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HABILITATION THESIS

BRAIN MICROVASCULARIZATION AND CEREBELLAR DISORDERS IN RODENT MODELS USING THE STEREOLOGY APPROACHES

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Declaration

I hereby declare that the habilitation thesis submitted, titled “Brain microvascularization and cerebellar disorders in rodent models using the stereology approaches”, is an original work created by me. It serves as a commentary on a collection of original papers published in peer-reviewed journals with impact factors and is supplemented by review articles of a similar nature.

I am the first author of six out of the ten publications selected for this habilitation thesis (Kolinko et al. 2016; Kolinko et al. 2015; Kolinko et al. 2023; Kolinko et al. 2018; Kolinko et al. 2022; Kolinko et al. 2021) (see section 10). I actively contributed to the publication of the remaining four articles as a member of the author's teams (Cendelin et al. 2018; Purkartova et al. 2019; Tuma et al. 2017; Tuma et al. 2015). Throughout the process of publishing scientific data and compiling first-author publications, I adhered to the universally accepted ethical principles of scientific activity and the specific criteria of the respective journals. This work has not been utilized to obtain another degree or the same degree. Projects and grants that provided support for addressing scientific questions are properly acknowledged in each of the publications.

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Yaroslav KOLINKO

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Abstrakt in Czech

Tato habilitační práce se zabývá rolí mikrocevního zasobení mozku u neurodegenerativních onemocnění s důrazem na funkci mozečku a kvantitativní histologickou analýzů. Je zdůrazněna zranitelnost nervové tkáně vůči metabolickým změnám, její citlivá reakce na difúzi živin a její jedinečná vaskularizace jako součást hematoencefalické bariéry. Jsou zde zdůrazněny procesy angiogeneze, změny v mikrocévách způsobené neurodegenerativními onemocněními a stereologické techniky pro kvantitativní hodnocení.

Předložená habilitační práce zkoumá různé aspekty mikrovaskularizace ve specifických oblastech mozku při neurodegenerativních poruchách s využitím nezaujatých stereologických přístupů na různých modelech hlodavců. Cílem je získat komplexní porozumění jejich rolí v neurodegenerativních onemocněních a potenciálních terapeutických intervencích.

Studie odhalily změny v hustotě kapilárů a snížení délky mikrovaskulární sítě. Tyto specifické změny mají dopady na výzvy spojené s integrací embryonálních mozečkových štěpů u mutovaných myší. Navíc upravené cévní zasobování v rámci mozečkových komponent zdůrazňuje cévní změny související s onemocněním, které jsou proporcionální vzhledem ke snížení objemu mozečku.

U neurodegenerativních onemocnění, jako je Alzheimerova choroba, odhalují stereologická hodnocení mikrocév hipokampu ničivé účinky ukládání amyloidních plaků na kapiláry. Věříme, že kvantifikace charakteristik mikrocév na základě stereologie by mohla podpořit vývoj nových strategií pro cílené terapeutické intervence. Kromě toho je role virtuální mikroskopie v systematickém jednotném náhodném vzorkování zkoumána v různých histologických kontextech.

Závěrem tato studie nabízí cenné poznatky o vaskularizaci mozečku a hipokampu za normálních podmínek a rovněž během neurodegenerace s využitím kvantitativních histologických metod. Tato zjištění představují slibné možnosti pro terapeutické přístupy a zlepšení strategie histologického odběru ve výzkumu neurologických onemocnění.

Abstract in English

This habilitation thesis delves into the role of brain microvascularization in neurodegenerative diseases, focusing on cerebellar function and quantitative histological analyses. The vulnerability of neural tissue to metabolic changes, its sensitive response to nutrient diffusion, and its unique vasculature as part of the blood–brain barrier are highlighted. Angiogenesis processes, neurodegenerative disease-induced microvascular changes, and stereological techniques for quantitative assessment are examined here.

The habilitation thesis examines various aspects of microvascularization in specific brain regions in neurodegenerative disorders, using unbiased stereological approaches in different rodent models. The goal is to gain a comprehensive understanding of the roles of microvascularization in neurodegenerative diseases and potential therapeutic interventions. Studies have revealed alterations in the density and a decrease in the length of the microvascular network. These particular changes have implications for the integration challenges experienced with embryonic cerebellar grafts in mutant mice. Furthermore, the modified vascularity within cerebellar components accentuates disease-related vascular changes proportionate to the reduction in cerebellar volume.

In neurodegenerative diseases such as Alzheimer's disease, stereological assessments of the hippocampal microvasculature have revealed the disruptive effects of amyloid plaque deposition on capillaries. We believe that by using a stereology-based approach to determine microvessel characteristics, we can help create new methods for specific and effective treatments. Additionally, the role of virtual microscopy in systematic uniform random sampling has been explored across various histological contexts.

In conclusion, this study offers valuable insights into the vascularization of the cerebellum and hippocampus under normal conditions and during neurodegeneration, via quantitative histological methods. These findings present promising possibilities for therapeutic approaches and improved histological sampling strategies in neurological research.

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List of abbreviations and symbols

AChA - Anterior choroidal artery
AD - Alzheimer disease
AICA - Anterior inferior cerebellar artery
ALS - Amyotrophic lateral sclerosis
A_P - Area per point
APP - Amyloid precursor protein
Aβ - Amyloid-beta
BBB - Blood brain barrier
CA - Cornu ammonis
CAA - Cerebral amyloid angiopathy
CE - Coefficient of error
CSF - Blood–cerebrospinal fluid
CSVD - Cerebral small vessel disease
D_D - Diffusion distance
DG - Dentate gyrus
ECs - Endothelial cells
EGFP - Enhanced green fluorescent protein
FOV - Fields of view
GFAP - Anti-glial acidic fibrillary protein
GL - Layer of the granular neurons
K - A constant interval between the sampled sections
Lc - Lurcher mice
L_{cap} - Total length of microvascular segments
L_{Vcap} - Average length density of capillary segments
ML - Molecular layer of the cerebellum
MMPs - Matrix metalloproteinases

N	- Cerebellar nuclei
N_{cap}	- Total number of microvascular segments
N_{Vcap}	- Average density of capillary segments
NDDs	- Neurodegenerative diseases
Pc	- Purkinje cell layer
PCA	- Posterior cerebral artery
pcd	- Purkinje cell degenerated mice
PCL	- Hippocampal principal cell layer
PICA	- Posterior inferior cerebellar artery
SCA	- Superior cerebellar artery
SURS	- Systematic uniform random sampling
t	- Measured section heights
TgF344-AD	- Transgenic rat models of AD
V	- Total region volume
VEGF	- Vascular endothelial growth factor
WM	- Inner white matter of the cerebellum
WT	- Wild type
ΣA	- The sum of the areas of all sections
∑P	- The sum of points hitting a subregion in a grid

1 Literature review

1.1 A brief history of the study of the cerebellum

The cerebellum has long been recognized as a distinct subdivision of the brain (Glickstein et al. 2009). Vesalius, examining the brains of various animals, first suggested that the cerebellum could be a separate part of the brain in 1543 (Vesalius 1964). A description of the gross anatomical structure of the cerebellar cortex and the cerebellar nuclei which are encased within its white matter was provided thirty years later (Ghosh and Narayan 2020; Varolio 1969). In 1776 (Malacarne 1776), named cerebellar subdivisions for their resemblance to other structures, e.g. the lingula, the tonsils of the cerebellum, and the conical eminence uvula, etc. Furthermore, he described his autopsy findings of two "cretins" (a historical term used for individuals with intellectual and developmental disabilities caused by severe iodine deficiency during early development) in whom the cerebellum was smaller than normal and contained fewer folia (~340 in cretins instead of 500 to 780 in healthy individuals). Therefore, by the end of the 18th century, there was an accurate picture of the gross anatomy of the cerebellum (Glickstein, Strata and Voogd 2009). The bits of knowledge about the nuclei and conducting pathways of the cerebellum continued to expand until the end of the 19th century and the beginning of the 20th century (Dum et al. 2002; Moreau de la Sarthe and Vicq-d'Azyr 1805; Stilling 1864; Vic-d'Azyr and Moreau 1805). The current systematic approaches to describing the morphology of the cerebellum were proposed by Larsell (Larsell 1952).

