic factor (BDNF) is one of the substances involved in the control of dendritic architecture. BDNF is an essential neurotrophin

with hippocampal-dependent activities, including cognition (Miranda et al., 2019). Additionally, the positive modulatory role of BDNF in hNG and the cytoarchitecture of newborn neurons is also a very consolidated concept (Numakawa et al., 2017). Increased neurogenesis in the granule cell layer after BDNF infusion into the hippocampus of adult rats (by implanted osmotic pumps for a month) was reported (Scharfman et al., 2005)

It is also demonstrated that BDNF is influenced by diet. Long-term chronic HFD consumption in mice lowers BDNF content in several brain locations, including the hippocampus, whereas dietary restriction improves brain BDNF content (Cavaliere et al., 2019).

When compared to animals fed a LFD, HFD was related to a substantial reduction in the expression of the active and precursor forms of BDNF, particularly in the dorsal and not the ventral hippocampus of adolescent mice and vice-versa in adult mice. Interestingly, returning HFD-treated animals to 1 week of LFD largely reversed BDNF alterations in both conditions altered (even if the difference between HFD-HFD and HFD-LFD groups does not reach a statistical difference). These data imply that lowering BDNF levels may contribute to the HFD-associated decrease in the complexity, length, and number of branches, tips, and bifurcations of the dendritic tree of DCX+ cells.

Previous research indicates that BDNF impacts the development of new hippocampus cells. BDNF is produced at high levels in mouse hippocampi, and BDNF conditional mutants affect the dendritic formation of neonatal granule neurons (Chan et al., 2008). It has been demonstrated that the BDNF receptor TrkB is expressed by neural stem cells and DCX+ cells inside the DG and that its expression in the latter cells is intimately associated with neuronal maturation (Donovan et al., 2008). Based on these findings, BDNF may directly and favorably impact the physiological maturation of DCX+ immature neurons, and its shortage, which we linked to brief HFD in the dorsal hippocampus, may contribute to the reduction and/or slowing of such maturation in a region-specific way. Of course, we cannot rule out the possibility that TrkB expression on other DG cells, both glial and neuronal, may

play a role in diet-related alterations in the DCX population In terms of the cellular source of BDNF, we can only conjecture at this point. Neurons, glia (both astrocytes and microglia), and even endothelial cells make and release BDNF. It's fascinating that established granule cells, which actively produce BDNF based on their activity, may impact the development of freshly formed neurons (Pardal & López Barneo, 2016). As a result, HFD may influence both locally and neuronally produced BDNF in the DG age specifically. Future research involving BDNF signal activation in HFD-treated animals should look at the role of the damaged BDNF/TrkB axis using proven pharmacological tools (Khazen et al., 2019). We currently have little information on intracellular processes implicated in the morphological alterations in the DCX+ populations of the DG, including those regulating cellular cytoskeleton structure. Intriguingly, a recent proteomic investigation found that 3 or 7-day-HFD lowered the expression of various cytoskeletal proteins in the hippocampus, specifically proteins involved in microtubule stability such as microtubule-associated protein 2 (MAP2) and stathmin (McLean et al., 2019). Our data suggest that brief changes in nutritional lifestyle differently affect areas related to cognition or mood in adolescence or adulthood.

Future research should be done to see if the fine and reversible morphological changes induced by a brief HFD in the DCX population correspond with hippocampal-dependent cognitive function and emotional behavior. Short-term HFD (7-9 days) affected the long-term memory of object placement as well as the production of *in vivo* long-term potentiation (LTP) in the CA1 of juvenile mice. Interestingly, 7-day HFD treatment improved *in vivo* LTP and object location memory in adult rats(Khazen et al., 2019). Although our current work focused on teenage mice and adults, we will investigate if brief HFD impacts the DCX+ population along the dorsoventral axis of the hippocampus differently at 10 months of age in the future. Furthermore, future studies will use a sectioning procedure that combines coronal sectioning for the dorsal hippocampus with horizontal sectioning for the ventral hippocampus to provide a more precise characterization of any variations

in dorsal versus ventral evaluation (as proposed by Egeland et al., 2017). This may aid in following the normal orientation of cells along the dorsal-ventral axis and coping with any sectioning bias.

One of our study's drawbacks is that we only looked at male mice. Indeed, very recent studies have revealed that continuous administration of an HFD (4 months starting at 2 months of age) to mice induces dramatic sex variations in hNG, which are not likely related to sex differences in food metabolism (Robison, 2020). The study discovered that HFD dramatically decreased cell proliferation and the amount of young/immature neurons in female mice but not in male mice. In the future, we will investigate if short HFD supply will determine consequences on hippocampal hNG differently not only at distinct ages but also as a function of animal sex.

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Chapter 2

ANOTHER FORM OF NEURAL PLASTICITY: ASTROCYTES PLASTICITY

2.1 The discovery of astrocytes

Astrocytes are glial cells that are present throughout the CNS. They interact with a variety of cell types, including neurons, other glial cells such as microglia and oligodendrocytes, and blood vessels, and are implicated or engaged in a variety of brain functions and diseases. Although progress has been made in studying astrocytes, more information is needed about how they carry out their many tasks, as well as how and when they influence the brain circuits they interact with. Given their now-acknowledged potential contributions to brain disorders (Chung et al., 2015), interest in studying fundamental astrocyte biology and evaluating the causative and correlative roles of astrocytes in neural circuits, as well as astrocytic contributions to behavior and disease or disease-related phenotypes, has exponentially grown in recent years (Yu et al., 2020).

For a long time, astrocytes and, generally speaking, glia were considered passive supporting cells that deserved little attention. Today, we know that they actively interact with neurons as well as with other cells of the CNS (Muthukumar, 2022). The discovery of a non-neuronal element, the neuroglia, in the CNS is generally attributed to Rudolph Virchow around 1850 (Wang & Bordey, 2008).

In 1895, Michael von Lenhossék coined the term astrocyte (*astron*, star, and *kytos*, a hollow vessel). Later on, Albert von Koelliker and William Lloyd Andriezen distinguished glia of grey and white matter, using the terms “protoplasmic astrocyte” for cells in grey matter and “fibrous astrocytes” for those in white matter (Verkhratsky & Nedergaard, 2018).

Andriezen hypothesized that protoplasmic and fibrous astrocytes developed separately. He also underlined the protoplasmic processes' complexity, describing them as having "*a shaggy, granular outline as if the protoplasmic processes were produced by a fine moss*." (Andriezen, 1893).

In the last two decades of the nineteenth century, Golgi developed and applied the Golgi potassium dichromate/silver staining method ("reazione nera") to brain tissue, as reviewed in Kettenmann & Ransom (2004). This staining revealed considerable morphological heterogeneity among neuroglia (Kimelberg, 2010).

From that moment on, most neuroscientists of the 19th and early 20th centuries assigned numerous functions to astroglia (Verkhratsky & Nedergaars, 2018). In particular, Carl Ludwig Schleich suggested that astroglial processes (by swelling and shrinking) might control synaptic transmission (Schleich CL., 1894). Similarly, Ramon y Cajal proposed that retraction of astroglial processes permits information to flow during alertness, whereas expansion of astroglial processes prevents interneuronal connection, resulting in sleep. He also proposed the central role of astrocytes in the control of cerebral vasculature (Ramón y Cajal S., 1895).

Later on, according to Robert Galambos, neurons "*follow out the instructions that glia sends them*," while neuroglia is "*essential to higher brain operations*" (Galambos, 1961). This idea needed additional evidence. The physiological research of neuroglia began in the late 1950s when these cells were investigated *in situ* and *in vivo* on vertebrate and mammalian preparations using electrophysiological and radiotracer techniques, yielding the first evidence of dynamic interactions between neurons and glia (Wardell WM, 1966). In the late 1980s, Jean de Villis established purified cultures of astroglial cells that allowed the direct study of astrocyte physiology at the single-cell level (Morrison & de Vellis, 1981).

2.2 Astrocyte generalities

The CNS evolved not just through brain volume and number of neurons, but also through a phenomenal expansion in the quantity and complexity of astrocytes.

In the human brain, the glia-to-neuron ratio is 1.65:1, whereas, in rodents, it is 0.3:1 (Nedergaard et al., 2003; Sherwood et al., 2006). Similarly, the complexity of human protoplasmic astrocytes enwrapping up to 2 million synapses is vastly more than that of rat astrocytes, which only contact 100,000 synapses (Oberheim et al., 2006). As a result, the astroglial syncytium regulates and influences neural networks, playing a role in many integrative processes in the CNS that is still not completely understood.

In a healthy mouse brain, astroglia shows physiological differences within the same brain regions. For example, gap junction coupling varies widely between astroglia in the hippocampus (Isokawa & McKhann, 2005; Matthias et al., 2003). The different mouse astroglial populations have been termed "passive" and "complex" based on their expression of glutamate receptors and transporters, ion channels (Zhang & Barres, 2010). Passive astroglia seems to express glutamate transporters but not ionotropic glutamate receptors. In contrast, complex astroglia express glutamate receptors but not transporters. This heterogeneity within the same brain region indicates that different populations of astroglia perform different functions in maintaining the environment (Miller, 2018).

So, the evidence clearly shows that astrocytes have a distinct identity; however, the accuracy of this positional specification has yet to be fully determined. Given the large and well-known diversity of neuronal subtypes, astrocyte specialization may reflect this to a higher extent than previously thought. Regional variability in astrocytes is a topic that is actively studied on a morphological, molecular, and functional level, with evidence of both interregional and intraregional variations (B. E. Clarke et al., 2021; Khakh & Deneen, 2019).

2.2.1 Morphological heterogeneity of astrocytes

The enormous morphological variation of astrocyte populations has already been mentioned by Ramon y Cajal. In particular, in the adult mouse brain, **protoplasmic astrocytes** have a small soma volume and 5-10 primary processes that develop into very complex secondary and tertiary branches. They have abundant terminal parts of their processes, called terminal feet, which contact blood vessels and meninges (Verkhratsky & Nedergaard, 2018). They are also closely related to synapses and their processes perform various functions, such as glutamate clearance from the synaptic cleft (Rothstein et al., 1996; Oliet et al., 2001), regulation of synaptic function (Henneberger et al., 2010; Uwechue et al., 2012), and local blood flow regulation in response to synaptic activity (Simard et al., 2003; Takano et al., 2005). Protoplasmic astrocytes are also involved in the formation and elimination of synapses (Kucukdereli et al., 2011; Pfrieger, 2010). Interestingly, the processes of two adjacent protoplasmic astrocytes are mutually exclusive and occupy non-overlapping domains (Halassa et al., 2007).

Fibrous astrocytes, on the other hand, have projections longer than 100 μm and are oriented radially to axons. The number of terminal feet is much smaller than in protoplasmic astrocytes (Verkhratsky & Nedergaard, 2018). In this type of cell, GFAP is an intermediate filament protein whose expression level is higher than that of protoplasmic astrocytes, where the GFAP protein is sometimes only present near blood vessels (Oberheim et al., 2009). The function of fibrous astrocytes is less studied compared to protoplasmic astrocytes, but, like protoplasmic astrocytes, they connect to blood vessels through their processes (Marín-Padilla, 1995).

In addition, there are also specialized astrocytes in Layer 1 of the mouse cerebral cortex that have a bushy appearance similar to protoplasmic astrocytes in the gray matter but significantly express GFAP like fibrous astrocytes (Tabata, 2015). The somata of these cells are positioned at the cortical surface and for this reason, they are called **surface-associated astrocytes**. The surface-associated astrocytes send two types of processes: one descending to layer I and the other extending to surround

pial vessels (Feig & Haberly, 2011; Verkhratsky & Nedergaard, 2018). Their processes form the glia-limiting membrane, which covers the outer surface of the brain parenchyma, just beneath the pia mater, and continues into the other half of the glia-limiting membrane formed by the protoplasmic astrocytes endfeet, as depicted in Figure 2.1. On the pial surface, GFAP-positive fibroblast-like cells have been found (García-Marqués & López-Mascaraque, 2013). These cells also contribute to the creation of the glial limiting membrane by covering the outer surface of the brain with their cell bodies (Tabata H., 2015).

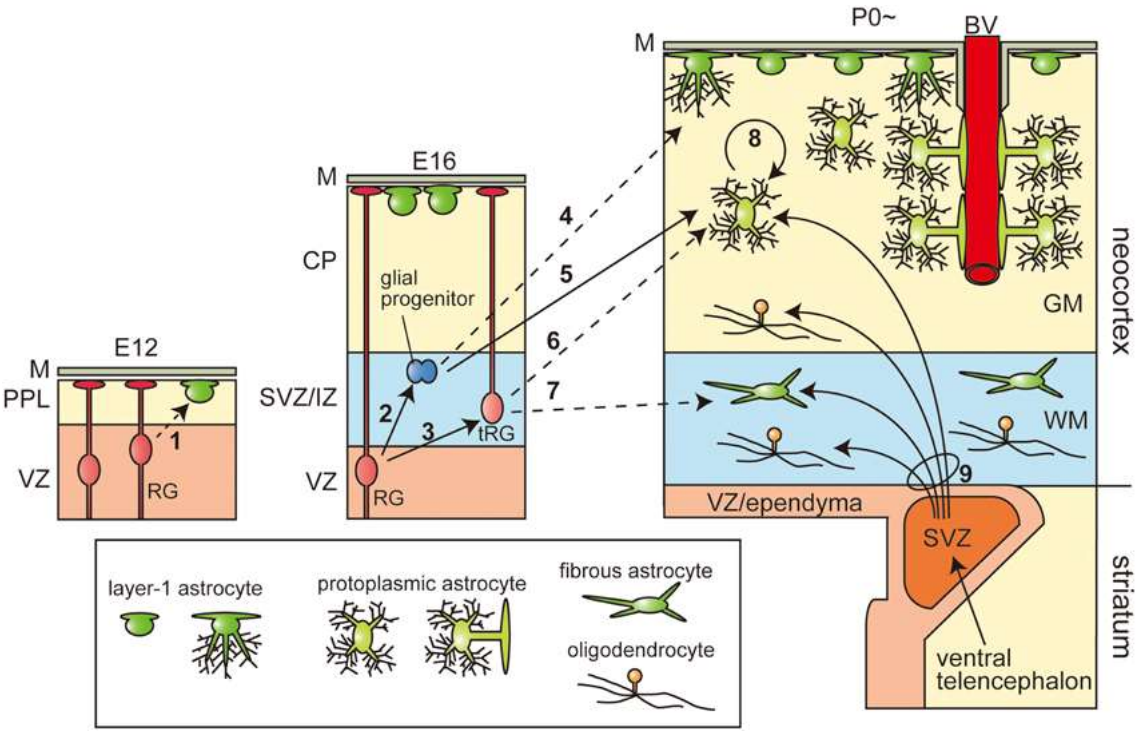

Figure 2.1: Heterogeneity of astrocytes and the multiplicity of their origin (from Tabata H., 2015)

Velate astrocytes represent a type of protoplasmic astrocyte present in areas of the brain that are densely packed with tiny neurons, such as the olfactory bulb or the granular layer of the cerebellar cortex (Chan-Palay & Palay, 1972). Velate astrocytes have tiny soma and short leaflike processes, with a high surface-to-volume ratio (Buffo & Rossi, 2013).

Perivascular astrocytes are found near the pia mater. They rarely come into contact with neurons, and their primary purpose is to form the pial and perivascular glia limitans barrier, which helps to separate the brain parenchyma from the vascular and subarachnoid compartments (X. Liu et al., 2013).

Using a combination of GFAP-driven green fluorescent protein (GFP) expression, GFAP protein expression, and S100ß immunostaining, scientists attempted to delineate types of astrocytes inside the mouse CNS. Emsley and Macklis (2006) classified separate groups of astrocytes using this combinatorial method for empiric classification. Recently new technologies, such as single cellomics, confirmed this distinction in the mouse brain (Batiuk et al., 2020).