At the beginning of the 19th century, the first attempts to describe the structures of the cerebellum histologically were registered (Burdach 1826; Reil 1807). The authors suggested that the alternating layers of gray and white matter constitute a type of voltaic pile that generates animal electricity. It should be noted that today, the description is still relevant. The first accurately described characteristic cells in the sheep cerebellum were provided in 1838 by Jan Evangelista Purkině (Cavero et al. 2017; Purkynje 1838). Among other structures, he described the large neurons in the cerebellar cortex. Later, the nucleolus of these cells was described by Valentin (Valentin 1836). He was a student of Purkinje and gave these cells the name of his teacher.

Shortly after the method of Golgi staining of nervous tissue was discovered, it was used to stain the cerebellar cross-sections. Ramon y Cajal emphasized that interaction between axons and dendrites is made through the contact of an axon with a dendrite or soma of the next cell in the pathway. Additionally, he described the fundamental afferents to the cerebellar cortex: the mossy and climbing fibers. Six years after this publication he reported on the fine structure of the retina, the olfactory bulb, the cerebral cortex and the cerebellum (Glickstein et al. 2009; Ramón y Cajal 1894), leading to a revolution in the current view of the structure and function of the cerebellum.

With the rapid development of electron microscopy in the 1960s, a new turn in cerebellar morphology investigation was started (Desclin 1974; Szentágothai and Rajkovits 1959). Through the use of light and electron microscopy studies and the electrophysiological analysis of the excitatory and the inhibitory cell types, the first time a complete picture of the functional architecture of the cerebellar cortex was obtained and published (Eccles 2013).

Scott (1963) and Hawkes & Leclerc (1987) demonstrated the zebrin zonation of a Purkinje cell within the cerebellar cortex. Furthermore, the olivocerebellar climbing fibers were shown to be congruent with particular zebrin-positive or zebrin -negative bands (Voogd et al. 2003) and innervated by different parts of the caudal medial accessory olive (Sugihara and Shinoda 2004).

Currently, PubMed contains more than 45,500 articles from the past 50 years describing the features of the cerebellar morphology and the possible role of the cerebellum in several forms of learning. These topics are still controversial, and differing points of view are expressed by several of the authors. Therefore, active morphological and physiological studies of the cerebellum in particular and of the brain in general are necessary in the future and continue to this day.

1.2 General principles of cerebellar blood supply

The cortex covers most of the cerebellum surface. Three layers are distinguished in the cerebellar cortex (Mai and Paxinos 2011): a) the cell-poor molecular layer (ML) is located superficially, b) large Purkinje cell somata form a monolayer in the middle and c) the deepest granular neurons are located in a dens layer of the granular layer (GL). The inner white matter (WM) does not contain any

neuron cell bodies and therefore will stain a lighter color then the gray matter cortex. The inner WM contains nerve fibers, supported by neuroglial cells and small blood vessels. In the central mass of the cerebellum, four pairs of nuclei (N) separated by the white matter are located. The cerebellar nuclear mass contains large stellate neurons (Irimescu et al. 2015), supported by glial cells and blood vessels.

In mice, the organization of the midbrain and metencephalon occurs around the 8th day of embryonic development (Butts et al. 2014; Larsell 1952; Millet et al. 1996). The metencephalon encompasses the cerebellum and pons, and originates from a region known as the hindbrain. During this time, the superior cerebellar artery starts to form as part of the upcoming basilar artery, becoming the initial blood supply for the cerebellum. Subsequently, the vertebral arteries connect to this vascular system (Burger et al. 2007). Three main branches serve as a vascular supply to the cerebellum. Two of these arteries (the superior cerebellar artery (SCA) and anterior inferior cerebellar artery (AICA)) originate from the basilar artery, and the third artery (the posterior inferior cerebellar artery (PICA)) originate from the vertebral artery. The anatomy of the AICA and PICA is strongly related to embryology, which is why they can undergo significant variations (Delion et al. 2017).

The fundamental principles governing the structure of the cerebellar microvascular network were first delineated in turtles (Kleiter and Lametschwandtner 1995). During the last decade, interest in the blood supply of the brain has increased significantly and precise 3D mouse cerebellar vascular detailed atlases with stereotaxic coordinates have been produced (Ghanavati et al. 2014; Xiong et al. 2017).

Briefly, the short second-order arteries (A2) depart from the superficial arteries (see *Figure 1*). Along with some of their recurring branches (A4 arterioles), the A3 arterioles provide blood to the capillary network of the subpial ML. Both the GL and the Purkinje cell layer (Pc) receive blood from the A4 arterioles and A3 arterioles. Furthermore, at the Purkinje cell level, the A4 and A3 arterioles give way to the horizontal branches ("parallel arteries"), the capillaries of which are joined to the granular and molecular layer capillary network (Kleiter and Lametschwandtner 1995). A part of the distal ends of the A4 arterioles located in the GL passes through the border of the WM and forms a capillary network or collaterals with the arteries supplying the nuclei.

In addition, the main sustenance for the Purkinje neuron cell bodies comes from capillaries primarily situated in the GL, whereas their dendrites are supplied

by microvessels located in the ML. These findings indicate that the ML and GL possess somewhat separate circulatory networks. Furthermore, capillary pericytes can enhance blood flow and regulate neural activity. (Hall et al. 2014; Kolinko et al. 2018).

The blood supply to the cerebellar nuclei is mainly provided by the SCA. In particular, this is due to further ramifications of its pontocerebellar branches (Delion et al. 2017). Nevertheless, depending on the embryology, collaterals from the AICA and/or PICA could also participate in the nuclear blood supply.