Radial astrocytes are a very important astrocytic subfamily involved in CNS development and the formation of new neurons. They are cells with very fine projections that have different names depending on the brain region in which they are found: **Tanicytes** are characteristic of the hypothalamus, particularly in the arcuate and ventromedial hypothalamic nuclei (Bolborea & Dale, 2013), **Mueller cells** and **Bergmann glia** are present in the retina and cerebellum, respectively (Bowser & Khakh, 2007; Israel et al., 2003). In contrast, the Arcuate Nucleus (ArcN), contains **Gomori astrocytes**, cells that are particularly rich in iron, an important element for the production of heme group enzymes, as well as high levels of glucose transporter 2 (GLUT2) (Young et al., 1990, 1996). **Pituicytes** are the most common kind of astroglia in neurohypophysis (Hatton, 1999). They express GFAP and S100B astroglial markers. Pituicytes show remarkable heterogeneity and, based on morphological criteria, are subclassified into the major, dark, ependymal, oncocytic, and granular pituicytes (Takey & Pearl, 1984). In contrast to other astroglia, pituicytes receive synaptic contacts, and they are sensitive to several neurotransmitters and neurohormones (Hatton, 1999).

Astrocytes also differ in their branching orientation and development. Chiu et al. (1996) identified six astrocytic phenotypes in the rat olfactory bulb, which are divided into unipolar astrocytes that

develop branches in one direction, elongated and linear astrocytes that have much longer branches than other cells, irregular astrocytes, circular astrocytes, and semicircular astrocytes.

Human astrocytes have a different morphology than rodent astrocytes. Both protoplasmic and fibrous astrocytes in the human brain are much more complex and larger than those of rodents (Matyash & Kettenmann, 2010; Placone et al., 2015).

Although the astrocyte subtypes listed above, notably fibrous, protoplasmic, and Layer-1 astrocytes, are generally found in mammalian brains, human or other primates have at least two distinct phenotypes (Colombo & Reisin, 2004; Oberheim et al., 2009; Sosunov et al., 2014). Interlaminar $GFAP^+/CD44^+$ astrocytes are densely packed astrocytes in Layer 1 of the primate cerebral cortex. These cells extend millimeter-long straight and poorly branching processes into the cortical gray matter, typically terminating on blood vessels in Layers 2–4 (Sosunov et al., 2014). This subtype appears after birth. Glial contents in Layer 1 in the fetal stages are comparable to those in rodents, suggesting that Layer-1 astrocytes with short processes can change into interlaminar astrocytes (Colombo & Reisin, 2004; Marín-padilla, 1995). The second primate-specific subtype is the varicose projection astrocytes, which are also $GFAP^+/CD44^+$ and are located mainly in Layers 5 and 6. Many varicosities extend from this cell type, which may terminate in the neuropil or on the vasculature (Oberheim et al., 2009; Sosunov et al., 2014).

Protoplasmic and fibrous astrocytes in humans have distinct structures, compared to rodents. The human cortex is reported to be 22.5 times thicker in diameter than the mouse cortex (Oberheim et al., 2009). Human protoplasmic astrocytes, like rodent cells, create unique domains, with each domain covering around 2,000,000 synapses. Protoplasmic astrocytes and varicose projection astrocytes coexist in the cortex layer of the human brain and their processes are intertwined, implying that they are distinct kinds of cells with different activities.

2.2.2 Functional heterogeneity of astrocytes

Astrocytes have a wide range of functional features that affect their ability to influence brain activity. In addition, there is evidence for adaptations in astrocyte function that are context- and region-specific (Boisvert et al., 2018; Itoh et al., 2018). An important research topic that is emerging is the extent to which differences in neuronal excitability and transmitter release are, in fact, a product of astrocyte heterogeneity.

It has been widely reported that astrocytic cells play protective roles in the nervous system, including ion buffering (Becerra-Calixto & Cardona-Gómez, 2017), uptake and synthesis of neurotransmitters (Bylicky et al., 2018; Kaczor et al., 2015), controlling cerebral blood flow (Newman, 2015), extracellular fluid ion and pH homeostasis (Kitchen et al., 2015; Linnerbauer & Rothhammer, 2020), energy metabolism (Beard et al., 2022), synapsis formation, and immunomodulation (Ahtiainen et al., 2021). Also, it has been described that astrocytes are involved in adult neurogenesis (Cassé et al., 2018; Nato et al., 2015), making them an integral and relevant part of the neurogenic niche (Becerra-Calixto and Cardona Gomez, 2017).

Role of astrocytes in synaptic modulation

Astrocyte processes at synapses play an important role in transmitter homeostasis by expressing transporters for neurotransmitters such as glutamate, GABA, and glycine, which clear neurotransmitters from the synaptic cleft (Sattler & Rothstein, 2006). After being taken up by astrocytes, the neurotransmitters are transformed into precursors and then circulated back to synapses for reconversion into active neurotransmitters. Networks of astrocytes can rapidly dissipate small molecules of glutamate and potassium and prevent their potentially detrimental accumulation (Seifert et al., 2006; Sofroniew & Vinters, 2010).

Astrocytes play a pivotal role in glutamatergic neurotransmission: they express group I metabotropic glutamate receptors (mGluR) mGlu1/5, which positively regulate the depolarization and synaptic excitability, and group II mGlu3 receptors which negatively regulate the release of neurotransmitters. Glutamate transporter proteins, such as GLAST and GLT-1 (EAAT2), are expressed by astrocytes (di Monte et al., 2006). Transgenic studies using the fluorescent proteins DsRed, under the control of the GLAST promoter, and GFP, under the control of the GLT-1 promoter, have revealed that these key proteins are expressed differently in astrocytes in different regions of the CNS and during development (Dietrich et al., 2005). GLAST is expressed primarily in radial glia as well as cortical astrocytes during development, as well as several niches in the forebrain such as the progenitor cells of the subgranular layer of the dentate gyrus. GLT-1 is the most commonly expressed glutamate transporter in adults, and it is highly active in both protoplasmic and fibrous astrocytes, accounting for 90% of glutamate absorption in the CNS (Donati et al., 2005). In the spinal cord, however, GLT-1 expression is tenfold lower than in the brain, which is linked to lower glutamate uptake (Seifert et al., 2006).

Moreover, to prevent glutamate-mediated excitotoxicity, astrocyte glutamate transporters can influence neuronal excitability in more subtle ways, such as modulating the activity of extrasynaptic glutamate receptors (Huang, 2004) or shaping the time course of postsynaptic currents (Murphy-Royal et al., 2015).

Also, GABA transporter expression varies greatly among different populations of astrocytes, similar to glutamate transporters (Boisvert et al., 2018), with higher levels detected in hypothalamic astrocytes, followed by cortical astrocytes, and cerebellar astrocytes having the lowest expression among the populations studied (Xin & Bonci, 2018).

Role of astrocytes in the regulation of cerebral blood flow

Astrocytes have numerous interactions with blood vessels, modulating the local CNS blood flow. According to recent research studies, astrocytes synthesize and release a variety of chemical mediators, including prostaglandins, nitric oxide, and arachidonic acid, which can raise or decrease blood vessel diameter and blood flow (Langen et al., 2019). Furthermore, astrocytes could be the principal mediators of changes in local blood flow in response to neuronal activity variations (Yamazaki & Kanekiyo, 2017). Astrocytes have processes that come into contact with blood arteries as well as synapses. Astrocytes titrate blood flow in response to synaptic activity via these connections, as recently revealed in the visual cortex, where detected variations in blood flow in response to visual stimuli were found to be dependent on astrocyte function (Batiuk et al., 2020).

Astrocyte-mediated control of extracellular fluid homeostasis

The water channel aquaporin 4 (AQP4) and K^+ transporters are abundant in astrocyte processes (Vandebroek & Yasui, 2020). The Na^+/H^+ exchanger, bicarbonate transporters, monocarboxylic acid transporters, and the vacuolar-type proton ATPase are all examples of proton shuttling systems found in astrocyte membranes (Vandebroek & Yasui, 2020). AQP4 channels are densely clustered along with astrocyte processes that contact blood vessels and play a critical role in regulating fluid homeostasis in healthy CNS and play roles in both vasogenic and cytotoxic edema (Sofroniew & Vinters, 2010; Ximenes-da-Silva, 2016).

The main astrocytic connexins, CX30 and CX43, have varied expression patterns across the brain, despite their apparent universality in function (Boisvert et al., 2018).

CX43 expression is highest in the thalamus and cerebellum and lowest in the cortex and hippocampus, whereas CX30 expression is highest in the thalamus and cerebellum and lowest in the cortex and hippocampus (Chai et al., 2017). As a result, the genetic deletion of CX30 reduces coupling in the

thalamus substantially, but the loss of CX43 simply affects coupling in the hippocampus (Griemsmann et al., 2015). These discrepancies in expression suggest that astrocyte capacity for potassium uptake and metabolic support to neurons may be uneven, limiting a local neural network's ability to sustain high-frequency firing or substantially synchronous activity.

The most common potassium channel is Kir4 (Cui et al., 2018). Kir4.1 deletion causes astrocyte membrane depolarization, potassium uptake inhibition, increased short-term synaptic potentiation in the hippocampus, and stress-induced seizures (Djukic et al., 2007; Sibille et al., 2014). Despite its obvious importance in astrocyte potassium buffering, this channel is not expressed evenly in astrocytes across the brain. Immunohistochemistry demonstrated significant Kir4.1 expression in spinal cord astrocytes, deep cerebellar nuclei, and hippocampus astrocytes (Götz et al., 2021), but not in other locations, such as astrocytes within white matter tracts (Poopalasundaram et al., 2000). A recent study found increased Kir4.1 expression in hypothalamic astrocytes and low expression in cerebellar astrocytes using the ribotag approach to identify astrocyte-specific mRNA (Boisvert et al., 2018). There is also a non-uniform expression pattern of Kir4.1 inside the spinal cord, with expression being substantially higher in the ventral horn than in the dorsal horn (Götz et al., 2021; Olsen et al., 2007).

If these differences in expression translate to functional differences in channel activity is not demonstrated.

Astrocytes and regulation of neuronal energy metabolism

Glycogen is an on-demand source of energy for the brain and it is stored in astrocytes where it is broken down into lactate when neurons seek extra energy sources (Tsacopoulos & Magistretti, 1996). Many studies contributed to propose that this type of energy transfer from astrocytes to neurons is necessary for learning and synaptic plasticity (Deitmer et al., 2019), although almost all of them were

carried out in the hippocampus. A recent study looked into the distribution of glycogen throughout the brain and discovered that it was most prevalent in astrocyte processes (Oe et al., 2016). However, there was a lot of variability within and between regions, with the hippocampus and cerebellar cortex having the highest levels of glycogen and the corpus callosum and thalamus having the lowest ones (Oe et al., 2016). Within the hippocampus, detected glycogen levels were extremely variable among astrocytes.

The heterogeneity in glycogen levels shows that astrocyte glycogen synthesis is not consistent and that the transfer of energy substrates from astrocytes to neurons varies for some brain circuits to function normally. Because the coupling of astrocyte glycolysis to neuronal activity appears to be robust at glutamatergic synapses but not at GABAergic synapses, areas that receive exclusively GABAergic inputs may require less metabolic coupling between astrocytes and neurons (Deitmer et al., 2019).

Regulation of synaptogenesis

The requirement of astrocyte-secreted proteins for synapse formation (Takano et al., 2020) is one of the most startling results in the field of astrocyte biology, but whether this requirement is consistent across the brain regions has been examined only recently. To answer this question, one group cultured astrocytes from the newborn murine cortex, hippocampus, midbrain, and cerebellum, and then looked at the expression of synaptogenic factors in these region-specific astrocyte cultures, as well as the effect of their conditioned media (ACM) on the formation of synapses (Buosi et al., 2018a). The authors discovered that various astrocyte populations have dramatically varying levels of synaptogenic factor expression. Furthermore, while all ACMs were able to stimulate synapse formation in neurons, ACM from cortex and hippocampus astrocytes significantly enhanced the amount of synaptophysin and PSD-95 puncta compared to ACM isolated from the midbrain and cerebellum. Another study used cortical or subcortical astrocytes and neurons in co-culture

experiments and discovered that neurons cultured with astrocytes from the same region developed significantly longer neurites and more functional synapses than neurons cultured with astrocytes from a different region (Morel et al., 2017). These findings show that there are not only absolute differences in the quantities of soluble substances produced by distinct astrocyte populations but that neurons within a certain region are tuned to be more receptive to astrocytes from the same region.

Although the existing literature has focused on synaptogenesis during development (Stogsdill et al., 2017), there may be parallels between developmental synaptogenesis and the formation and/or plasticity of synapses in adulthood as a result of learning, environmental changes, or pathology. Indeed, several of the chemicals implicated in synapse formation throughout development, such as thrombospondins and SPARC, are still produced by astrocytes in adulthood, albeit in varying quantities across regions (Boisvert et al., 2018; Morel et al., 2017). Surprisingly, while the synapse-inducing factors SPARC, and Thbs1 were significantly enriched in hypothalamic astrocytes compared to cortical astrocytes, the synapse-eliminating genes C3, C4b, and Mertk were also significantly higher (Boisvert et al., 2018), possibly reflecting a higher need for synapse turnover in the hypothalamus. More in-vivo research with genetic tools will be needed to determine the functional relevance of these discrepancies, which could have significant implications for our models of synaptic plasticity in distinct brain regions.

Gliotransmission

Gliotransmission, or the release of neuroactive chemicals from astrocytes in response to intracellular calcium rise, is perhaps one of the most contentious aspects of astrocyte biology (Savtchouk & Volterra, 2018).

Despite the lack of membrane electrical excitability, astrocytes show significant ionic handling in response to a variety of stimuli, which is critical for the appropriate regulation of brain-controlled physiological processes (Verkhratsky & Nedergaard, 2018).

Internal K^+, Na^+, Ca^{2+}, and H^+ fluctuations in astrocytes, for example, are linked to increased synaptic activity, while Cl^- permeability is linked to variations in astrocyte size. Intracellular Ca^{2+} signaling in astrocytes has been intensively researched since persuasive evidence implies the presence of Ca^{2+}-dependent astrocyte-neuron interaction (Savtchouk and Volterra 2018).

Activation of particular metabotropic G-protein coupled receptors (GPCRs) by synaptic neurotransmitter spillovers, such as glutamate (Panatier et al., 2011), GABA (Perea et al., 2016), ATP (Darabid et al., 2018), acetylcholine (Papouin et al., 2017) and dopamine (Corkrum et al., 2020), has been found to result in astrocyte Ca^{2+} elevations following synaptic neurotransmitter spillover.

On the question of astrocyte heterogeneity, one group found that claimed astrocyte glutamate release characteristics (for example the slow inward current) are circuit-specific in the dorsal striatum, rather than being observed uniformly across neuronal populations (Martín et al., 2015). However, a more recent study (Chai et al., 2017) found no link between the occurrence of slow inward currents and astrocyte activity, casting doubt on the slow inward currents and their presumed astrocytic origin. On the other hand, the same study found that striatal and hippocampal astrocytes have different calcium kinetics. These findings show that, like other aspects of astrocyte physiology, the rules governing astrocyte calcium signaling and the potential release of any signaling molecules are likely to be area and circuit-specific.

Immunomodulatory properties of astrocytes

Under stress and degenerative conditions, astrocytes can change to a reactive state. The expression of the glial fibrillary acidic protein (Lebkuechner et al., 2015) is directly related to individual

morphology. GFAP overexpression is dependent on the type of damage, the distance between the astrocyte and the site of injury, and the time after injury (D. Sun et al., 2010). Reactive astrogliosis and astrocyte proliferation, on the other hand, are neuroprotective, because glial cells can release substances that increase cell survival against severe injury or degeneration in this circumstance (Mohn & Koob, 2015; figure 2.2B). Hyperreactive astrocytes, on the other hand, intensify their varied functions under pathological situations, playing an opposing role that contributes to CNS disequilibrium (see figure 2.2 for a schematic representation of these concepts).

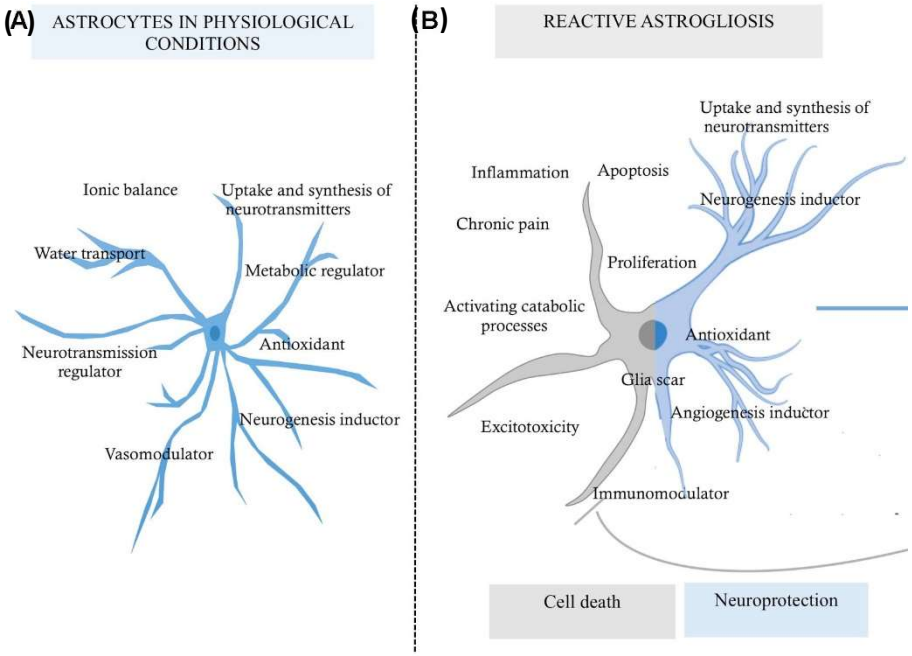

Figure 2.2: Role of astrocytes in a micro-environment dependent-mode. (**A**) Functions of the astrocytes in physiological conditions, which are in favor of the homeostasis of the nervous tissue. (**B**) Reactive astrocytosis, which has a double function highly discussed, one for cell death and one for pro-neuroprotection probably in a context dependent-mode (Becerra-Calixto and Cardona Gomez, 2017).

Astrocytes were the first CNS cell type where expression of class II major histocompatibility complex (MHC) molecules was initially observed (Dong & Benveniste, 2001). MHC II is a molecule that is generally expressed on professional antigen-presenting cells (APC) and plays a vital role in the development of immune responses by presenting processed antigens to $CD4^+$ T-helper cells. MHC II expression allows cytokines, neurotransmitters, and neuropeptides to regulate astrocytes (Dong and Benveniste, 2001). In astrocytes, however, MHC is involved in an increased inflammatory response.

In addition, cytokines play neuroprotective and neurotrophic activities that are necessary for neurodevelopment and proper CNS function (Morganti-Kossmann et al., 2007).

Astrocytes are also capable of synthesizing cytokines and chemokines; they express pattern-recognition receptors (PRRs), such as TLRs, scavenger receptors, and complement proteins. There is evidence that astrocytes have a dual role in immunological reactivity modulation at the local level. Astrocytes are resistant to apoptosis caused by death receptors [such as Apoptosis antigen 1 and tumor necrosis factor (TNF)-related apoptosis-inducing ligand FAS, TRAIL] after inflammation, indicating that these cells are well prepared to survive inflammatory shocks (Farina et al., 2007). TLRs in astrocytes can be activated by neurotrophic mediators such as glial-monocyte colony-stimulating factor (GM-CSF), vascular endothelial growth factor (VEGF), neurotrophin 4 (NT-4), and ciliary neurotrophic factor (CNTF) (Bsibsi et al., 2006).

Furthermore, reactive astrocytes and microglia can demarcate the injured area and limit leukocyte extravasation, facilitating blood-brain barrier (BBB) repair and neuronal survival (Farina et al., 2007). Some cytokines, including IL-1 and IL-6, which are linked to harmful inflammatory responses in various processes, may also act as neuroprotection mediators. Some studies have demonstrated that deletion of IL-6 and IL-1β increases BBB permeability and decreases the production of neurotrophic factors such as CNTF and insulin growth factor (IGF), indicating that cytokine-induced astrogliosis following trauma is important to restore the integrity of the BBB and to repair the lesion (Herx et al., 2000; Lampron et al., 2013). These characteristics make the astrocyte a highly sensitive inductor and possibly regulator of immune responses.

Astrocytes' involvement in adult neurogenesis

The first neurogenic niches to be discovered were the SVZ, close to the third ventricle (V3), and the area below the granular cell layer of the DG in the hippocampus, an area delegated to learning and

cognitive functions. Recently, other niches have also been identified as neurogenic with cells with proliferative activity (tanycytes) close to the mid-basal margin of the V3 in the hypothalamic region. In particular, at least in rodents, aNG occurs in two hypothalamic nuclei, the arcuate nucleus (ArcN) and the paraventricular nucleus (PVN) (Feliciano et al., 2015; D. A. Lee & Blackshaw, 2012).

aNG is a highly modulated process by external factors. Indeed, environmental enrichment and physical exercise promote it; on the contrary, stress, and aging reduce neurogenesis (Bortolotto et al., 2014). The proliferation/differentiation of NPC/NSC occurs in response to the microenvironment created in neurogenic niches also for the release of permissive paracrine signals. *In vitro* studies identified how signals released by neural cells (astrocytes and neurons) in the niche microenvironment, for example, FGF-2 (fibroblast growth factor 2), can activate NSC directing them towards cell division to reconstitute the NSC pool or towards neuronal differentiation (Israsena et al., 2004). In previous tests conducted in our laboratory, the importance of the p50 subunit of the transcription factor NF-κB in adult hippocampal neurogenesis has been demonstrated (Denis-Donini et al., 2008). This subunit covers a key role in the neuronal differentiation of hippocampal murine NPCs (Bortolotto et al., 2014), but it also influences the soluble signals released by astrocytes in the neurogenic niche (Cvijetic et al., 2017). The conditioned medium collected from primary cultures of hippocampal astrocytes from WT mice can promote neuronal differentiation of murine hippocampal NPCs *in vitro*. On the contrary, ACM from the hippocampal glia of p50 knockout (p50 KO) mice is devoid of pro neurogenic activity on hippocampal NPCs (Cvijetic et al., 2017). Through mass spectrometry analysis of ACM, it was possible to identify proteins differentially expressed in WT and p50 KO media, such as lipocalin-2. This astrocytic protein has a marked pro neurogenic effect on WT NPCs, while this effect is lower in NPCs from p50 KO mice (Cvijetic et al., 2017). Our group demonstrated that at least in part this may be explained by reduced expression levels of lipocalin-2 receptors in p50 KO hippocampal NPC.

Interest in the soluble signals released by astrocytes in neurogenic niches is growing. Many molecules released by astrocytes can modulate the aNG (Spampinato et al., 2020). Among them there are: i) morphogenic signals, like Wnt3 and Wnt7 factors, that through their receptors favor aNG; ii) gliotransmitters, like D-serine and D-glutamate, that have been proposed to regulate maturation, integration, and survival of adult-born neurons; iii) extracellular matrix (ECM) proteins, like thrombospondin-1; iv) cytokines and acute phase proteins, like IL-1β and IL-6, which may favor NSC glial differentiation (Santos et al., 2022).

2.3 Astrocyte plasticity

Astrocytes exhibit structural plasticity in response to synaptic activity and behavior, which helps to remodel the synapses around them. Understanding the chemical foundation for learning, memory, and other brain functions requires an understanding of astrocyte structural plasticity. In response to significant behavioral cues like parturition, lactation, osmotic stimulation, and stress, astrocytes demonstrate rapid and reversible structural remodeling that happens in perisynaptic astrocytic processes (PAPs; Theodosis DT., 2002).

During the transition of brain states, astrocyte structural change happens as well. Increased extracellular space (ECS) volume was observed during natural sleep and general anesthesia, but inverse changes in ECS volume were observed during waking and general anesthesia recovery (Ding et al., 2016; Tønnesen et al., 2018). PAP plasticity modulates these state-dependent variations in ECS volume (Syková & Nicholson, 2008).

Astrocytes may thus have a role in the on/off switch for consciousness. The high-order processes of astrocytes in the mediobasal hypothalamus shortened during fasting and elongated after feeding (Zhang, Reichel, et al., 2017). Neuronal activities also communicate astrocyte structural remodeling, as revealed by *in vitro* slice preparation (Nishida and Okabe., 2007) and *in vivo* detection (Bernardinelli et al., 2014; Nishida & Okabe, 2007).

Synaptic activity that causes hippocampus long-term potentiation (LTP) or *in vivo* whisker stimulation, for example, is enough to cause fast PAP movement, associated with an enhanced astrocytic covering of spines, within minutes (Bernardinelli et al., 2014). Other examples of structural plasticity of astrocytes are observed in the PVN of the hypothalamus during breastfeeding in rats. The PAPs retract leading to reduced removal of the glutamate from the extracellular space and an increase in the release of oxytocin which regulates milk production. At the time of weaning, the astrocytes

stretch again reaching the synapses and the release of oxytocin returns to normal levels (Bender et al., 2020).

In a nutshell, PAPs are extremely dynamic structures whose plasticity can occur between minutes to hours as a result of brain activity in multiple locations. Synaptic activity has been shown to govern PAP plasticity (Jones & Greenough, 1996). *In vivo* observations in the mouse somatosensory cortex corroborate this finding (Perez-Alvarez et al., 2014). PAP activity-related structural plasticity appears to be glutamate-dependent, mediated by metabotropic glutamate receptors (mGluRs), but not GABAergic transmission (Haber, 2006). PAP basal motility, on the other hand, maybe independent of their action potential (Verbich et al., 2012). The application of mGluR3 and 5 agonists enhanced structure plasticity in primary astrocytes, but a combination of glutamate and mGluR antagonists reversed it (Lavialle et al., 2011). Together, these data indicate that neuronal activity-dependent PAPs plasticity is mediated by mGluRs.

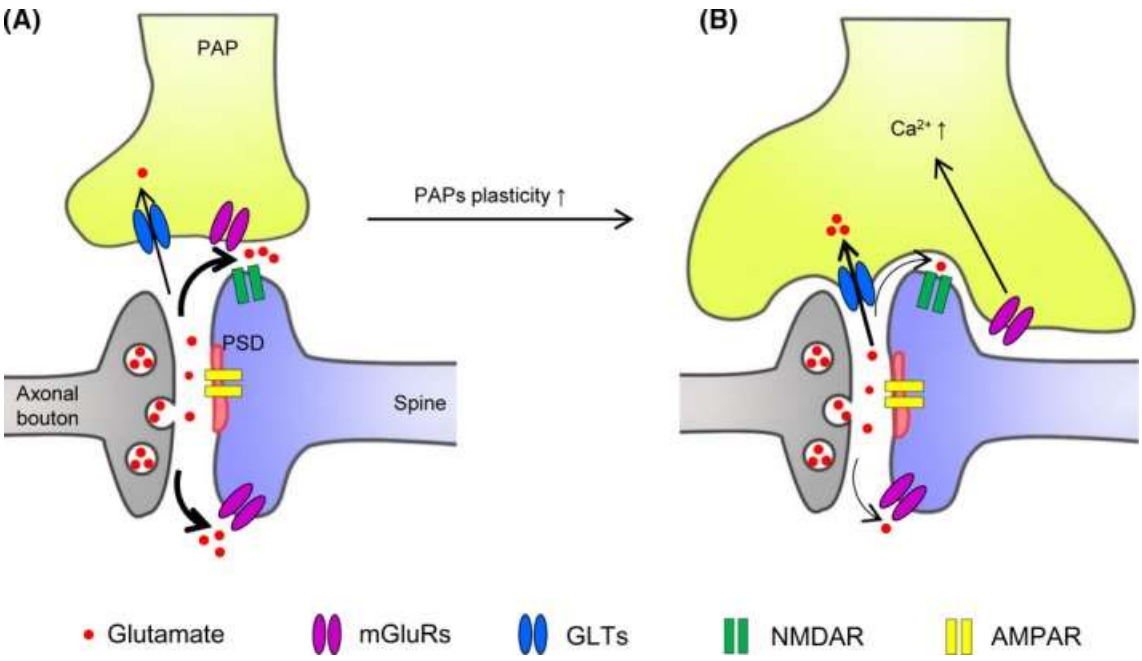

Figure 2.3: PAPs plasticity regulates the astrocytic coverage of synapse and synaptic transmission. (**A**), A synapse with minimal astrocytic coverage, poor glutamate absorption by GLT, but sufficient to extrasynaptic NMDAR and mGluR activation. (**B**) Increased PAPs plasticity, generated by mGluRs-mediated Ca^{2+} signals, improves astrocytic synapse coverage, with reduced glutamate release into the extracellular space (ECS) and extrasynaptic activation but increased glutamate absorption by GLTs. AMPAR is for amino3hydroxy5methyl4isoxazolepropionic acid receptor; GLTs stand for glial glutamate transporters, which include GLT1 and GLAST; mGluRs stand for metabotropic glutamate receptors; NMDAR stands for NMethylDasparticacid receptor; PSD stands for postsynaptic density (Zhou et al., 2019).

2.3.1 Astrocyte plasticity in aging

According to earlier research, astrocyte regional identity is established early in development and is retained throughout maturity (H. Tsai et al., 2012). Aging, on the other hand, causes major changes in astrocytic gene expression, including region-specific modifications. A new study comparing gene expression in multiple regions of elderly and young human brains found that astrocytes endure considerably more gene expression changes than neurons, including apparent loss of regional identity (Boisvert et al., 2018; L. E. Clarke et al., 2018; Soreq et al., 2017). The hippocampus and substantia nigra, which are typical regions affected by Alzheimer's and Parkinson's diseases, showed the most significant alterations (Soreq et al., 2017).

The hippocampus, striatum, and cortex all had reactive astrocytes during normal aging, but the three areas had different reactive states. Several markers that are expressed in a neuroinflammatory A1-like reactive state were shown to be elevated. An increase in neurotoxic pro-inflammatory cytokines and a decrease in astrocytic homeostatic activities have previously been linked to an A1 reactive state (Liddelow et al., 2017). These findings imply that when astrocytes age, they may lose their homeostatic activities, which could have implications for region-specific neurodegenerative risk. There appears to be a reduction in synapse function and number in the aging brain, as well as a general reduction in neuronal activity, but no significant decline in neuron or astrocyte number (Samson & Barnes, 2013). Across many brain regions, analysis of astrocytic gene expression revealed a downregulation of genes involved in synapse regulation and an increase in the expression of genes involved in synapse removal (Boisvert et al., 2018). This could be exacerbated by intrinsic variations in astrocyte synaptogenic factors that have been found between postnatal areas (Buosi et al., 2018b). During aging, changes in cytokine production and increased oxidative stress may have negative consequences for astrocytic activities, such as altered blood-brain barrier regulation and neuronal metabolic balance, although the significance of astrocyte heterogeneity in these processes is currently unknown (Palmer & Ousman, 2018). As a result, aging may result in a neurotoxic reactive state in

astrocytes, as well as a loss of supporting skills across several brain regions. However, the impact of regional variability on astrocyte function during the aging process is still underexplored, and more functional testing of old astrocytes is needed to corroborate molecular evidence for their hypothesized neurotoxicity or loss of homeostatic function (B. E. Clarke et al., 2021).

2.3.2 Astrocyte plasticity and chronic stress

Stress is a natural physiological response that prepares the body to deal with physical or psychological danger. When stresses are persistent, disruptive, and out of proportion to the actual threat, pathology can develop (Franklin et al., 2021).

In reality, stress is a substantial risk factor for anxiety disorders, serious depression, and neurodegenerative illnesses like Parkinson's disease PD (Jyothi et al., 2015).