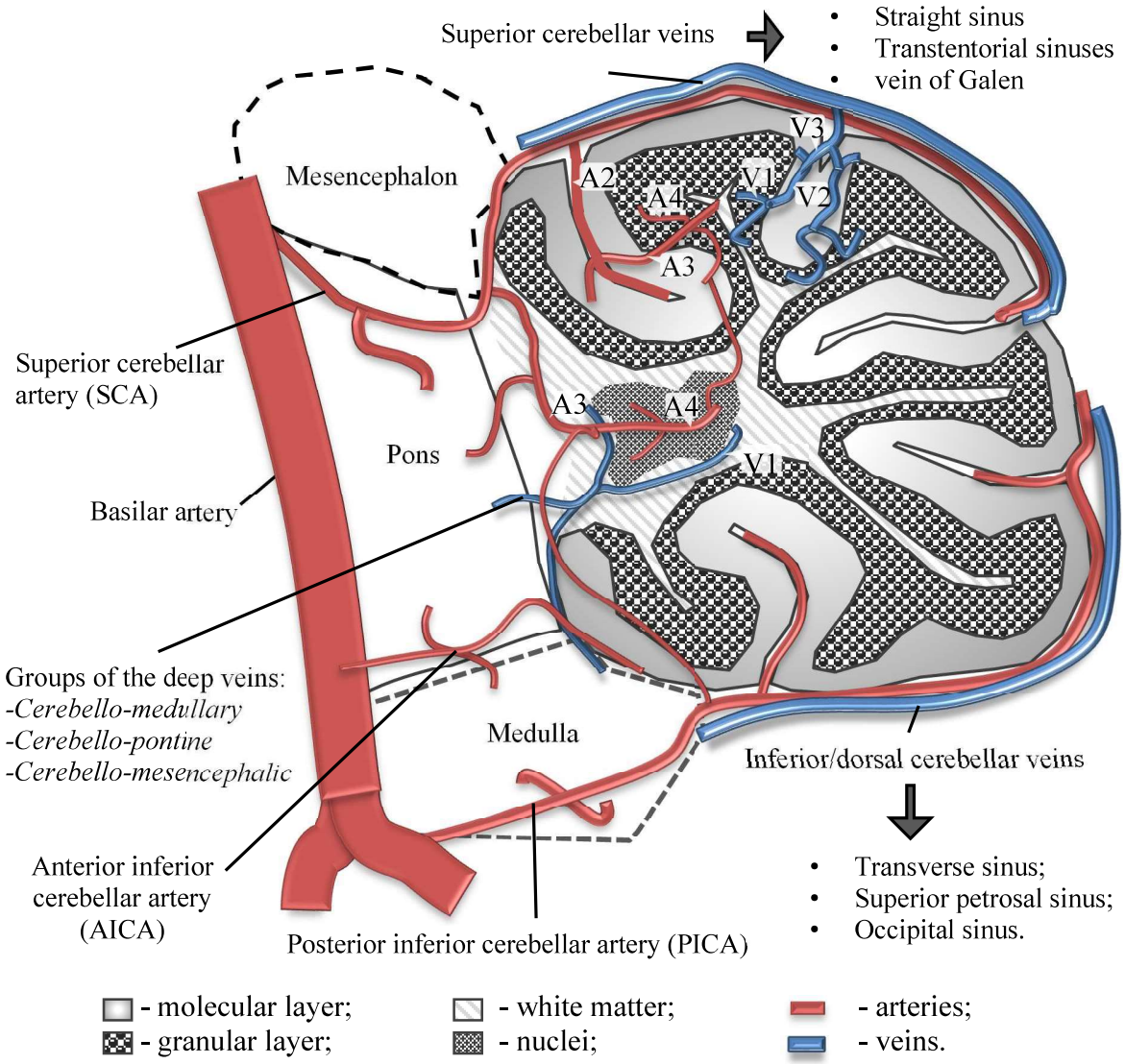

Figure 1 - *General principles of organization of the cerebellar microcirculatory network*

The three groups of cerebellar veins can be described as follows: the superior and inferior superficial veins, which drain the cortical surface of the cerebellum, and the deep veins. All these veins terminate as bridging veins (Delion et al. 2017; Lang 1983; Mai and Paxinos 2011; Matsushima et al. 1983; Rhoton 2000). The cerebellar drainage system is built in such a way as to remove blood to the dense network of superficial veins as quickly as possible (Delion et al. 2017).

The regions supplied by A4 arterioles are drained through V1 venules. V2 and V3 venules primarily drain the capillary network of the ML (Kleiter and Lametschwandtner 1995). The V1 venules, which drain the nuclei, are formed within the WM surrounding them. The outflow of blood from the nuclei to the surface of the cerebellum is occurs through the cerebro-medular subgroup of deep cerebellar veins. The capillary network mainly forms the anastomoses between the V1 cortical venules and V1 nuclei venules.

This structure creates a dense network of vessels within the cerebellar cortex and nuclei. In the cerebellum of healthy mice, the white matter has nearly half the capillary density of the gray matter.

1.3 Organization of the hippocampus and its vascularization

The hippocampus is segmented axially into three parts: the head, body, and tail (Grivas et al. 2003; Ogawa et al. 2018). In the coronal section of the body, two gray matter areas are identified: the cornu ammonis (CA) and the dentate gyrus (DG) (Lee et al. 2007). Tha CA, also known as Ammon's horn, comprises four subdivisions (CA1, CA2, CA3, and CA4) (Lee et al. 2007; Ogawa et al. 2018). The pyramidal cell layer in these regions collectively forms the principal cell layer (PCL).

Arterial vascularization of the hippocampus relies on collateral branches originating from the PCA and, to a lesser extent, the anterior choroidal artery (AChA) (Erdem et al. 1993). Variations exist in the origin of hippocampal arteries and in the contribution of these primary vessels to blood circulation in the hippocampus. In cases where the hippocampal arteries mainly branch from the PCA, the involvement of the AChA varies greatly and is not consistent (Marinkovic et al. 1999; Morandi et al. 1996). Additionally, the number of hippocampal arteries can vary, potentially resulting in multiple posterior

hippocampal arteries. Despite these possible modifications, generally, the PCA and AChA form longitudinal hippocampal arteries, supplying different regions: the anterior hippocampal artery serves the hippocampal head and uncus, while the middle and posterior hippocampal arteries supply the body and tail, respectively (Marco et al. 2019). Along the course of the hippocampal arteries, a number of sector (in some sources transverse) arteries depart under them (*Figure 2*), penetrate into the hippocampus, and branch there (Coyle 1976; Tayebi Meybodi et al. 2023). These arteries typically run parallel to each other across the free surface (margo denticulatus) of the dentate gyrus (Marinkovic et al. 1992; Tayebi Meybodi et al. 2023).

Typically, two primary types of major arteries, ventral and dorsal, are observed branching from the sectoral arteries. The large ventral artery enters the medial portion of the margo denticulatus before proceeding through the ventromedial region of the DG or entering the hippocampal sulcus positioned between the DG and the subiculum. The artery then follows a curved trajectory through the medullary lamina (essentially, the intrahippocampal extension of the hippocampal sulcus) located between the DG and the CA1 sector of the hippocampus (Marinkovic et al. 1992; Tayebi Meybodi et al. 2023). This artery gaves rise to lateral branches, which primarily supplied the CA1 sector and, at

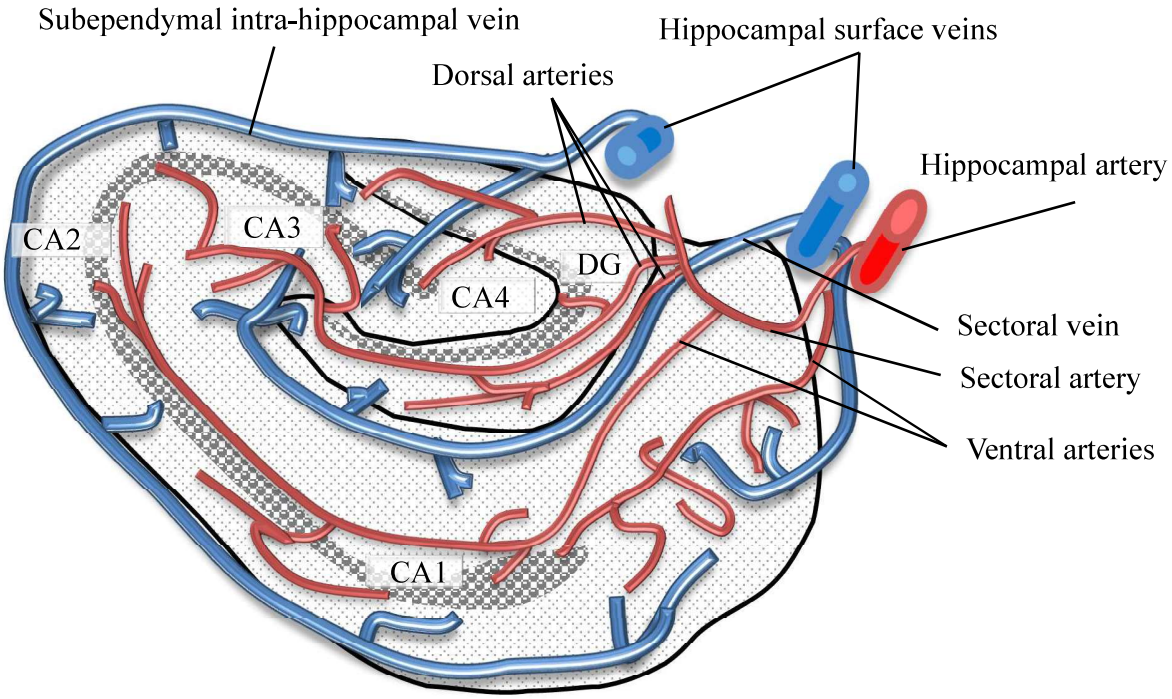

Figure 2 - *Illustrations of the microvascular supply of the hippocampus. CA - cornu ammonis; DG - dentate gyrus*

times, the prosubiculum or a segment of the CA2 sector (Enzinger et al. 2008; Lee et al. 2007; Sander and Sander 2005).

On the other hand, the substantial dorsal arteries occasionally follow a path akin to the ventral arteries but more commonly course between the DG and the CA4 sector (Tatu and Vuillier 2014; Tayebi Meybodi et al. 2023). Typically, the substantial dorsal arteries provided the blood supply to the CA2 and CA3 sectors and sometimes the uppermost region of the CA1 sector and/or DG.

This microvascular network originating from both ventral and dorsal vessels converges within the hippocampal PCL. Unlike that of WM, the vascularization of the PCL is distinguished by a denser microvascular network lacking distinct orientations (Kubikova et al. 2018; Ogawa et al. 2018). Additionally, several large vessels traverse through the CA regions (Grivas et al. 2003).

The internal sectoral veins of the hippocampus, positioned within the hippocampal fissure, exhibit alternating positions with the sectoral arteries (Coyle 1976; Tatu and Vuillier 2014). These veins seemed to be associated with and drained regions that are supplied by the sectoral arteries. Deeper sectoral veins, unaccompanied by arteries, receiv branches within the intraventricular alveus and the adjacent stratum oriens of CA3 (Coyle 1976). Sectoral vein drainage occurs through several longitudinal vessels joining the basal vein (the vein of Galen) (Tatu and Vuillier 2014).

A comparison of the studies conducted on the cerebellum and hippocampus, focusing on vascular anatomy, imaging, and histology, is provided in *Table 1*.

1.4 Known morphological aspects of microcirculation in various neurodegenerative diseases

1.4.1 General morphological assessment of the brain microcirculation

The brain is composed of an intricate network of small components that interact closely with each other. This interaction is facilitated by essential elements such as brain microvascular endothelial cells (ECs), the basement membrane, and

Table 1 - *Comparative analysis of methods and models in studying the vascular network anatomy of the cerebellum and hippocampus at various levels*

	Method	***Cerebellum***	***Hippocampus***
Main vessels	MR imaging	Human *(Burger et al. 2007)*	Human *(Enzinger et al. 2008; Lee et al. 2007; Marco et al. 2019; Ogawa et al. 2018; Tatu and Vuillier 2014)*
	Topographic anatomy	Human *(Delion et al. 2017; Matsushima et al. 1983)* Mice *(Rhoton 2000)*	Human *(Erdem et al. 1993; Marinkovic et al. 1992)* Rats (Coyle 1976)
Small vessels	Histology	Tortoises *(Kleiter and Lametschwandtner 1995)* Mice *(Xiong, et al. 2017)*	Rats *(Grivas et al. 2003)*
	Micro-CT images	Mice *(Ghanavati et al.2014)*	-
	MRI/CT imaging	-	Human *(Enzinger et al. 2008; Lee, et al. 2007; Marco et al. 2019; Ogawa, et al. 2018; Tatu and Vuillier 2014)*
Microvascular patterns	Histology	Tortoises *(Kleiter and Lametschwandtner 1995)*	Human *(Marinkovic et al. 1999; Morandi et al. 1996)*
	Micro-CT images	Mice *(Ghanavati et al. 2014)*	
	Stereology	Mice *(Kolinko et al. 2016; Kolinko et al. 2023)*	Mice *(Lee et al. 2005)*

various cell types, including neurons and glial cells positioned near capillaries. Blood vessels, functioning with the assistance of the blood–brain barrier (BBB), act as a shield for the brain, preventing toxic substances from entering the brain

from the bloodstream (Persidsky et al. 2006). They also supply nutrients to brain tissues and enable harmful compounds to exit the brain and enter the bloodstream. As a result, any abnormalities in the neurovascular system could significantly contribute to nervous system pathology (Farkas and Luiten 2001; Pantoni 2010; Zhang et al. 2011).

The structure of the brain microvascular network is remarkably similar across different mammalian species, accounting for approximately 3% of the brain total volume (Nicholson 2001). Arteries and arterioles that supply the brain extend into the cerebral tissue, forming a network of the continuous capillaries. Notably, cerebral arterioles are unique because they are surrounded by astrocytic endfeet that cover different layers (the intima, media, and adventitia) (Blevins et al. 2021; Wardlaw et al. 2020). The internal elastic lamina might not be consistently present throughout the entire arteriolar network but is visible in the feeding arterioles of the cerebral region. (Martinez-Lemus 2012).

Capillaries in the brain can intermittently change their diameter, yet they are constantly supplied with blood (Gobel et al. 1990; Hudetz 1997). Typically, brain capillaries have an average diameter of approximately 7–10 μm, and the distance between them is approximately 40 μm on average (Duvernoy et al. 1983; Nicholson 2001). This proximity means that each neuron is within approximately 20 μm of a capillary. Additionally, the density of capillaries in the gray matter is 2–4 times greater than the brain average (Borowsky and Collins 1989; Heinzer et al. 2008), reflecting a higher neural activity level in gray matter than in white matter (Kubikova et al. 2018; Tonar et al. 2011; Zhu et al. 2012). These findings indicate that any potential abnormalities in the microvessels of the brain should be evaluated separately in white and gray matter to comprehend their impact accurately.

The BBB acts as a gatekeeper, limiting the passage of blood components such as plasma, red blood cells, and white blood cells from the bloodstream into the brain. Traditionally, the BBB is defined as the layer of ECs that form vessel walls. This system is highly dynamic, with cells interpreting chemical and mechanical signals within complex microenvironments (Andrew et al. 2013). In this intricate process, various elements such as smooth muscle cells, pericytes, astrocytes, and the extracellular matrix play roles. These elements are arranged into different layers within the vessel walls.

Studies examining biochemical aspects have revealed that the expression levels of transporters and pumps differ among various mammalian species,

suggesting that they contribute to the distinctive characteristics of the human BBB (Hammarlund-Udenaes et al. 2008).

ECs within the BBB act as checkpoints, monitoring various chemical and mechanical influences within the local microenvironment of the nervous system. Their functionality is closely tied to factors such as cell shape, the expression of proteins and genes, cell multiplication, and transport processes (Aird 2007; Dejana 2004). Endothelial cell–cell junctions play a crucial role in maintaining the integrity of the microvasculature and in regulating paracellular transport. The integrity of the microvasculature is ensured through the formation of adherens junctions between ECs via tight junctions (Aird 2007; Bazzoni and Dejana 2004; Dejana 2004). The stability of the tight junctions is no less important and has great importance in the correct functioning of these cells under the pressure effects associated with directional blood flow (Aird 2007; Caplan et al. 1974; Nerem et al. 1981; Sato and Ohashi 2005) on small capillaries. This is why more than 20% of the cell's claudin family proteins are used to ensure the stability of these tight junctions (Bazzoni and Dejana 2004; Dejana 2004). Accordingly, ECs can wrap around to form tight junctions with themselves, as well as with their neighbors (Nag 2003). Shear stresses can also upregulate the expression of genes associated with junctional proteins and transporters (Cucullo et al. 2011).

Astrocytes in the brain typically have a star-like shape, with multiple extensions branching out from the central cell body, spanning an average diameter of approximately 140 μm (Oberheim et al. 2009). They interact with small blood vessels by wrapping their cellular extensions, called endfeet, around the capillaries (Abbott et al. 2006). Additionally, a single astrocyte can connect with several capillaries(Oberheim et al. 2009). The manner in which astrocytes connect is crucial for regulating local blood flow to match oxygen and glucose transport with neural activity (Iadecola 2004; Iadecola and Nedergaard 2007; Takano et al. 2006; Zonta et al. 2003).

Pericytes in the brain surround capillaries and small blood vessels (Bonkowski et al. 2011; Krueger and Bechmann 2010; Winkler et al. 2011), thus engaging in communication with endothelial cells, astrocytes, and neurons, and initiating various signaling pathways (Bonkowski et al. 2011; Kolinko et al. 2018). These contractile cells contain actin fibers and contribute significantly to controlling blood flow by controlling the diameter of capillaries (Dalkara et al. 2011; Hamilton et al. 2010; Peppiatt et al. 2006). Separating pericytes from both endothelial cells and surrounding astrocytes are formation via a thin layer called the basement membrane, which consists of fibronectin, laminin (Aumailley et al.

2005), and type IV collagen (Hartmann et al. 2007; Tilling et al. 2002). The ratio of ECs to pericytes is typically approximately 1:3 (Shepro and Morel 1993).