Chronic stress causes a neuroendocrine change that causes excessive quantities of glucocorticoids to be released into the bloodstream, adversely affecting plasticity processes over time (Pittenger & Duman, 2008). As it has been clearly demonstrated in mouse animal models, changes in the microenvironment cause structural changes in the parts of the CNS involved in the response to stress stimuli. Chronic stress has a particularly high impact on the hippocampus.

The hippocampal DG, for example, shrinks in size in tandem with the volume and density of neurons' dendritic spines (Runge et al., 2020).

Furthermore, prolonged stress affects the DG SGZ by significantly lowering aNG (Toda & Gage, 2018).

Chronic stress causes glial responses in addition to morphological changes in neurons because astrocytes produce neurotransmitter and stress hormone receptors (X. Zhou et al., 2019).

Stress can change the morphology of astrocytes and the expression of various proteins in the prefrontal cortex, hippocampus, hypothalamus, and amygdala, which all play a role in emotional processing (Shin & Liberzon, 2010).

Understanding the impact of stress on astrocytes and how these changes contribute to the development of neuropsychiatric illnesses is crucial for a better understanding of mental illness as well as the development of innovative treatment methods. Adult males of Tupaia (a phylogenetically near relative of primates) were treated with 5 weeks of psychosocial stress in one of the first studies to identify the effect of stress on astrocytes. Czéh et al. (2006) found a decrease in the volume of soma and the number of GFAP+ astrocytes in the hippocampus of stressed animals compared to unstressed controls.

In the rat's infralimbic cortex, chronic unpredictable stress can cause a decrease in the number of GFAP+ cells (Tynan et al., 2013). The anterior cingulated cortex, dorsal prefrontal cortex, and amygdala all showed a reduction in the quantity and density of astrocytes in postmortem investigations of individuals with severe depressive illness (B. Zhou et al., 2019). In a different study, the number and structure of astrocytes in the rat hippocampus and amygdala following chronic immobilization stress were examined. 1 day after the end of 10 days of chronic stress, there were fewer GFAP+ astrocytes in the basal amygdala (BA). A morphometric analysis of GFAP+ astrocytes revealed that BA had decreased levels of tiny astrocytic protrusions and the volume that these astrocytes occupied in the neuropil. However, the same chronic stress had no impact on the number or morphology of astrocytes in the CA3 area of the hippocampus (Naskar & Chattarji, 2019). The GFAP+ cells were reduced in the hippocampus, prefrontal cortex, and amygdala, but not in the cortical regions, in Wistar Kyoto rats, who are more susceptible to stresses and display comparable depressive-like behavior more pronounced than in other preclinical models. However, no change in the number of astrocytes was detected when another astrocyte marker, the calcium-binding protein

s100, was used (Bender et al., 2016). As a result of this finding, it has been argued that stress does not result in a major decrease in the number of astrocytes, but rather in a decrease in the levels of GFAP protein expression (Bender et al., 2016). Recently, Du Preez and collaborators (2021) showed morphological changes in astrocytes in the dorsal and ventral DG of mice subjected to UCMS-I (unpredictable moderate chronic stress with isolation). In detail, in DG Molecular Layer, greater morphological complexity of astrocytes was observed in stressed/isolated mice compared to the control group. These effects appeared as region-specific findings since in the same animals no structural changes were observed in the astrocytes of the prefrontal cortex (du Preez et al., 2021). In this thesis, we will focus on another part of the brain: the hypothalamus.

2.3.2.1 The involvement of the hypothalamus in chronic stress

The hypothalamus is made up of several highly linked nuclei, including the PVN, which is positioned along the lateral wall of the V3, and the ArcN, which is placed between the basal portion of the V3 walls and the median eminence. To integrate the stress response, the PVN gets input from the amygdala and the ventral hippocampus (Saper & Lowell, 2014). In particular, in response to stressful stimuli, the PVN secretes corticotropin-releasing hormone (CRH), which increases the pituitary gland's synthesis of adrenocorticotropic hormone (ACTH). ACTH activates the adrenal glands, causing them to produce the stress hormone glucocorticoid corticosterone (cortisol in humans, figure 2.4).

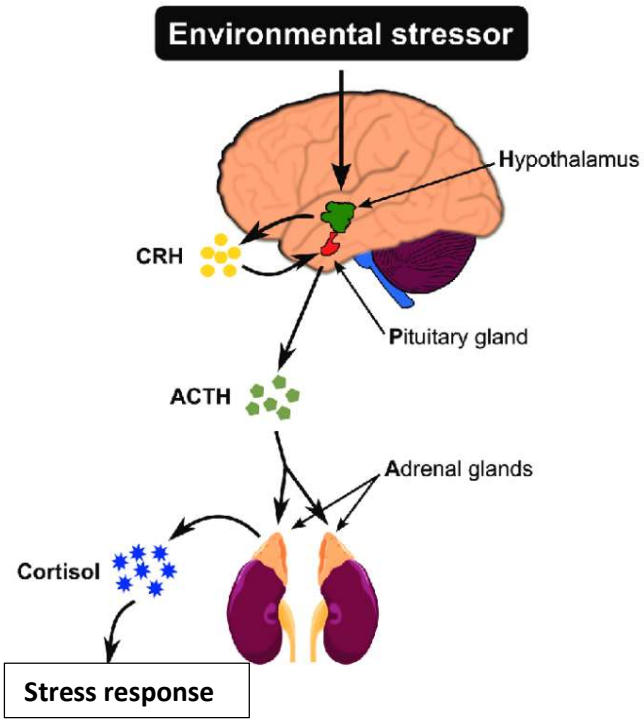

Figure 2.4 HPA (hypothalamic-pituitary-adrenal) axis. The activation of the HPA axis occurs when the brain perceives an external stressor. As a result, the hypothalamus will release corticotrophin-releasing hormone (CRH). CRH promotes the release of adrenocorticotropic hormone in the pituitary gland's anterior lobe (ACTH). In reaction to ACTH, the cortex of the adrenal glands produces glucocorticoids (cortisol in humans). Cortisol will then cause a stress reaction (Lanoix & Plusquellec, 2013).

Cortisol may travel through the BBB, reach brain cells, and generate a variety of actions, including the synthesis of glucose, facilitating information processing in the limbic neural networks involved in emotions and increasing memory formation (Saaltink & Vreugdenhil, 2014). In stressful conditions, the PVN and pituitary gland generate prolactin, a hormone that protects adult neurogenesis in the hippocampus of male and female mice by inhibiting the hypothalamus-pituitary-adrenal axis (Torner, 2016). The emotional reaction is mediated by the arcuate nucleus (ArcN). This region is distinguished by the presence of neurons that generate a peptide linked to the Agouti protein (Agouti-Related Peptide, AgRP) and are engaged in emotional states, eating behavior, and food reward processing. The consequences of stress on these cells are poorly known. An *in vivo* mouse study found that AgRP neurons in the ArcN are an important component of the neuronal circuits mediating depressive-like behaviors. Indeed, UCMS promotes AgRP neuron malfunction, with an increase in inhibitory neurotransmission and a decrease in excitatory neurotransmission, which might

be linked to depressive-like behavior (Fang et al., 2021). ArcN has also recently been identified as an adult neurogenic niche (D. A. Lee & Blackshaw, 2012).

Through interactions with neighboring neurons, astrocytes in brain areas play crucial roles in the control of metabolism and anxiety-like behavior. However, it is unclear whether astrocytes in the ventromedial hypothalamus (vmH) influence neural activity and thereby control chronic stress-induced anxiety. Liu et al discovered that vmH astrocytes are activated during chronic stress-induced anxiety. Pharmacogenetic stimulation of the Gi and Gq pathways in vmH astrocytes decreased anxiety. Furthermore, optogenetic stimulation of vmH astrocytes caused depolarization in nearby steroidogenic factor-1 (SF-1) neurons, which was reduced by N-methyl-D-aspartic acid (NMDA) receptor blocker but not by alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor blocker. These findings point to a functioning "glial-neuron microcircuit" in vmH nuclei that modulates anxiety caused by prolonged stress (Y. Liu et al., 2021).

Sun et al proposed the involvement of hypothalamic astrocytes in restraint water-immersion stress RWIS (a compound stress paradigm that combines both psychological and physical stimuli) together with interaction with neurons controlling RWIS-induced stomach mucosal injury. Following the RWIS, the expression of GFAP and c-Fos in the PVN and supraoptic nucleus rose dramatically. GFAP and c-Fos expression follow a similar temporal pattern, peaking at 1 h after the RWIS, then progressively decreasing and peaking again after 5 h, exhibiting "double-peak" features. Intracerebroventricular treatment of the astroglial toxin L-α-aminoadipate and c-Fos antisense oligo deoxy nucleotides both reduced RWIS-induced hypothalamic activation of astrocytes and neurons as well as RWIS-induced gastric mucosal injury. These findings demonstrated that a hypothalamic neuron-astrocyte "network" was implicated in RWIS-induced stomach mucosal injury (H. Sun et al., 2016).

2.4 Astrocyte plasticity in pathology

Astrocyte plasticity can evolve in reactive astrogliosis, which is a prevalent characteristic and pathological hallmark of many CNS disorders. In response to CNS damage, it consists of a finely graded continuum of molecular, cellular, and functional alterations in astrocytes.

These changes vary depending on the severity of the disease (Anderson et al., 2014) and are regulated in a context-specific manner by inter-and intracellular signaling molecules (Sofroniew, 2009a). Variable increases in GFAP expression, as well as cell body and process hypertrophy, have been reported, although astrocyte organization into specific unique domains has not changed (Wilhelmsson et al., 2006). If the initial triggering insult resolves or is removed, reactive astrogliosis in mild or moderate forms can be resolved; in this instance, cells return to a state similar to that in healthy tissue (Sofroniew, 2009a). Severe diffuse astrogliosis, on the other hand, is characterized by increased astrocytic proliferation near localized lesions, infections, or neurodegenerative regions. Although the molecular mechanisms that promote reactive astrocyte proliferation are not fully understood, epidermal growth factor, fibroblast growth factor, endothelin 1, ATP, lipopolysaccharide, and nitric oxide have all been implicated (Sofroniew & Vinters, 2010). Individual astrocyte domains are disrupted as a result of increased astrocytic proliferation, which causes intermingling and overlapping of neighboring astrocytic processes. This powerful astrocytic reaction might lead to the creation of a dense glial scar in rare situations. These structural changes are long-lasting and persist after the insult has resolved (Sofroniew, 2009a). Furthermore, mature glial scars operate as barriers to inflammatory cells, protecting nearby healthy tissue from areas of severe inflammation. By uptaking excitotoxic glutamate, generating glutathione against oxidative stress, decomposing amyloid peptides, regulating extracellular space volume and ion balance, promoting blood-brain barrier repair, and regulating CNS inflammation, reactive astrocytes can also protect CNS cells and tissue. Nonetheless, mounting data suggest that reactive astrocytes can play a role in CNS physiopathology or perhaps be the fundamental cause of it. Collagen and sulfate proteoglycans are synthesized by reactive astrocytes from glial scars,

which impede axon regrowth (Chen & Swanson, 2003). Furthermore, genetic abnormalities change the physiological functioning of astrocytes, which contributes to brain illnesses like Alexander's disease and amyotrophic lateral sclerosis (Brenner et al., 2001; Nagai et al., 2007). These opposing actions of reactive astrocytes suggest that astrocytic plasticity has two functions (Sofroniew, 2009a; Sofroniew & Vinters, 2010).

Another aspect of astrocyte plasticity in pathology is astrocyte atrophy.

Analysis of GFAP-positive astroglial profiles in the hippocampus of transgenic Alzheimer's disease mice of different ages, demonstrated that there is a generalized atrophy of astrocytes, without association with cell loss. The early stages of the illness are characterized by this atrophy, which is exhibited by a reduced surface and volume of GFAP-positive profiles. Diminished glial homeostatic function, altered synaptic connection, and early imbalances in neurotransmission can all be attributed to reduced astroglial synaptic coverage as well as general atrophic alterations in astrocytes. Recently, atrophic changes in astrocytes have been seen in a number of chronic neurodegenerative disorders, such as schizophrenia, major depressive disorder, Wernicke encephalopathy, and amyotrophic lateral sclerosis (Rossi et al., 2008; Rossi & Volterra, 2009). The early disturbances of synaptic connection in all kinds of dementia may have a similar mechanism that is represented by the degenerative/atrophic alterations in astroglia (Olabarria et al., 2010).

Even PD causes astrocytes to become dysfunctional and lose their protective properties rather than mounting reactive astrogliosis, an evolutionary conserved defensive response. So, neurological conditions are influenced by astrocyte atrophy, asthenia, and loss of homoeostatic and protective function (Ramos-Gonzalez et al., 2021; Verkhratsky et al., 2015).

2.4.1 Parkinson's Disease (PD)

PD is a progressive neurodegenerative disorder in which dopaminergic neurons in the *Substantia Nigra pars compacta* (SNpc) die. As a result, motor symptoms such as akinesia/bradykinesia, tremor, rigidity, and postural instability are caused by dopamine (DA) deficit in the striatal circuit, and more generally in extrapyramidal circuit (Schneider et al., 2017). Also, non-motor symptoms, which appear before the motor ones, are present in the human disorder. They include hyposmia, autonomic disruption, mood alterations, and REM sleep behavior disorder (Schapira et al., 2017). Pathologically, in PD patients central and peripheral nervous systems show neurodegeneration with an accumulation of α-synuclein, a constituent of the Lewy bodies (Orimo et al., 2008). Although the cause of neurodegeneration in sporadic PD is unknown, apoptosis is triggered by oxidative stress, neuroinflammation, α -synuclein toxicity, and mitochondrial dysfunction. The reasons behind selective neuronal subpopulation susceptibility to neurodegeneration are also unknown. Finally, non-neuronal cells are thought to have a role in PD pathogenesis (Gleichman & Carmichael, 2020; Miyazaki & Asanuma, 2020).

It is also unclear why the abnormality primarily affects the SN, however, it might be due to the variability of astrocytes. Growth differentiation factor 15 (GDF15) is expressed roughly 230 times more by astrocytes in the ventral tegmental area (VTA), than in the SN (Kostuk et al., 2019). Through the activation of the extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) pathways, GDF15-expressing astrocytes demonstrated neuroprotection of DA neurons generated from both rat midbrain and iPSCs (induced pluripotent stem cells; Naoi et al., 2019). Given that astrocytes unique to the VTA exhibit stronger GDF15-induced neuroprotection whereas astrocytes specific to the SN exhibit a lesser degree of neuroprotection, it may be hypothesized that α-synuclein aggregation causes more DA neuronal cell death in the SN than the VTA (Figure 2.5, J. Lee et al., 2022).