The space outside cells, known as the extracellular space, serves as the primary route for transport between cells. Transport between cells within this space is generally more efficient than transport across the BBB (Berselli et al. 2022; Khan et al. 2022). The extracellular matrix in the brain is composed of five main components: hyaluronic acid, tenascin, lecticans, hyaluronan and proteoglycan linkage proteins (Zimmermann and Dours-Zimmermann 2008). This matrix, largely composed of hyaluronan, can occupy up to 30% volume of the extracellular space (Sykova and Nicholson 2008). The extracellular matrix acts as a liquid medium facilitating the transportation of molecules, including vital nutrients and neurotransmitters, between microvessels and brain cells (Andrew et al. 2013). Interestingly, some common proteins, such as collagen type I and fibronectin are not typically found in the brain's extracellular matrix (Sanes 1989).

Another significant barrier worth noting is the blood–cerebrospinal fluid (CSF) barrier, which is present at the choroid plexus. This barrier forms between the neuroependymal cells lining the walls of the ventricles (which float in the CSF-filled space) and the fenestrated blood capillaries that supply them (Pardridge 2016). These structures are responsible for generating approximately 500 liters of CSF per day in humans and approximately 450 millilitres per day in mice (Pardridge 2016). This high production rate helps refresh the content within the ventricles and the subarachnoid space approximately 3 to 4 times daily (Marques et al. 2013).

Molecules and cells primarily move across the CSF barrier by using a transport system that passes through the cells themselves (transcellular transport). While it is also feasible for substances to traverse this barrier between cells (for paracellular transport), this method is restricted by the tight junctions between epithelial cells (Saunders et al. 2013; Segal 2001). Recent investigations into the blood–CSF barrier have revealed its involvement in various aspects of brain equilibrium, indicating that this barrier plays a more significant role than previously understood (Baruch and Schwartz 2013; Emerich et al. 2005; Falcao et al. 2012; Johanson et al. 2011).

Although the specific control of brain capillaries by the autonomic nervous system has not been fully explained (Fisher 2009; Krueger and Bechmann 2010; Peppiatt et al. 2006), the maintenance of the BBB largely relies on biochemical and biomechanical signals from the vascular system. Additionally, multiple

paracrine signaling pathways operate among ECs, astrocytes, and pericytes, contributing significantly to BBB maintenance (Abbott et al. 2010; Aird 2007).

1.4.2 Features of angiogenesis mechanisms in the brain

The formation of the vascular system occurs via two separate mechanisms: vasculogenesis and angiogenesis. (Reynolds et al. 2000). Vasculogenesis is the de novo formation of blood vessels from angioblasts (endothelial precursor cells derived from the mesoderm) during embryonic development (Ferguson et al. 2005; Risau 1997). Vasculogenesis in the brain proceeds through the intraembryonic mesoderm transformation pathway without the formation of hematopoietic stem cells in the lumen (DeSesso 2017). The initial vascular network comes together in three key stages (*Figure 3A*): first, the proliferation and differentiation of hemangioblasts and angioblasts; second, the creation of initial primordial blood vessels; and third, the continuous growth and enlargement of these blood vessels through angiogenesis (Risau 1997; Zygmunt et al. 2003).

Angiogenesis, on the other hand, is the process of neovascularization from preexisting vessels (Clark and Clark 1940; Zygmunt et al. 2003). Hypoxia is the primary factor that induces angiogenesis (Arden and Sivaprasad 2012; Konisti et al. 2012; Liu et al. 2003; Taylor and Sivakumar 2005; Zhong et al. 2008). Angiogenesis can occur through two pathways: sprouting and intussusception (nonsprouting angiogenesis). Angiogenesis begins when ECs are activated by proangiogenic factors, such as vascular endothelial growth factor (VEGF) (Stevenson et al. 2018; Stevenson et al. 2020), angiopoietin (Ding et al. 2006b; Ding et al. 2004b; Morland et al. 2017; Stevenson et al. 2018), viewing bromodeoxyuridine, placental growth factor or fibroblast growth factor (Lopez-Lopez et al. 2004). These factors usually secreted by astrocytes in avascular regions (Eilken and Adams 2010). Numerous proangiogenic factors are also synthesized by other brain cells. A good example is angiopoietins, which are also synthesized by microglia after massive inflammation (for example, after a stroke or in a tumor) to moderate the inflammatory response of blood vessels (Sheikh et al. 2023).

Along a gradient of proangiogenic factors, particularly VEGF, isolated ECs acquire a "tip cell" phenotype (*Figure 3B*). The determination of tip cells is overseen by receptors from the Notch family and a specific ligand known as Delta-

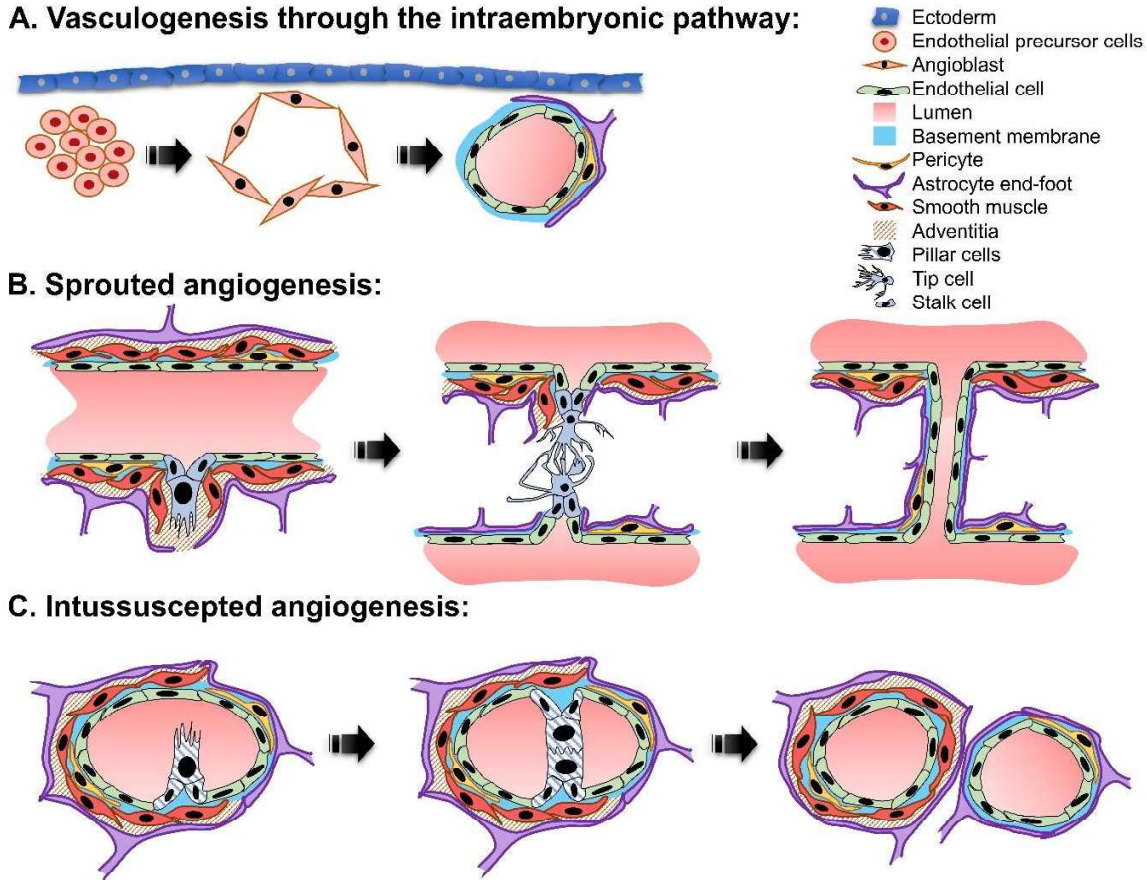

Figure 3 - *Vasculogenesis and angiogenesis*

like ligand 4 (Dll4) (Liu et al. 2003; Tahergorabi and Khazaei 2012). Neighboring ECs, influenced by both astrocyte and apical cell signals, acquire a vascular sprout "stalk cell" phenotype (Hellstrom et al. 2007; Suchting et al. 2007; Tammela et al. 2008), maintaining the integrity and perfusion of the growing vasculature (Eilken and Adams 2010).

Tip cells play a pivotal roles in several essential processes, such as disrupting the basement membrane, separating pericytes, detaching the perivascular feet of astrocytes from the glial limiting membrane, and loosening the junctions between ECs (Heinke et al. 2012). They also establish connections with other sprouts or neighboring capillaries, becoming embedded in the endothelial lining of new vessels. Additionally, the interaction between VEGF and its receptor (Greenway et al. 2006) mediates these processes. The formation of a lumen limited by the functional endothelium is associated with stalk cell maturation (Risau 1997).

During this process, nascent ECs are covered by pericytes and smooth muscle cells (Carmeliet 2005), which provide strength and regulate vessel perfusion. There is significant overlap in the signaling systems utilized by growing blood vessels and neural cells (Egea and Klein 2007; Palmer and Klein 2003; Stein and Tessier-Lavigne 2001), which may facilitate the coordinated formation of both systems (Ferguson et al. 2005; Makita et al. 2008; Mukouyama et al. 2002; Mukouyama et al. 2005). Interestingly, ephrin molecules, which primarily provide repulsive signals for growing nerve cells, also play a role in this process (Egea and Klein 2007; Palmer and Klein 2003; Stein and Tessier-Lavigne 2001; Wakayama and Yamagishi 2023).

Processes for slowing down and ultimately terminating angiogenesis are carried out due to an increase in the concentration gradient of factors such as angio- or endostatin (Distler et al. 2003; MacDonald et al. 2001; Pulsatelli et al. 2020; Rege et al. 2005), thrombospondin-1 (TSP-1) (Jayakumar et al. 2017; Loron et al. 2023), tissue inhibitors of metalloproteinases (TIMPs) (Chena et al. 2018; Lenci et al. 2021; Zheng et al. 2013), and pigment epithelium-derived factor (PEDF) (Bahrami et al. 2019; Rege, Fears and Gladson 2005). Furthermore, neurons can also influence angiogenesis in the brain. These proteins release factors such as semaphorins and netrins, which can guide and regulate the growth of blood vessels, especially during the development (Colotti et al. 2022; Wakayama and Yamagishi 2023). In addition, these proteins exert antiangiogenic effects through the inhibition or displacement of the proangiogenic molecules (Rege, Fears and Gladson 2005).

Intussusceptive angiogenesis (*Figure 3C*), also known as nonsprouting angiogenesis or splitting angiogenesis, is a distinct mechanism of blood vessel formation and remodeling (Caduff et al. 1986; Mentzer and Konerding 2014). Unlike sprouting angiogenesis, intussusceptive angiogenesis involves the splitting and expansion of preexisting blood vessels to create new vessel branches.

The process of intussusceptive angiogenesis, the process begins with the formation of pillar-like structures within the existing vessel lumen (Caduff et al. 1986). These structures consist of modified ECs that are called “pillar cells” (Mongera et al. 2013); these cells protrude toward each other and meet in the center of the vessel. Subsequently, the pillars fuse together, dividing the vessel lumen into two separate lumens (Caduff et al. 1986). Pillar cells have morphologies similar to those tip cells but differ in terms of membrane proteins (Konerding et al. 2010; Mentzer and Konerding 2014).

Intussusceptive angiogenesis plays a crucial role in various physiological and pathological conditions. It contributes to vascular remodeling during tissue growth and development, wound healing, and organ regeneration (Eming et al. 2007; Song and Ott 2011). It is also involved in pathological conditions such as tumor angiogenesis (Zhao et al. 2011), where the formation of new blood vessel branches supports tumor growth and progression (Ribatti and Djonov 2012).

The mechanisms underlying intussusceptive angiogenesis involve a combination of cellular processes, including endothelial cell proliferation and migration, and the remodeling of the extracellular matrix. One of the reasons for the onset of angiogenesis via intussusception is chronic peripheral dilatation of arterioles (Hudlicka et al. 1981). Signaling molecules such as VEGF (Gerhardt et al. 2003; Hellstrom et al. 2007), angiopoietins, and MMPs (Konerding et al. 2010; Mentzer and Konerding 2014) are implicated in the regulation of intussusceptive angiogenesis.

Intussusceptive angiogenesis provides an alternative mechanism for blood vessel formation and remodeling, complementing the sprouting angiogenesis process. Both sprouting and intussusceptive angiogenesis can coexist and act in coordination to ensure proper vascular network development and tissue perfusion.

The factors associated with the regression of blood vessels, known as vascular regression, include apoptosis regulated by factors such as TSP-1 and endostatin (Jayakumar et al. 2017; Pulsatelli et al. 2020); EC detachment due to reduced adhesion and an altered extracellular matrix; the withdrawal of proangiogenic factors such as VEGF and Ang-2 (Ding et al. 2006b; Ding et al. 2004b; Morland et al. 2017; Stevenson et al. 2018); the inhibition of the Dll4-Notch pathway, which promotes vessel regression (Hellstrom et al. 2007; Kim et al. 2020; Suchting et al. 2007); hemodynamic changes; and increased MMP activity, which degrades the extracellular matrix, contributing to vessel regression (Chena et al. 2018; Lenci et al. 2021; Rege et al. 2005). Another important factor in the decline of the vascular bed is the development of vasculitis and fibrinoid necrosis of the microvessel wall, which are associated with associated inflammatory cell infiltration and organization (Iglesias-Gamarra et al. 2007). These factors work together in various physiological and pathological conditions to regulate blood vessel regression.

1.4.3 Alterations in the density of microvessels within the brain throughout life

Among all organs, the brain exhibits the highest metabolic activity. In younger individuals, the brain can generate blood vessels when oxygen levels are low, but this ability diminishes as the brain matures and ages (Harb et al. 2013). During early development, blood vessels from the pia mater infiltrate the brain and converge toward the ventricles in a centripetal manner. The vessels surrounding the brain ventricles stem as secondary branches from deeply penetrating vessels (Greenberg and Jin 2005). Another process involves the outward extension of vessels toward the pia mater (Greenberg and Jin 2005).

Several researchers have explored how aging affects the density of brain vessels (MacDonald et al. 2001; Tsunemi et al. 2013; Wang et al. 2014). Their findings, based on vessel density, conflict as some report decreases, increases, or no change in vascular density (Riddle et al. 2003). These conflicting data can be attributed to a phenomenon known as a "referent trap" (Braendgaard and Gundersen 1986). However, it can be reasonably stated that increased blood vessel density might be influenced by exercise, particularly in motor brain areas affected by strokes in rat models (Ding et al. 2004a; Ding et al. 2006a; Ding et al. 2004b; Zhang et al. 2013).

In addition, various structural changes related to aging have been observed in the walls of brain vessels. These changes include reductions in smooth muscle and elastin content, as well as thickening of the basement membrane (Keuker et al. 2000; Peters and Sethares 2012). Furthermore, pericytes in the aging brain are characterized by larger mitochondria (Hicks et al. 1983), although the coverage by ECs and pericytes and the number of mitochondria in endothelial cells remain largely unchanged (Farkas and Luiten 2001; Peters and Sethares 2012).

1.5 Morphological assessments of the microcirculation in degenerative diseases

The brain is sensitive to even short episodes of low oxygen levels, which significantly contribute to the development of both cerebrovascular diseases and

neurodegenerative diseases (NDDs) (de la Torre and Stefano 2000; Lipinski and Pretorius 2013; Nemoto and Betterman 2007). Changes in brain blood vessels can impact the condition and function of neuronal tissue through several mechanisms:

- Obliterating the vessel lumen limits the blood perfusion of the tissue (Ding et al. 2006a; Ding et al. 2004b; Zhang et al. 2013);
- Reduced vessel density increases the space between capillaries and brain cells, elongating the distance for oxygen, nutrients, waste, and other substances to diffuse (Moreno et al. 2013; Tsunemi et al. 2013; Wang et al. 2014);
- Hemorrhages result in damage to brain tissue;
- BBB dysfunction permits harmful molecules to enter brain tissue (Josowitz et al. 2023; Sheikh et al. 2023). Additionally, blood vessels are involved in the development of brain edema, which heightens tissue pressure, reduces perfusion pressure, and extends diffusion pathways.
- Blood vessels also play a role in triggering inflammation, with the endothelium releasing various biologically active substances.