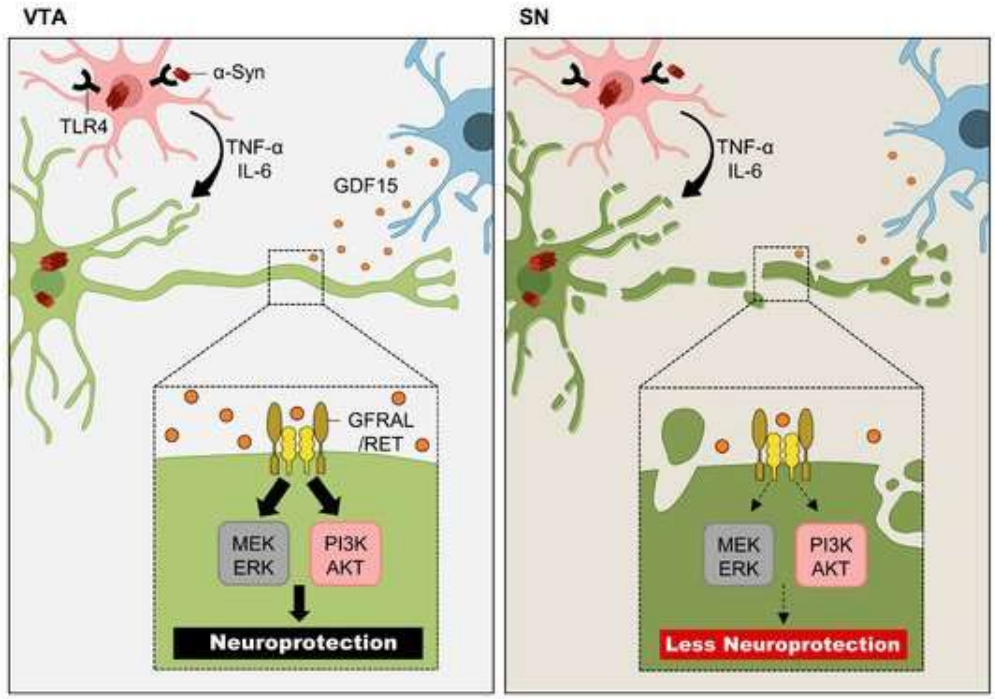

Figure 2.5. Regional astrocytic and microglial heterogeneity's effects on Parkinson's disease. The spatial variability of astrocytes and microglia may be the cause of the dopaminergic neuron loss that occurs specifically in the *Substantial nigra* (SN) during Parkinson's disease (PD). The pink, midbrain-specific microglia frequently exhibit an immune-alerted phenotype and have strong Toll-like receptor 4 expressions (TLR4). The production of pro-inflammatory cytokines including tumor necrosis factor (TNF) and interleukin-6 (IL-6) that are damaging to neurons occurs when the microglia absorb α-synuclein through TLR4. The growth differentiation factor 15 (GDF15) that astrocytes (blue, left panel) produce in the ventral tegmental region (VTA) binds to the GFRAL/RET complex (GDNF-family receptor-like/rearranged after transfection), activating it. The extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) signaling pathways that govern neuroprotection are subsequently further stimulated by the active GFRAL/RET complex. Astrocytes in SN (blue, right panel) release 230 times less GDF15, on the other hand. As a result, there is less neuroprotection and less ERK and AKT signaling activity (J. Lee et al., 2022).

Multiple neuroprotective mechanisms exhibited in astrocytes determine neuronal survival (Verkhratsky et al., 2016). The density of astrocytes in the SN is low, which may put a strain on their ability to effectively support and preserve neurons (Ramos-Gonzalez et al., 2021; von Bartheld et al., 2016). Reactive astrocytes have recently been classified as damaging A1 astrocytes and protective A2 astrocytes (Liddelow et al., 2017). In general, reactive astrocytes accumulate in the brain in pathological situations, particularly in damaged areas. However, post-mortem PD cases have been proposed to have a slight increase in astrocytes with GFAP positivity in the SNpc (McGeer & McGeer, 2008; Mirza et al., 1999). Other studies suggested that the number and shape of astrocytes in the PD brain are unaffected (Tong et al., 2015). Damier et al. (2015) reported that the density of GFAP-positive cells in the different dopaminergic areas in control brains was significantly correlated with the intensity of neuronal injury in PD brains. These findings suggest that dopaminergic neurons in locations where astrocytes are few tend to decline. The increase of reactive astrocytes in the brain of murine models of PD was significant: animals injected with 6-hydroxydopamine hydrobromide (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), toxins which cause dopaminergic neuron degeneration, were observed to have a notable increase in the expression and immunoreactivity of GFAP in the striatum and SN (Zhu et al., 2020). Although the function of reactive astrocytes is unknown, one study suggested that neuroprotective molecules such as antioxidants are mainly detectable in GFAP-positive astrocytes (Michael et al., 2011).

On the other hand, Charron et al. investigated PD-related changes in astrocytic morphology in different animal models of PD such as mice and primates, and in post-mortem human brains. They discovered that DA depletion or denervation results in a large increase in astrocyte number (+20%), volume (+60%), and the number of glutamatergic synapses contacted by $GLT1^{+}$ astrocytic contacts (+15%) in the striatum (Charron et al., 2014). The studies in animal models showed that astrocytes undergo phenotypic changes known as astrogliosis in response to DA denervation, a non-specific but

highly characteristic response that involves various morphological and molecular changes (Figure 2.6; Charron et al., 2014).

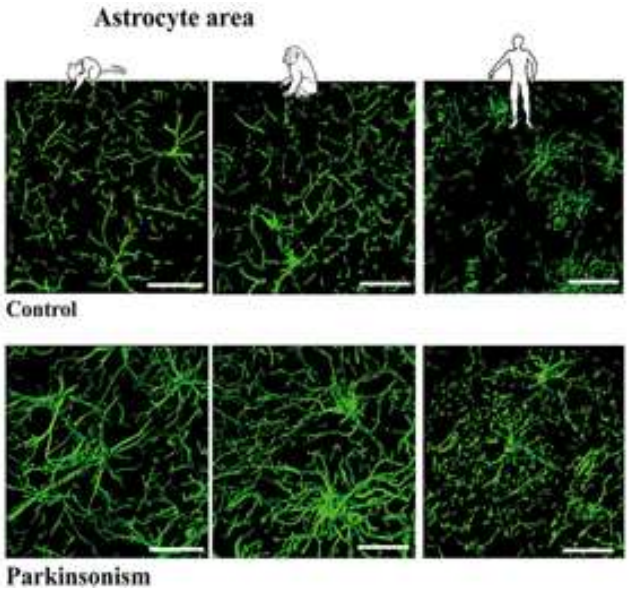

Figure 2.6 Area analysis of astrocytic processes after GFAP immunostaining and 3D-reconstruction. Representative examples of GFAP immunostaining in the striatum of 6-OHDA-treated rat and MPTP monkeys(models of PD) as well as in PD patients (Scale bar = 30 µm) (Charron et al., 2014).

In the striatum, Charron and colleagues reported an enlargement of the astrocyte cell body, an increased complexity modification of processes, and a rise in the astrocyte population, all of which are indicators of reactive gliosis, in agreement with prior investigations (Dervan et al., 2004; Gomide & Chadi, 2005; Henning et al., 2008; Même et al., 2006; Muramatsu et al., 2003). It is yet unknown how astrocytes contribute to the pathogenic development of Parkinson's disease. However, early *in vitro* studies have unequivocally shown that astrocytes maintain and safeguard the survival of dopaminergic neurons (Mena et al., 1996). Later research established functional fatigue and loss of astroglial homoeostatic support as the primary glial contributions to PD, leading to the creation of a unique description of "dysfunctional" astrocytes (Booth et al., 2017a). In contrast to earlier research, examination of *substantia nigra* post-mortem tissues from PD patients revealed a substantial reduction in astroglial marker expression compared to healthy controls (Verkhratsky et al., 2015);

these results were generally consistent with the theory linking astroglial atrophy to the illness. Astroglial atrophy, therefore, represents a distinct type of astrogliopathy (Verkhratsky et al., 2019); astroglial asthenia, atrophy, and loss of homoeostatic and neuroprotective properties were identified in aging (Grubman et al., 2019) and in other neurodegenerative and neuropsychiatric diseases (Verkhratsky et al., 2021a).

Ramos-Gonzalez et al. studied human astrocytes with pathophysiological signatures through a pure population of iPSC-derived astrocytes. They've found that PD LRRK2G2019S patient-produced astrocytes have a distinctly aberrant morphology. Differentiated astrocyte cultures from individuals with PD and health showed classic astrocyte markers (GFAP, S100β, CD49f, and EAAT2). However, the PD astrocytes have reduced area and perimeter, and high-content screening and Sholl analysis have shown that their primary and secondary processes are less complex (Ramos-Gonzalez et al., 2021).

These controversial results show how the pathogenesis of PD and astrocytes' plasticity role in this pathology is yet to be fully elucidated.

2.4.2 Major depressive disorder (MDD)

Depressed mood, lack of interest and pleasure, sleep variations, loss of energy, concentration difficulties, thoughts of death, and suicide are all symptoms of MDD, a chronic recurrent, and debilitating mental disease (American Psychiatric Association, 2013). MDD is a condition with prominent pathological astrocytic abnormalities, which include changes in astrocyte density, shape, protein expression, and membrane channel functioning, according to numerous investigations. However, astrocytic changes in MDD differ significantly from those seen in other neurological and neurodegenerative disorders (Sofroniew, 2009, Sofroniew and Vinters, 2010), since the disorder does not show astrogliosis or prominent neuronal pathology.

When compared to age-matched non-psychiatric controls, many histological studies on post-mortem brain samples have revealed significant declines in astrocyte number and density in MDD patients (D. Cotter, 2002; D. R. Cotter et al., 2001; Gittins & Harrison, 2011). Several brain regions, including the dorsolateral prefrontal cortex (D. Cotter, 2002; Rajkowska et al., 1999), orbitofrontal cortex (Rajkowska et al., 1999), subgenual cortex (Öngür et al., 1998), anterior cingulate cortex (D. Cotter, 2002), and amygdala, show a reduced astrocytic population (Altshuler et al., 2010; Bowley et al., 2002). On the contrary, an increase in glial cell density has been reported in MDD patients' hippocampal regions and dentate gyrus (Stockmeier & Rajkowska, 2004). No change has been observed in the orbitofrontal cortex and suprarenal region of the anterior cingulate cortex in late-life depressed patients (A. Khundakar et al., 2011; A. A. Khundakar et al., 2011) and in the hippocampus (Cobb et al., 2013).

These highly contradictory findings may in part be related to patient age. The density of $GFAP^+$ astrocytes in the grey matter of the dorsolateral prefrontal cortex of younger depressive patients (under 50 years of age) is much lower than in controls of similar age. Older people with late-onset depression, on the other hand, had a higher astrocytic population in the same location (Miguel-Hidalgo et al., 2000), which could be a compensatory response to neuronal loss seen in older MDD patients (Rajkowska et al., 2005).

In MDD, the size of glial nuclei appears to be changed in combination with changes in astrocyte packing density. Fibrous astrocytes in the dorsolateral prefrontal cortex (Rajkowska et al., 1999) and the grey and white matter of the anterior cingulate cortex showed bigger cell bodies and more ramified processes in depressed people committing suicide compared to matched sudden-death controls (Chana et al., 2003; Torres-Platas et al., 2011). Three additional investigations, on the other hand, found no changes in glial size in the prefrontal and orbitofrontal cortex, as well as in the hippocampus (D. Cotter, 2002; D. Cotter et al., 2005; Stockmeier & Rajkowska, 2004).

GFAP expression was also shown to be significantly altered in MDD patients. The immunohistochemical analysis quantified the area covered by $GFAP^+$ cell bodies and processes' in young, depressed subjects compared to controls revealed a predominant decrease of GFAP. The brain area analyzed were: the grey matter of the prefrontal cortex (Miguel-Hidalgo et al., 2000), the white matter of the anterior cingulate cortex (Gittins & Harrison, 2011), orbitofrontal cortex (Miguel-Hidalgo et al., 2010), CA1 and CA2 hippocampal regions (Müller et al., 2001), locus coeruleus (Chandley et al., 2013) and cerebellum (Fatemi et al., 2004).

Furthermore, the decrease in GFAP has been confirmed at both the mRNA and protein levels (Chandley et al., 2013, Fatemi et al., 2004, Miguel-Hidalgo et al., 2000, Webster et al., 2005), and it is linked to age and the onset of depression. GFAP protein levels are significantly lower in depressed patients under 60 years of age compared to age-matched controls, with no difference observed between older MDD patients and their controls (Si et al., 2004). In contrast, an increase of GFAP occurred in the dorsolateral prefrontal cortex in late-onset MDD patients (Davis, 2002; Miguel-Hidalgo et al., 2000; Vasile et al., 2017).

Third-line research using postmortem brain tissue reveals that individuals with mood disorders have abnormalities in astrocyte gene transcription and protein expression. For instance, numerous astrocyte function-related proteins, like glutamine synthetase, glutamate transporters, and even gap junction proteins, have decreased gene and protein expression in depressed individuals (Bernard et al., 2011). Glutamate synthetase, which is linked with astrocytes, converts glutamate into glutamine, and glutamate transporters, which indicate astrocyte activity in glutamate transmission (Norenberg & Martinez-Hernandez, 1979). Patients with depression had reduced levels of glutamine synthetase expression in their dorsolateral prefrontal cortex, premotor cortex, and amygdala (Sequeira et al., 2009).

Aquaporin-4 (AQP4), a protein mostly found in astrocytic endfeet, has recently been shown to have reduced expression levels in MDD patients compared to non-psychiatric control participants (Rajkowska et al., 2013). The lowering of AQP4 may affect a variety of astrocytic processes, including glutamate turnover, synaptic plasticity (Nico et al., 2001), and maintenance of the blood-brain barrier (X. Zhou et al., 2019).

Mounting evidence points to astrocytes' direct involvement in the modulation of complex emotions and metabolic control (Sweeney et al., 2016). Through the Kir4.1 potassium channel, which is only expressed in astrocytes, astrocytes in the lateral habenula influence depressed behavior in rats (Cui et al., 2018).

The hippocampus is a brain region particularly involved in MDD as well as the impact of antidepressant medications (Nestler et al., 2002).

In MDD patients, astrocyte density in the hippocampus is significantly reduced, and this corresponds substantially with the illness prognosis. Furthermore, the connection between astrocyte densities in different subfields of the hippocampus and illness prognosis varies (Cobb et al., 2013, 2016). The pursuit of a mechanistic understanding of these varied vulnerabilities among various astrocytic subpopulations of the hippocampus demands meticulous characterization in a tractable model system like mice. Virmani et al (2020) employed the Cmus mouse model to examine its impact on the cell densities and shape of hippocampus astrocytes from distinct subfields (CA1, CA3, hilus, and ML). They discovered that cell density was dramatically reduced in specific hippocampus subfields, with the rostral region being particularly sensitive. Furthermore, the molecular layer was discovered to be the most impacted sector in terms of morphological traits, followed by the hilus. CA3 astrocytes were significantly less impacted, while CA1 astrocytes were substantially unaffected. These findings support previous findings in MDD patients that astrocytic subpopulations from various hippocampus subfields are variably sensitive to MDD pathology (Virmani et al., 2021).

It is also known that hippocampus has functional segregation, this idea was supported by the finding that astrocyte cell density in CA1 and DG of the front hippocampus was reduced in sad female monkeys (Willard et al., 2013).

Intriguingly, in Virmani et al (2020) the stressed mice showed a lower density of SOX 9 and S100-immunopositive cells in rostral (Bregma 1.46 to 1.94) coronal sections of HP, which correspond to the dorsal hippocampus, whereas in sections from the more caudal (ventral) hippocampus, cell density remained unchanged, except for SOX9-expressing cells in the molecular layer. This is intriguing, considering that the hypothalamus, the master regulator of stress reactions, innervates the ventral hippocampus more densely (Virmani et al., 2021).

2.4.2.1 The involvement of hypothalamic astrocytes in MDD

Anxiety and depression are also associated with vmH. Studies have revealed that cats with anxiety-like symptoms have considerably higher vmH brain activity (Adamec, 1998) while inhibiting vmH glutamate signals can dramatically lessen anxiety in animals (Cheung et al., 2015), indicating that the vmH is involved in the control of mood disorders.

Reduction in astrocytic transport related to the development of depressive behaviors extends not only to cortical areas of the brain but also to subcortical structures that have long been known to significantly contribute to the pathophysiology of stress effects and depression.

In mice with depression-like behaviors caused by early life stress, the immunostaining of GLT1 astrocyte transporters and the thickness of astrocyte processes are reduced in the corticotrophin-releasing- factor-expressing dorsal-medial neurons of the hypothalamus, effects that are consequent of increased excitability of the neurons (Gunn et al., 2013).