In middle and later ages of life, NDDs are the most frequently observed among CNS conditions (Mayeux 2003; Palop et al. 2006). These progressive disorders involve the gradual loss of particular groups of neurons, leading to specific clinical symptoms and manifestations (Matej and Rusina 2012). Vascular changes observed in some NDDs often occur as secondary responses to alterations in nervous tissue resulting from changes in signaling between vessels and neurons (Iadecola 2013; Nation et al. 2019; Zlokovic 2011). These cumulative changes in the microcirculatory system subsequently impact the neurodegenerative process.

In essence, vascular pathological changes generally involve two main mechanisms. First, the narrowing (e.g., changes in the surface area of ECs or the formation of micropinocytotic bubbles) or obstruction (e.g., thrombosis or embolism) of vessel lumens cause ischemia in specific brain regions. Second, the weakening, expansion, or breaking of vessel walls, such as microstructural damage, ECs disruption, and basal lamina exposure or breakdown, can lead to brain edema and the escape of blood components from vessels (Kumar et al. 2014). Although various vessel types can be impacted, smaller vessels usually exhibit initial signs of change (Iglesias-Gamarra et al. 2007).

In cases of brain tissue damage, the activity of various lipases is stimulated, leading to the hydrolysis of membrane lipids. Initially, this may be triggered by an increased influx of calcium ions (Klein et al. 2000). Shortly after brain injury,

there is an influx of neutrophils, astrocytosis, edema, and the release of both pro- and anti-inflammatory cytokines (McColl et al. 2009; Stella and Piomelli 2001; Sulimai et al. 2023).

Studies have revealed that preceding systemic inflammation can have detrimental effects on various components of the neurovascular unit (McColl et al. 2009; Sulimai et al. 2023). Moreover, chronic systemic inflammation leads to neuronal damage, resulting in dementia and death (Doyle and Buckwalter 2020; Li et al. 2013). Systemic proinflammatory mediators influence the integrity of the BBB, causing an increase in its permeability (Muccioli and Stella 2008; Trickler et al. 2014). The breakdown of the BBB, including alterations to the neuronal environment, occurs due to the disruption of tight junctions, resulting in abnormal transport of molecules between the blood and the brain, as well as aberrant angiogenesis, vessel regression, brain hypoperfusion, and an inflammatory response (Wardlaw et al. 2020; Zlokovic 2008). This establishes a "vicious circle" of the disease process, triggered by various conditions. Consequently, progressive synaptic and neuronal dysfunction, along with the characteristic neuron loss observed in NDDs, ensues. However, this process progresses slowly and is time dependent.

The processes driving angiogenesis are not exclusively active during growth and development; they are also crucial for certain physiological and pathological occurrences throughout adulthood. For instance, angiogenesis is involved in regular physical activity (Ding et al. 2004a; Ding et al. 2006a; Ding et al. 2004b; Zhang et al. 2013), atherosclerosis (Blevins et al. 2021), retinopathies (Cavallaro et al. 2014), hypertension, and especially during the development of some NDDs (Brown et al. 2007; Moreno et al. 2013) and tumors (Claesson-Welsh and Welsh 2013; Josowitz, Bindra and Saltzman 2023; Pellerino et al. 2023). Inhibiting angiogenesis is a crucial approach in the treatment of numerous diseases, especially neoplasias, as adequate vascularization is essential for tumor growth (Jayakumar et al. 2017; Josowitz et al. 2023; Lenci et al. 2021; Pulsatelli et al. 2020; Wang et al. 2012).

Abnormal capillary density or alterations in the capillary bed and abnormal angiogenesis have been observed in certain NDDs (Fernandez-Klett et al. 2020; Kolinko et al. 2015; Skaaraas et al. 2021). The vasculature within the tissue is essential for delivering oxygen and nutrients and removing metabolic waste products. Additionally, the vasculature serves as a source for various immune system cells and mediators. Therefore, the capillary network is vital for tissue function, nourishment, tissue repair, inflammation, and the transport or removal

of signaling molecules that regulate cell survival and death—with both beneficial and adverse effects. The density of the vascular network can also influence the success or failure of graft survival processes (Roitbak et al. 2008).

1.5.1 BBB breakdown and extravasation of blood cells

The significance of vascular structure and function in brain health is underscored by the central role played by cerebral blood vessels in a broad range of pathologies associated with cognitive impairment. One of the distinctive features of cerebral vascularization is the presence of specialized tight junctions that limit the diffusion of molecules and endocytic vesicles, and reduce the rate of transcytosis compared to that in the peripheral vasculature (Zlokovic 2008). Consequently, under normal conditions, caveolar transcytosis is minimal, and only a limited amount of macromolecular cargo is allowed to cross the endothelium of cerebral capillaries (Tuma and Hubbard 2003). However, during BBB dysfunction, the activation of ECs leads to enhanced caveolar transcytosis, which can have detrimental effects on brain cells (Muradashvili et al. 2012; Muradashvili et al. 2016; Sulimai and Lominadze 2020). The increased capillary permeability and significant transcytosis associated with these processes give rise to a characteristic pathological manifestation known as cerebral purpura (Iadecola 2013; Montagne et al. 2017; Zlokovic 2011). Cerebral purpura can result from various causes, including blood diseases, immunological disorders associated with demyelination, fat embolism, infections, poisoning (such as arsenic or anticoagulants), head trauma, heatstroke, septicemia, and disseminated intravascular coagulation. The microscopic areas (microbleeds) associated with blood extravasation are limited to the perivascular space and do not disrupt the brain parenchyma (De Reuck 2012), but the access of nutrients to neurons is complicated. Cortical microbleeds often accompany cerebral amyloid angiopathy (CAA) (De Reuck 2012; Park et al. 2013). Typically, this condition is accompanied by severe impairment of brain function, leading to NDD and dementia development.

Another result of changing the capillary configuration is the blockage of microvessels. The loss of large vessels elasticity increases the pulsatile stress on microvessels, especiallyon the microvessels that branch directly from them, which is the basis of parenchymal damage (Scuteri et al. 2011; Thompson and

Hakim 2009). In contrast to large- and middle-sized vessels, the loss of microvessels elasticity cannot be adequately compensated for by anastomotic branches (Blinder et al. 2013; Kleinfeld et al. 2011). This results in reduced blood flow that is inadequate and thus the creation of small ischemic spots similar to microinfarcts (Nguyen et al. 2011; Nishimura et al. 2010; Shih et al. 2013). These microinfarcts are distinct lesions characterized by necrosis, cavities, and inflammation (such as astrocytosis, microgliosis, and macrophage infiltration) (Thal et al. 2012) caused by the blockage of in small blood vessels. This process shapes how the response of th body to neural activation occurs with a precise and specific timing in terms of space and time (Iadecola 2004; Iadecola 2013).

In addition, endothelial dysfunction has another significant outcome: an elevated permeability of the BBB, resulting in the leakage of plasma proteins, including fibrinogen, into the brain (Iadecola 2013; Nguyen et al. 2011). Fibrinogen activation triggers the activation of CD11b/CD18 receptors, which in turn leads to the production of reactive oxygen species, proinflammatory cytokines, and MMPs by activated microglia, reactive astrocytes, and oligodendrocyte progenitor cells (Alruwaili et al. 2023; Brill et al. 2011; Lam et al. 2023). Furthermore, MMPs directly influence junction proteins and extracellular matrix proteins within the basement membrane (Rosenberg 2009) whith increases in many NDDs and after ischemic CNS injury (Rosenberg 2009). However, it is important to highlight that the alterations in blood flow triggered by activation rely on the coordinated collaboration among neurons, astrocytes, and vascular cells. This collaboration involves a diverse array of molecular signals, including ions, arachidonic acid byproducts, nitric oxide, adenosine, neurotransmitters, and neuropeptides (Cauli and Hamel 2010; Drake and Iadecola 2007; Kleinfeld et al. 2011).