Because early life stress (ELS) also involves the activation of hormonal responses mediated by the hypothalamic-pituitary-adrenal axis, some study has focused on hypothalamic cellular and

neurotransmitter dysfunction, as well as astrocyte involvement. ELS inhibited the capacity of neurosteroids to attenuate overactivation in mature hypothalamic neurons. This impact is due to an increase in glutamatergic activation, which is caused in part by decreased astrocytic control of extracellular glutamate levels (Gunn et al., 2013). This modification was accompanied by morphological alterations in GFAP-immunoreactive astrocyte processes as well as a decrease in the positivity of astrocytic glutamate transporters (Gunn et al., 2013, Miguel-Hidalgo, 2022).

2.5 Outline of the study

Aging is defined as the time-dependent deterioration of a living organism's physiological integrity. However, the brain is relatively resistant to this process, as neuronal and glial cell numbers appear to be preserved in many brain areas during physiological aging. Nonetheless, certain areas are more vulnerable to age-related diseases (Verkerke et al., 2021). The SN, one of the basal ganglia nuclei of the ventral midbrain, is particularly sensitive to aging. The SN can be divided into two functional and morphological regions: a dorsal stratum called the *pars compacta* (SNpc), which is populated by dopaminergic neurons (expressing tyrosine hydroxylase, TH+), and a larger ventral region called the *pars reticulata* (SNpr), which contains GABAergic and dopaminergic neurons (Sonne et al., 2022). Degeneration of TH+ neurons, specifically in SNpc, is thought to be a hallmark of Parkinson's disease (PD), with age being the most important risk factor for its development (Collier et al., 2011). Age-related neurodegeneration is a complex process that includes, in addition to neuronal cells, other neural cells in the SN environment, such as astroglial cells, and is fastened by other stimuli such as stress. Astrocytes are a highly heterogeneous cellular group among glial cells in terms of molecular, morphological, and functional characteristics. They play critical roles in brain homeostasis and function, such as providing trophic support to neurons, participating in synaptic function and plasticity, mediating neurotransmitter uptake and recycling, and maintaining the blood-brain barrier (Spampinato et al., 2020; Verkhratsky & Nedergaard, 2018). Aside from these homeostatic functions, astrocytes can undergo profound genetic, morphological, and functional changes in response to a variety of endogenous and exogenous stimuli signals (Reid & Kuipers, 2021). Given the wide range of functions performed by astrocytes, age-related and stress-related morphofunctional changes may have a significant impact on brain activity functioning (Verkhratsky et al., 2021b). Interestingly, astrocytes' morphological structure changes in response to aging in a regional and sub-regional specific manner (H. Bondi et al., 2021; Rodríguez et al., 2014). This morpho-functional heterogeneity in astrocyte response to aging, in part different from stress, may explain regional vulnerability in

specific brain regions. We investigated structural changes in astrocytes in SNpc and SNpr of the murine brain during aging and in SNpc after UCMS, two risk factors for PD.

Moreover, chronic stress is also a major risk factor for MDD. Depression is currently the most common mental condition in the world (World Health Organization), becoming more common as people become older, increasing the possibility to develop neurodegenerative disorders. Stress is described as an internal dynamic equilibrium condition that is endangered (or perceived to be threatened) by external or internal stimuli (Kazakou et al., 2022). The extremely conservative regulatory neuroendocrine system, known as the "stress system", is triggered to establish homeostasis by coordinated interaction between the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (Kazakou et al., 2022). In this system, the role of the hypothalamus is widely recognized (Dolotov et al., 2022). The effect of chronic stress on glial cells, in particular on hypothalamic astrocytes, represents a subject that is still little studied, but of great interest (Cvijetic et al., 2017), Given the importance that astrocytes play in the functioning of the CNS, characterize the stress-induced alterations on these cells represents a fundamental element for both improve understanding of neuropsychiatric diseases, but also to develop new pharmacological approaches in the treatment of these pathologies.

This thesis work aims to contribute to broadening the knowledge about the possible alterations induced by chronic stress on the morphology of astrocytes.

In recent years, by using morphometric analysis, our group discovered a remarkable region/subregion-specificity in the response of astrocytes to aging and environmental stimuli (Bondi et al., 2021). Based on these premises, herein we investigated, using a morphometric approach, morphological changes occurring in GFAP+ astrocytes in response to unpredictable chronic mild stress (UCMS) in C57BL/6 male mice. We focused our study on hypothalamus subfields: PVN and ArcN involved in MDD.

2.6 Materials and methods

Animals. C57BL/6 male mice were evaluated at three ages: young (4-6 months, n = 6); middle-aged (14-17 months, n= 6 SNpr n=8 SNpc); old (20-24 months, n=6). For stress studies, a standardized UCMS protocol was utilized (Cuccurazzu et al., 2013). Briefly, C57BL/6 male mice were analyzed at 8 months of age after 12 weeks of chronic stress. Stress-induced depressive-like behavior was demonstrated by anhedonia and increased immobility in the forced swim test. UCMS (n =4), and control (CTR, n=4) mice were used for such morphometric studies.

Mice, kept in a cage with access to water and food ad libitum, were housed in a light- and temperature-controlled room in high-efficiency particulate air-filtered Thoren nits (Thoren Caging Systems) at the University of Piemonte Orientale animal facility. Animal care and handling were performed following the Italian law on animal care (D.L. 26/2014), as well as European Directive (2010/63/UE) and approved by the Organismo Preposto al Benessere Animale of University of Piemonte Orientale, Novara, Italy.

Tissue preparation. Mice were deeply anesthetized and transcardially perfused with saline solution and then with 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer, pH 7.4. After PFA perfusion, brains were rapidly removed, post-fixed in PFA for 24 hours, dehydrated in 15% sucrose for 24 hours, and then transferred in sucrose 30% for at least 24 hours. Then, 40 µm-thick coronal sections were cut with cryostat and collected in cryoprotectant solution at -20°C until use.

Immunohistochemistry and image acquisition. The different brain areas included in the analysis were delineated according to the Paxinos Mouse Brain Atlas (Paxinos & Franklin, 2004). From a complete series of one in 8 brain sections throughout the entire DG, 3 corresponding sections were selected from Bregma -2.52 to -3,70 for analysis of astrocytes in the SNpc. For astrocytes in the SNpr,

4 corresponding sections/mice located from Bregma -2.48 to 4.04 mm were analyzed. While, for the hypothalamus: ArcN, from Bregma -1,22 to -2,92 mm, PVN from Bregma -0,46 to -2,18 mm.

Staining was performed on free-floating sections. Endogenous peroxidase activity was blocked with 0.3% H_2O_2 in 0.1 M tris-buffered saline (TBS) for 10 minutes. Sections were subsequently treated at 4° C for 1 hour in a blocking solution containing 10% horse serum (HS), 0.3% Triton X-100 in 0.1 M TBS, pH 7.4, and incubated with goat polyclonal anti-GFAP antibody (cod. SC-6170, 1:100; Santa Cruz Biotechnology) in 2% HS, 0.1% Triton X-100 in 0.1 M TBS, overnight at 4°C. Then, sections were incubated with biotinylated horse anti-goat secondary antibody (cod. BA-9500, 1:200; Vector Laboratories) in 2% HS, in 0.1 M TBS for 1.5 hours at 4 °C. Labeled cells were visualized using the ABC system (cod. PK-6100, Vectastain Elite; Vector Laboratories) with 3,30-diaminobenzidine as chromogen (cod. D3939; Sigma-Aldrich), and nuclei were counterstained with hematoxylin (cod. H3404; Vector Laboratories). Images were acquired using an LSM700 laser-scanning confocal microscope (Carl Zeiss, Le Pecq, France) with 20X magnification (objective: EC Plan-Neofluar 20x/0.5 M27) with an image matrix of 1024 x 1024 pixels, a pixel scaling of 0.313 x 0.313 mm, and a depth of 8 bit. Confocal images were collected in Z-stacks with a slice distance of 0.4 mm.

Three-dimensional astrocyte and neurons reconstruction and quantitative morphometry. The image stacks were imported into FIJI software (version 1.52), where three-dimensional (3D) reconstructions were performed with the Simple Neurite Tracer plugin (Longair et al., 2011) by an investigator blinded to the animal group. For the first study, only astrocytes that exhibited fully intact GFAP-immunostained processes were chosen for reconstruction (n = 12 astrocytes per animal, per region). Morphological analysis was performed on 3D reconstructions of astrocytes by the Sholl analysis plugin (Ferreira et al., 2014), using default settings (enclosing radius cutoff = 1 intersection, Sholl method = linear) with radii increasing by 5 μm. The Sholl intersection profile (SIP) counts the number of intersections between the astrocytic process and concentric spheres emanating from the

center of cell soma. Some morphometric descriptors have been also included in our analysis (i.e., the total number of intersections and radius of the highest count of intersections). Moreover, 3D reconstructions were exported as SWC files and analyzed with the L-measure tool to evaluate additional morphometric features such as the number of processes, total length, and maximum process extension (Scorcioni et al., 2008).

Statistical analysis. All statistical analyses and data visualizations were performed in RStudio version 1.2.5 (RStudio Team, 2015) using R version 3.5.1 (R Core Team, 2016) and the packages ggplot2 (Wickham, 2016), dplyr (Wickham et al., 2018), lme4 (Bates et al., 2014), and multcomp (Hothorn et al., 2008). For statistical analysis of morphological parameters, a linear mixed-effects model was used to model the data of each parameter, with age as a fixed effects and animal as a random effect (with lmer package). Using this approach, it is possible to overcome the dependency of repeated observations within each animal (Bortolotto et al., 2019). The presence of significant differences was tested using a one-way analysis of variance. SIPs were analyzed by mixed-effects nested analysis of variance approach with an individual animal as random effect and radius nested within astrocytes nested within age. Statistical analysis of morphological differences between brain areas within each age group was performed using mixed-effect models with post hoc Tukey's honestly significant difference (HSD) correction (using multcomp package). For all analyses, significance was defined as $p < 0.05$. Data are presented as mean +/- SEM.

2.7 Results

Aging specifically affects astrocytic complexity in SNpc but not in SNpr. First, we performed three-dimensional (3D) reconstruction of GFAP immunolabeled astrocytes in the SNpc (figure 2.7 A). The Sholl intersection profile (SIP) gives a one-dimensional representation of the complexity of the 3D cell structure by counting the number of intersections between astrocytic branches and concentric spheres of increasing radius emanating from the centre of astrocyte soma. This method allows an intuitive comparison of the cell morphological complexity. In middle aged mice, we observed a significant increase in the number of intersections at 10 –25 µm distances from the soma, as compared to young mice. Moreover, there is a sharp increase in the number of intersections at 0–45 µm radii in old mice as compared to both young and middle-aged mice (figure 2.7 B). Furthermore, the radius of highest count of intersections was significantly increased in Middle-aged and Old groups, indicating that their astrocytes reached maximum complexity at higher distance from soma compared to younger animals (13.47 ± 5.15µm in Young; 16.09 ± 4.37 µm in Middle-aged; 17.01 ± 4.33µm in Old; p=0.0127 Young vs Middle-aged; p=0.0021 Young vs Old; p=0.5 Middle-Aged vs Old). The results of the Sholl analysis suggest that astrocytes might gain complexity with aging. To confirm the increase in astrocyte complexity with aging in the SNpc, we performed a quantitative analysis of morphology. By this approach, we measured the number of branches, the maximum process length, and the sum of the process lengths of each individual astrocyte in SNpc (figure 2.7 C). The number of branches shows a significant increase in an age-dependent manner (22.14 ± 6.92 in Young; 32.79 ± 10.28 in Middle-aged; 46.28 ± 10.55 in Old; p=0.008 Young vs Middle-aged; p<0.001 Young vs Old; p=0.0011 Middle-Aged vs Old). The total length of processes also increased with aging (358.46 ± 130.56µm in Young; 541.64 ± 166.01µm in Middle-aged; 777.12 ± 167.81µm in Old; p=0.0009 Young vs Middle-aged; p<0.0001 Young vs Old; p=0.0001 Middle-Aged vs Old). The maximum process length was significant longer in Middle-aged and Old groups in comparison

to younger mice (45.47 ± 9.45µm in Young; 52.99 ± 10.57µm in Middle-aged; 57.78 ± 9.29µm in Old; p=0.0036 Young vs Middle-aged; p=0.0001 Young vs Old; p=0.064 Middle-Aged vs Old).

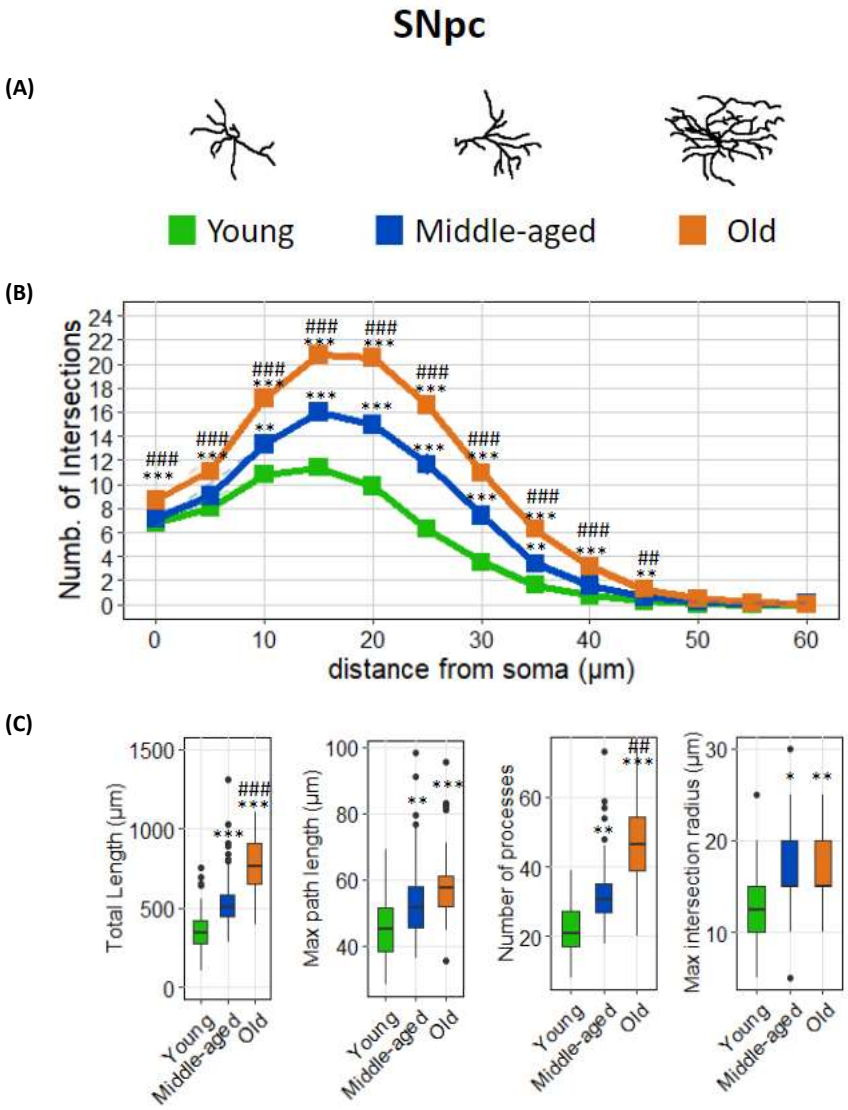

Figure 2.7. **Aging specifically affects astrocytic complexity in SNpc A.** Representative 3D reconstructions of astrocytes in SNpc. **B.** Sholl Intersection Profile: data are presented as mean ± SEM ** p < 0.01, *** p < 0.001 vs Young; ## p < 0.01, ### p < 0.001 vs Middle-aged (Nested-ANOVA on linear mixed-effect model). **C**. Morphometric parameters: the heavy line represents the sample median, the box marks the range from 25% to 75% of the data, limits of vertical lines (whiskers) represent the min and max values, excluding outliers (dots). * p < 0.05, ** p < 0.01, *** p < 0.001, ## p < 0.01, ### p < 0.001 vs Middle-aged (ANOVA on linear mixed-effect model).

Although SNpc and SNpr are anatomically and functionally different, these regions are intimately connected. Indeed, SNpc dopaminergic neurons extend their dendrites into the SNpr and influence the activity of GABAergic neurons. We performed 3D reconstruction of GFAP+ astrocytes in the

SNpr (figure 2.8 A) and, unlike what we observed in adjacent SNpc, the analysis of SIP (figure 2.8 B) and the other morphological parameters (figure 2.8 C) does not reveal any significant change in the number of intersections with aging.

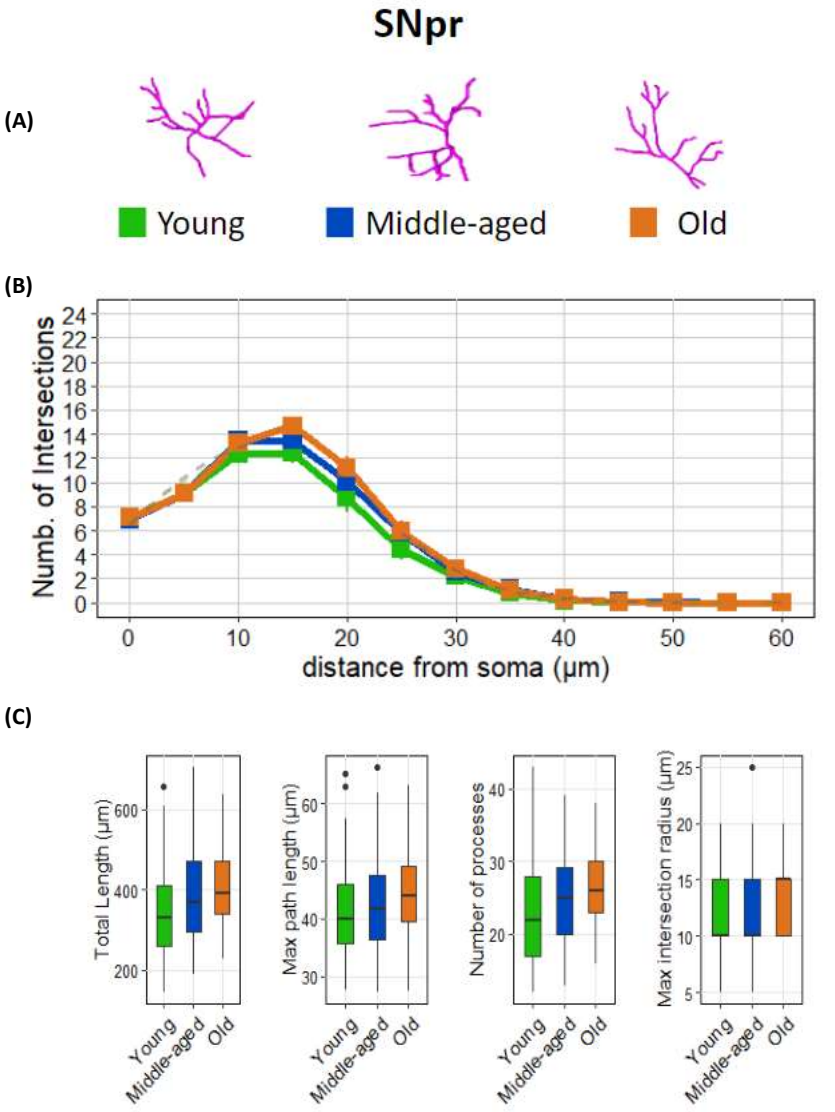

Figure 2.8 Aging does not affect astrocytic complexity in SNpr A. Representative 3D reconstructions of astrocytes in SNpr. **B**. Sholl Intersection Profile: data are presented as mean ± SEM. (Nested-ANOVA on linear mixed-effect model). **C**. Morphometric parameters: the heavy line represents the sample median, the box marks the range from 25% to 75% of the data, limits of vertical lines (whiskers) represent the min and max values, excluding outliers (dots).

Chronic stress is one of the main risk factors for PD. So we wanted to understand the effect of chronic stress on the astrocytes of SN subregions, the main area involved in PD damages.

In particular, we analyzed the 3D reconstructions of the astrocytes of the animals subjected to the UCMS treatment for 12 weeks and which, subsequently, showed the appearance of a depressive-like phenotype (Cuccurazzu et al., 2013). We compared SNpc astrocytes of UCMS mice and the control ones.

In SNpc with UCMS, unlike what we observed with aging, morphological complexity of astrocytes was not different in the two experimental groups (figure 2.9), suggesting no effect of UCMS in this brain subregion.

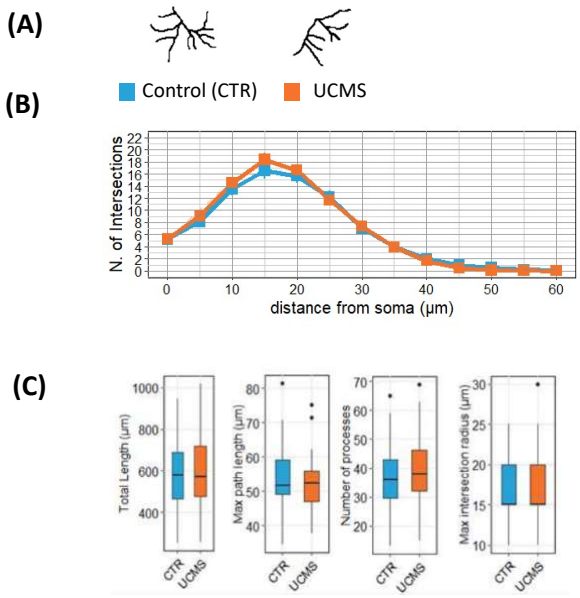

Figure 2.9 Chronic stress has not effect on astrocyte morphological complexity in SNpc A. Representative 3D reconstructions of astrocytes in SNpc after chronic stress (UCMS) or under control conditions (CTR). **B**. Sholl Intersection Profile: data are mean ± SEM (Nested ANOVA on linear mixed-effect model). **C**. Morphometric parameters: the heavy line represents the sample median, the box marks the range from 25% to 75% of the data, limits of vertical lines (whiskers) represent the min and max values, excluding outliers (dots).

Chronic stress induces an increase in the morphological complexity of astrocytes in the arcuate nucleus and paraventricular nuclei. Then, we focused our attention on the hypothalamus. We evaluate the effects of chronic stress characterizing the morphology of GFAP+ astrocytes from the ArcN and PVN, hypothalamic nuclei involved in stress response (Kishi et al., 2006; Pikkarainen & Pitkänen, 2001; Veena et al., 2011). In particular, we analyzed 3D reconstructions of the astrocytes and Sholl intersection profiles (SIP) were compared in stressed mice (UCMS) versus unstressed, control animals (CTR). In ArcN the SIPs of astrocytes in CTR and UCMS mice were significantly different. In particular, UCMS mice have astrocytes with greater complexity at distances of 5–25 μm from the soma, compared to the CTR group (Figure 3.0 b). The total number of the sum of the intersections was significantly increased in the UCMS group compared to the control group (CTR: 47.73 ± 15.51; UCMS: 82.23 ± 36.22; p.value: 0.00076), as was the mean of intersections (CTR: 6.85 ± 2.14; UCMS: 10.10 ± 2.80; p.value: 0.0005). Finally, a significant increase is observed in the UCMS group for the number of maximum intersections in comparison to the control (CTR: 11.83 ± 4.19; UCMS: 18.37 ± 5.23; p.value: 0.002), while there were not significant differences in the radius and the radius where the maximum number of intersections occur (Figure 3.0 b). Regarding additional morphometric parameters taken into consideration (Figure 3.0 c), we observed an increase in the total process length in astrocytes belonging to UCMS mice compared to CTRs (CTR: 330.07 ± 105.77 μm; UCMS: 569.21 ± 254, 30 μm; p.value: 0.0079). Furthermore, exposure to UCMS induced an increase in the number of processes (CTR: 19.85 ± 6.72; UCMS: 32.05 ± 8.0; p.value: 0.0001). The results obtained demonstrated, for the first time, that UCMS induces an increase in the morphological complexity of astrocytes in the ArcN.

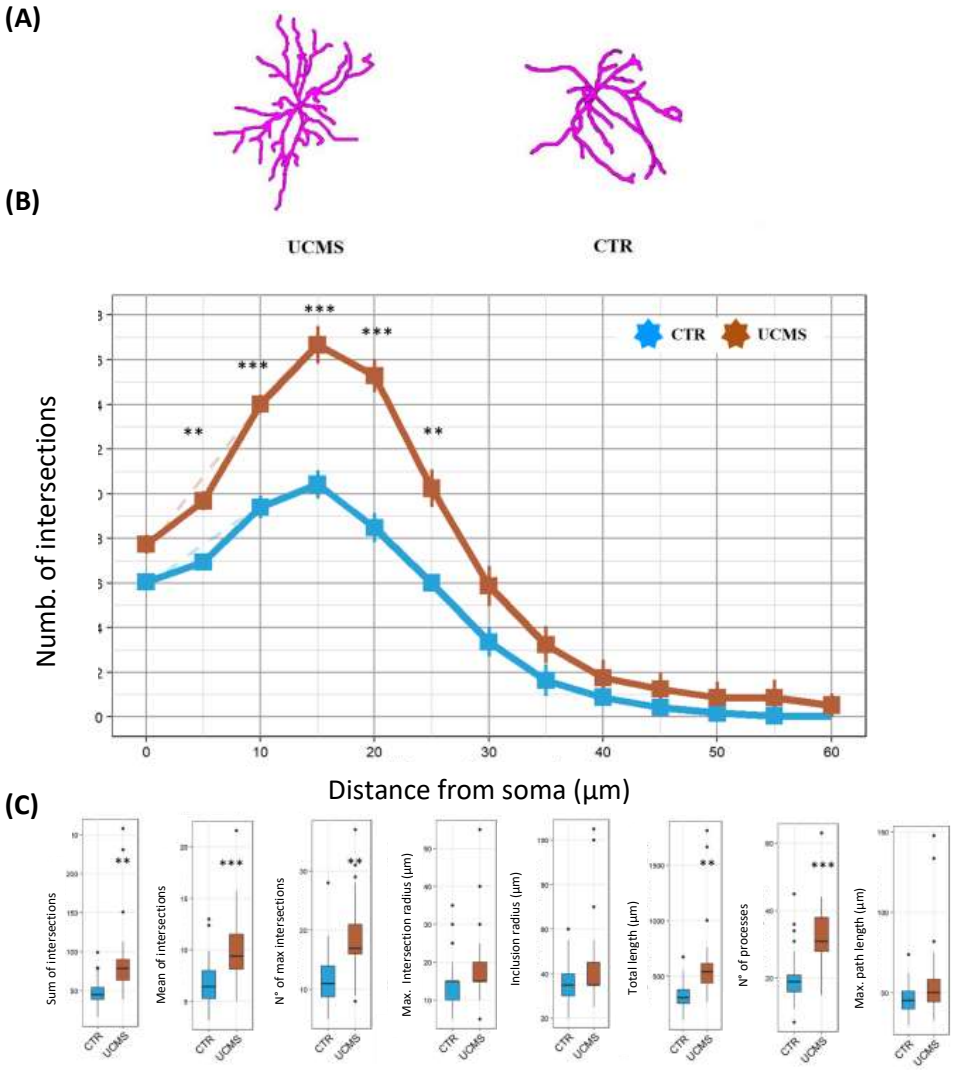

Figure 3.0: Arcuate nucleus (ArcN) astrocytes show increased morphological complexity in mice subjected to chronic stress. A. 3D reconstructions representative of the morphology of astrocytes in the ArcN of mice subjected to UCMS treatment (UCMS) and control mice (CTR). **B**. Analysis of the intersection profiles of the Sholl analysis. Data are represented as mean ± S.E.M. ** p <0.01, *** p <0.001; One-way nested ANOVA test performed on a linear mixed effects model, with the animal as a random effect and the treatment as a fixed effect. **C**. Analysis of the parameters deriving from the Sholl analysis and of the quantified morphometric parameters. The data is represented through a box and whiskers chart. Each box (box) represents the interval between the first and third quartiles, while the line inside the box indicates the median. The vertical lines, the whiskers, describe the values lower than the first quartile and higher than the third quartile, the outliers instead are represented with a point. ** p <0.01, *** p <0.001; one-way ANOVA test performed on linear models with mixed effects, the animal as a causal effect and treatment as a fixed effect.

We continued with the analysis of the astrocytes present in the PVN (Figure 3.1 a). The comparison of SIP obtained from the astrocytes of CTR and UCMS mice showed a significant increase in astrocyte complexity at distances of 5–20 µm from the soma in the UCMS group compared to the CTR group (figure 3.1 b). In UCMS mice astrocytes had significantly greater mean of intersections (CTR: 7.02 ± 1.62; UCMS: 9.39 ± 3.246; p.value: 0.024) and maximum number of intersections

(CTR: 11.96 ± 3.53; UCMS: 15.90 ± 5.24; p.value: 0.0332) with respect to the CTR group. Furthermore, the sum of the intersections and the radius of inclusion show a trend to increase, which however does not reach significance, in the UCMS group with respect to astrocytes of CTR mice. There is no significant difference in radius with the maximum number of processes (Figure 3.1 c). Astrocytes in stressed mice, compared with CTR mice, also showed a significant increase in morphometric parameters such as the total length of processes (CTR: 275.74 ± 95.72 μm; UCMS: 401.85 ± 159.65 μm; p.value: 0.0416), the number of processes (CTR: 20.67 ± 5.61; UCMS: 28.33 ± 9.81; p.value: 0.0169) and maximum extension of processes (CTR: 36.85 ± 7.51 μm; UCMS: 43.39 ± 8.12 μm; p.value: 0.0151).

In conclusion, the results confirmed that chronic stress induces an increase in complexity of the arborization of astrocytes in both ArcN and PVN.

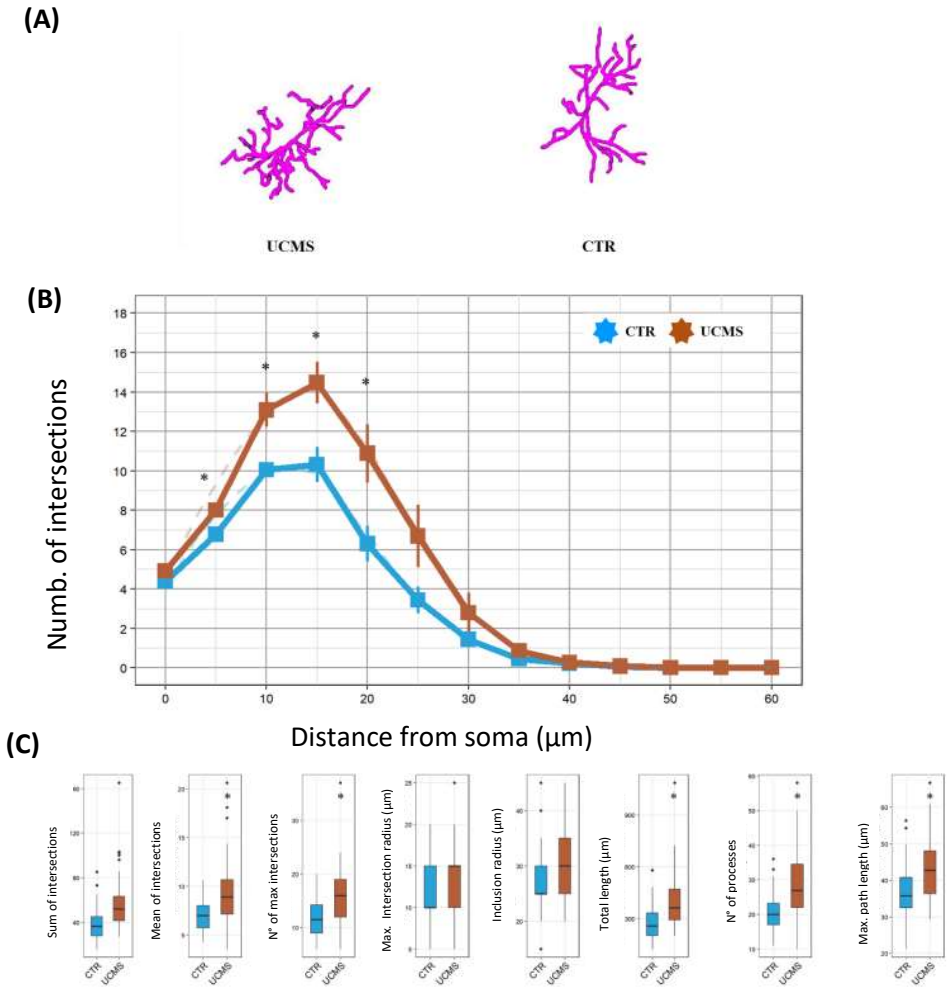

Figure 3.1: Astrocytes in the paraventricular nucleus (PVN) show increased morphological complexity in mice subjected to chronic stress. **A**. Representative 3D reconstructions of astrocyte morphology in the PVN of UCMS-treated mice (UCMS) and control group mice (CTR). **B**. Analysis of the intersection profiles of the Sholl analysis. Data are represented as mean ± S.E.M. ∗ $p < 0.05$; One-way nested ANOVA test performed on a linear mixed effects model, with the animal as a random effect and the treatment as a fixed effect. **C**. Analysis of the parameters deriving from the Sholl analysis and of the quantified morphometric parameters. The data is represented through a box and whiskers chart. Each box (box) represents the interval between the first and third quartiles, while the line inside the box indicates the median. The vertical lines, the whiskers, describe the values lower than the first quartile and higher than the third quartile, the outliers instead are represented with a point. ∗ $p < 0.05$; one-way ANOVA test performed on linear models with mixed effects, the animal as a causal effect and treatment as a fixed effect.

2.8 Conclusions

Our study of brain plasticity carried on focusing on astrocytes morphology in response to aging and stress. Previous research has shown that astrocytes undergo considerable morphological and functional change as they age. Aging has been linked to decreased astroglial coverage of synapses and synaptogenic factor production, decreased astroglial metabolic supply to neurons, decreased astroglial-vascular connection, and decreased ability to mount reactive astrogliosis, among other alterations (as recently reviewed by Verkhratsky et al., 2021). Overall, these findings support the notion that astroglial loss of homeostatic function, or asthenia, rather than enhanced responsiveness, may prevail throughout brain aging.

It is well-accepted that physiological aging is not connected with changes in the number of astrocytes in several CNS areas (Long et al., 1998; Verkhratsky et al., 2021c). In contrast, morphological astrocytic alterations throughout age have been observed, with both increased and reduced size and complexity recorded, with the majority of investigations utilizing GFAP for immunolabeling (Verkhratsky et al., 2021c).

Next-generation sequencing methods have enabled a thorough study of the transcriptional alterations that occur particularly in astrocytes throughout aging. Such efforts lead to the hypothesis that distinct brain areas are more susceptible to aging-induced changes in astrocytic gene expression and function (Boisvert et al., 2018).

Rodríguez et al. (2014) previously studied the subregional morphological alterations of hippocampus GFAP+ astrocytes throughout aging. These researchers discovered an age-dependent hypertrophy of GFAP+ astrocytes in DG, as evidenced by increased surface, volume, and somata size.

The morphological research of Bondi et al., (2021) gives further precise information on the increased morphological complexity of astrocytes with aging, notably in GCL and ML. Their investigation was

also extended to the hilus. In this study, astrocyte complexity remained impressively steady in middle-aged (14-mo) versus young adult mice (6 mo), with no change seen between the two experimental groups. Bondi et al also explored outside of the DG, in the CA1 area the stratum Lacunosum Molecular (sLM), where astrocytes interact with hippocampal interneurons and EC afferent fibers (Witter, 2013) founding that sLM astrocytes from 14-mo mice had a more complicated structure than those from 6-mo animals (H. Bondi et al., 2021).

Although this is a developing field, current and future knowledge on the regional specificity of age-related glial changes may aid in understanding why discrete brain regions are more vulnerable to synaptic and neuronal dysfunction, aging, and age-related neurodegenerative disorders, as seen in Parkinson's disease with SN (Burke & Barnes, 2006).

Morphological changes have been seen in human parkinsonian SN, in particular glial scarring, thought to follow neuron loss (Forno LS., 1996) and might constitute a barrier to axon regrowth implicating it in the disease process (Knott et al., 1999).

In our study we focused on aging and stress as risk factors of PD, we analyzed astrocytes in SN, the main brain region interested in the pathology.

In particular, we reported a subregion-specific structural reorganization of SN astrocytes during mouse aging. We found that GFAP+ astrocytes in the SNpc, but not in the SNpr, alter morphological complexity with age in the midbrain. These structural alterations were measured in mice aged 14-17 months (middle age group) and 20-24 months (old age group).

We conducted a morphometric investigation of astrocyte structural characteristics in the SNpc and SNpr subregions. GFAP immunolabeling was used to create 3D reconstructions of astrocytes for this purpose. Even if GFAP is mostly expressed in mature astrocytes' bigger cell processes and not in fine processes such as peri-synaptic processes, this labeling strategy for comparative investigation of

important morphometric aspects of astrocytes is already adopted (H. Bondi et al., 2021). Our morphometric study verified that GFAP+ astrocytes exhibit a substantial rise in morphological complexity only in the SNpc but not in the SNpr during aging.

GFAP protein and mRNA levels in astrocytes rise with age in several CNS areas, implying a link between age-related astrogliosis and neurodegeneration (Wyss-Coray, 2016). In Alzheimer's disease, glial proteins are selectively upregulated in the cortex. Age-related increase in astrogliosis in the brain was connected with increased nitric oxide release in 'senescence-accelerated mice' (J. Han et al., 2010).

While investigations on astroglia in experimental animals or PD brains have shown contradictory results (Barcia et al., 2011; Kanaan et al., 2008). Following MPTP injection, the number of GFAP immunoreactive glia increased in the *substantia nigra* of nonhuman primates (Barcia et al., 2011), indicating that astrocytic activation may be important in pathogenesis. However, among investigations on autopsied tissues from Parkinson's disease patients, some show little astrogliosis (Banati et al., 1998; Mirza et al., 1999), while others show extensive astrogliosis (Michel et al., 2016). Mirza et al. (2000) proposed that the absence of astrogliosis may be suggestive of a distinct inflammatory process in Parkinson's disease. Because the active pathological process in people cannot be traced, neuropathological investigation of the aged midbrain can improve knowledge of Parkinson's disease etiopathogenesis. Despite this, just a few research have been published. Kanaan et al. (2010) demonstrated the presence of structural alterations in astrocytes without an increase in their quantity in aged rhesus monkeys (Kanaan et al., 2010). Jiothy et al. (2015) discovered that in younger participants, the glia had long slender processes, however, in the elderly, few glia with short and stubby processes and mildly strong staining seemed to form clusters. As GFAP expression did not increase with age, this implies a progressive morphological transition without frank astrogliosis (Jyothi et al., 2015b).

While the overall result of GFAP expression in this study does not suggest frank astrogliosis with aging, it does suggest that the *pars compacta* are vulnerable to neurodegeneration. We have to consider that the two different sections of SN have different roles and connections. SNpr has connections relating to the movement of the eyes and the ability to learn and think. The cells in this area release the chemical GABA that inhibits activity in the brain cells. While SNpc contains neurons releasing dopamine. This section has connections that involve motor control, emotions, the ability to learn, and risk judgment (Zhang, Larcher, et al., 2017). These two subregions differently react to environmental stimuli, as we see in aging. Age-dependent morphological changes in GFAP+ astrocytes in the SNpc might explain changes in astroglial activities and the neuronal death proper of the area in PD.

Other analyses should be performed to find biochemical/molecular correlates that may link structural remodeling with functional alterations.

No published studies have examined the aging of astrocytes in the SNpr. The current study is the first to perform a thorough examination of the two SN subregions in mice of various ages. To expand our investigation into subregion-specific astrocytic changes associated with aging, we examined SNpc and SNpr astrocytes at each age. Interestingly, the morphological profiles of astrocytes in SNpc and SNpr were relatively identical in young mice, but as the animals aged, the profiles increasingly diverged, reaching their highest divergence in senior animals. Overall, our data support the idea that astrocyte responses to aging varied amongst SN subregions.

Another peculiar result is in SNpc with UCMS, unlike what we observed with aging, arbor complexity of astrocytes was not different in the 2 age groups, suggesting no effect of UCMS in this SN subregion.

Astrocytes become reactive in response to injury or other pathological situations. Upregulation of GFAP, the main component of astrocyte intermediate filaments, has been identified as a trait of reactive astrocytes in primates and rats (Burda & Sofroniew, 2014; Ceyzériat et al., 2018). GFAP immunostaining has demonstrated a rise in the number and length of GFAP-positive processes in a variety of clinical circumstances, and it is commonly used to define astrocytic morphological changes such as cellular hypertrophy (Pekny & Pekna, 2014). However, because GFAP labeling only shows the cytoskeletal structure and not the total cellular shape, cytoskeletal hypertrophy is a better word to explain astrocyte response in terms of GFAP expression.

Indeed, a complete morphological examination of astrocytes in neurotrauma models found a significant increase in GFAP expression with little change in the extent of overlap between different astrocyte domains and no evident cellular hypertrophy (Wilhelmsson et al., 2006).

A rising amount of evidence suggests that astrocytes have a role in Parkinson's disease. PARK7, PARK2, and SNCA were identified to have important roles in astrocyte biology and contribute to Parkinson's disease pathogenesis (Booth et al., 2017b). However, the relevance of astrocyte morphology in Parkinson's disease progression is uncertain. Autopsies of the *substantia nigra* and putamen from Parkinson's disease patients revealed little or only mild reactive astrogliosis when stained with GFAP (Tong et al., 2015). Interestingly, in the striatum of MPTP-treated parkinsonian monkeys, there is a significant increase in astrocyte coverage of striatal vGluT1- or vGluT2-positive glutamatergic synapses (Villalba & Smith, 2011). According to these findings, Parkinson's disease increased the degree of astrocyte ensheathment of pre-and postsynaptic components, with a larger astrocyte process surface area and volume around synapses. The underlying molecular basis and significance of the astrocyte structural abnormalities are unclear, but they may have important implications for Parkinson's disease's diminished synapse strength, plasticity, and excitotoxicity (B. Zhou et al., 2019b).

Then, to investigate the influence of stress on astrocytes within separate hypothalamic subfields, we performed a semi-automated morphological study of astrocytes from 8-month C57BL/6J male mice that received UCMS treatment and displayed depressive characteristics.

When stress is continuous and unpredictable, it is a major risk factor in the genesis of neuropsychiatric illnesses because the organism is unable to put in place effective systems to manage and cope with it (Bender et al., 2016; Franklin et al., 2021). Following persistent stress, neurotransmitters and chemicals capable of modifying brain structure are released. Furthermore, persistent stress affects neurogenic niches in the CNS, lowering aNG in mouse models (Toda & Gage, 2018). Initially, we decided to investigate the astrocytic response to chronic stress, focusing on the possible morphological changes of localized astrocytes of brain subregions involved in MDD (Kishi et al., 2006; Morris et al., 1982; Pikkarainen, 2001; RajMohan & Mohandas, 2007; Srikumar et al., 2011). Although the hypothalamus is an important component of stress, little is known about the impact of chronic stress on the astrocytes that reside in these locations. The morphological flexibility of astrocytes following chronic stress in the hypothalamic nuclei PVN and ArcN was investigated for the first time in this thesis study. On the contrary, following UCMS treatment in adult male mice, we found an increase in the complexity and size of astrocytes in the PVN. PVN is the initial component of the HPA axis, which causes the synthesis of adrenal hormones, particularly glucocorticoids such as corticosterone, by the release of the hormone-releasing corticotropin (cortisol in humans). The PVN receives numerous afferents from different limbic system areas (including the hippocampus, amygdala, and prefrontal cortex) and is closely linked with the other hypothalamic nuclei, including the ArcN (Gold & Chrousos, 2002). The morphological study of astrocytes in this location likewise revealed a significant increase in cell complexity in animals treated with UCMS. If astrocytic shrinkage is related to a loss in synaptic coverage, we may argue that the increased complexity of

hypothalamic astrocytes is a protective response to stress, encouraging higher coverage of synapses and therefore preserving proper glutamate homeostasis.

Finally, we proved in our thesis study that the effects of chronic stress on astrocytes are region-specific. While we found no stress-induced changes in the SNpc, we did find a substantial increase in the complexity of arborization following chronic stress in the two hypothalamic nuclei, PVN and ArcN. To the best of our knowledge, we were the first to characterize the morphological changes in SN and hypothalamic astrocytes caused by UCMS.

Antidepressants, like every other medicine that may cross the blood-brain barrier, come into direct touch with astrocytes (Czéh & di Benedetto, 2013). Research in rats employing the chronic unpredictable stress paradigm for depression discovered that therapy with the tricyclic antidepressant clomipramine corrected the stress-induced decrease in hippocampus GFAP expression (Q. Liu et al., 2009). Antidepressant treatments influence a variety of astrocytic functions, including the regulation of the availability of various neurotransmitters such as serotonin, glutamate, or GABA, the regulation of energy homeostasis, and the control of blood-brain barrier integrity.

Furthermore, antidepressant therapy causes mild to moderate reactive astrocytosis (Jensen et al., 2008). However, such astrocyte activation is not always associated with negative outcomes since reactive astrocytes do not just have a negative side, but as new results indicate, they may also perform a variety of neuroprotective and repair-related tasks in response to CNS injuries (Sofroniew, 2009b). We hypothesize that antidepressant medication not only impacts neurons but also stimulates astrocytes, causing them to perform certain actions that result in the reactivation of cortical plasticity and can lead to the realignment of neural networks, which can aid in the treatment of depression.

Furthermore, our lab discovered in a preliminary study that even treatment with Acetyl-L-carnitine (ALC), a molecule with known neuroprotective and antidepressant activities, can promote an increase

in the morphological complexity of astrocytes in the ArcN. We can speculate that the morphological plasticity of the astrocytes may represent a neuroprotective response and contribute to the effective treatment of drugs used to treat mood disorders. In the future, we want to confirm and understand if the morphological alterations of the astrocytes induced by UCMS correspond also to functional changes in the cells, it would be interesting: to study the astrocyte of the different areas of the limbic circuit of the CNS; to verify if ALC produces similar effects also in other regions of the CNS, such as the PVN or in the SN and to investigate the molecular pathway at the basis of modification. Finally, the evidence implies that chronic stress causes a rise in glucocorticoid levels and that astrocytes can respond to these changes. Given that several types of region-specific glucocorticoid receptors are expressed in the CNS (Mifsud & Reul, 2018), we may test whether differences in astrocyte stress responses are impacted by an expression profile of these unique receptors in different brain areas.

Major depressive disorder (MDD) impacts more than cognition and has a temporal link with Parkinson's disease neuroinflammatory pathways (PD). Although epidemiological and clinical investigations indicate this connection, the underlying processes remain unknown. Astrocytes play important roles in the pathogenesis of both MDD and Parkinson's disease. In Parkinson's disease, misfolded forms of the protein α-synuclein can activate these cells, causing them to release cytokines that can interact with a variety of physiological processes, including monoamine transport and availability, the hypothalamus-pituitary axis, and neurogenesis, to produce depressive symptoms. Glial cell activation in MDD can be caused by peripheral inflammatory drugs that penetrate the blood-brain barrier and/or neuronal c-Fos signaling. The resultant neuroinflammation can produce neurodegeneration owing to oxidative stress and glutamate excitotoxicity, which contributes to the pathophysiology of Parkinson's disease (Tran et al., 2020). So, astrocytes are an important connection between the two pathologies that deserve to be understood deeper.

List of pubblications

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