Due to its crucial role in development and stability, alterations in the Notch signaling pathway often contribute to the loss of vascular smooth muscle cells and pericytes (Hofmann and Iruela-Arispe 2007). This loss can lead to a narrowing (constriction) and/or occlusion of the capillary lumen. In these situations, changes in the connection between ECs and pericytes, particularly within peg-and-socket junctions, have been observed (Dziewulska and Lewandowska 2012; Glinskii et al. 2013). Consequently, the brain microvascular network becomes unstable and undergoes remodeling. Additionally, the ischemia caused by pericyte dysfunction may hinder brain regeneration by limiting the delivery of nutrients and drugs to the tissue and by promoting metabolic stress (Yemisci et al. 2009). Furthermore, pericyte dissociation promotes a deficiency in the contribution of MMPs (Trivedi et al. 2016; Winkler et al. 2011), resulting in a significant reduction in both the

formation of new blood vessels and the stability of existing vessels, especially during the initial stages of regeneration.

Moreover, pericytes play diverse roles in the breakdown of the BBB during age-related learning and memory impairments associated with NDDs (Bell et al. 2010). Several disorders, including AD (Kisler et al. 2017; Montagne et al. 2015), Parkinson's disease (Padel et al. 2016), multiple sclerosis (Geraldes et al. 2017; Ortiz et al. 2014) and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Dziewulska and Lewandowska 2012), are commonly linked to pericyte dysfunction. The development of BBB dysfunction is similar among these disorders, and the presence of neuroinflammatory agents can further exacerbate this dysfunction.

A notable feature of neurovascular unit injuries is the loss of pericytes and endothelial cells, accompanied by the deposition of IgG and fibrin outside the blood vessels (Iadecola 2013; Sengillo et al. 2013). The loss of pericytes causes damage to the BBB through two simultaneous pathways. First, it leads to a decrease in microcirculation within the brain, creating continuous stress on blood flow and oxygen levels. This stress contributes to reduced blood supply in brain capillaries due to occlusion (Craggs et al. 2015; Dziewulska and Lewandowska 2012). Second, there is an accumulation of serum proteins and harmful large molecules in the brain, leading to subsequent degeneration in neuronal function(Armulik et al. 2010; Bell et al. 2010; Montagne et al.2015).

Both pericytes and perivascular macrophages can potentially present antigens, which marks the initial phase of adaptive immunity. Moreover, ECs and microglia contain receptors associated with innate immunity, such as CD36, Toll-like receptors, and the receptor for advanced glycation end products. (Kim et al. 2020; Lampron et al. 2013; Park et al. 2011).

1.5.2 Inflammation and thrombogenesis in neurodegeneration

Inflammation of the vessel wall or vasculitis can present in various forms depending on the size of the affected vessels and the specific histological changes observed (Povýšil and Šteiner 2007). In neurodegenerative diseases, vasculitis of small vessels and capillaries is the most common manifestation. Studying the characteristics of capillary wall vasculitis in NDDs provides valuable insights into

the underlying pathological processes and contributes to improved diagnostic and therapeutic approaches.

Microvessel vasculitis in NDDs is characterized by specific histological features that indicate inflammation and damage to the capillary walls. Inflammatory cell infiltration, including lymphocytes and mononuclear cells, observed within and around the wall of brain microvessels (Griffin et al. 1996; Reich et al. 2018). Additionally, vasculitic changes lead to a thickening of the capillary walls, often associated with edema and the deposition of immune complexes (Ropper et al. 2014; Willison and Yuki 2002). The activation and injury of endothelial cells are also evident, as ECs may show swelling, detachment, or damage (Reich et al. 2018; Willison and Yuki 2002). Furthermore, perivascular spaces can exhibit infiltrates of inflammatory cells, contributing to the overall inflammatory response (Griffin et al. 1996; Willison and Yuki 2002). These histological features have been described in various studies, including research on conditions such as Guillain–Barré syndrome and multiple sclerosis.

In addition, damage to ECs can arise from direct immune cell attack or exposure to various active substances released by adjacent cells (Iadecola 2013; Sengillo et al. 2013). In either scenario, EC damage triggers a cascade of events, including basement membrane exposure, fibrin release (Alruwaili et al. 2023; Iadecola 2013; Nguyen et al. 2011), platelet activation, and the formation of microthrombi (Reich et al. 2018; Willison and Yuki 2002). These changes encompass the activation and swelling of neighboring ECs, leading to the disruption of tight junctions between them. In response to the injury, inflammatory infiltrates consisting of lymphocytes and mononuclear cells surround the damaged ECs. These alterations in the endothelial barrier play a significant role in the pathogenesis of various neurodegenerative diseases, contributing to the breakdown of the BBB and potentially exacerbating neuronal degeneration.

Platelets play dual roles in pathological processes, as they can both be activated in response to inflammation during disease and contribute to the progression of such diseases, leading to additional neurodegeneration (Sulimai et al. 2023). In the context of the area of traumatic damage that surrounds the regional primary lesions, the formation of thrombi in the microcirculation contributes to reduced cerebral blood flow in the traumatic penumbra (Schwarzmaier et al. 2010), resulting in secondary damage that impairs neuronal function and ultimately leads to neurodegeneration (Birdsill et al. 2013). Additionally, platelet extravasation has been observed in inflammatory reactions, often resulting from vascular rupture or increased permeability of undamaged venular endothelium via

a transcellular route (Feng et al. 1998). These mechanisms highlight the involvement of platelets in pathological processes and their potential contribution to neurodegenerative conditions.

Inflammatory changes and atherosclerosis can contribute to the formation of microaneurysms (diameter 50-150 μm) (Armulik et al. 2010; Kisler et al.2017; Montagne et al. 2015; Zlokovic 2011), which can lead to significant bleeding in the brain (cerebral purpura) (Iadecola 2013; Montagne et al. 2017), particularly in hypertensive patients. Additionally, edema resulting from ischemic damage can further limit blood flow and contribute to an increase in intracranial pressure and reduced perfusion through the brain (Yemisci et al. 2009).

The perivascular space serves as the pathway through which brain antigens reach the systemic immune system (Galea et al. 2007), eventually draining into the cervical lymph nodes (Laman and Weller 2013). Perivascular macrophages, positioned alongside the vascular basement membrane, play a crucial role in facilitating lymphocyte movement from the perivascular space across the glial basement membrane and into brain tissue (Tran et al. 1998). Furthermore, infiltrating immune cells release proinflammatory molecules, including cytokines (e.g., interleukin-1β and tumor necrosis factor-α) and chemokines, contributing to neuroinflammation and further recruitment of immune cells (Kovac et al. 2004; Manich et al. 2019). Astrocytes express “death” ligands (CD95L) on their perivascular end feet and control immune trafficking by triggering the apoptosis of CD95+ lymphocytes attempting to enter the brain (Bechmann et al. 1999; Galea et al. 2007).

It should be noted that inflammatory changes do not indicate a definite infectious etiology. A predominance of neutrophils in exudate can be a reaction to aseptic necrosis (cerebral infarction), whereas lymphocytic exudation is part of demyelinating processes. Capillary proliferation is part of both inflammatory (abscess surrounding) and non inflammatory changes (hypoxic changes and Wernicke's encephalopathy). The detrimental effects of the nitrative/oxidative stress induced by ischemia/reperfusion on affected microcirculatory areas have profound implications for nutrient delivery to the tissue and play a critical role in neuronal activity and survival (Dalkara and Alarcon-Martinez 2015; Dalkara et al. 2011; Hall et al.2014; Jespersen and Ostergaard 2012). The calcium-sensing receptor (CaSR), a G-protein-coupled receptor, acts as a modulator of systemic calcium homeostasis and is predominantly expressed in reactive astrocytes and some neurons. Its expression regulates the altered extracellular ionic environment within the ischemic and border zones, where it interacts with specific endothelial

cells and pericytes (Noh et al. 2015). In severe cases of reduced blood flow, pericytes might undergo intense and irreversible contraction, causing the blockage of small capillaries. Surprisingly, this blockage can trigger the growth of new blood vessels (angiogenesis and neovascularization) by activating the versatile stem cell capabilities of other pericytes in the brain. This process holds promise for achieving brain restorative effects (Eyden 2005; Padel et al. 2016; Truettner et al. 2013; Yao et al. 2016).

1.6 Circulatory-system changes in neurodegenerative disorders

As described in the previous section, the condition of microvessels in NDDs is associated with changes in other brain compartments that affect the local environment. These changes can influence regenerative capacity, neural plasticity, and subsequently impact therapeutic options. Changes in the brain can involve alterations in the number or function of glial cells (Gyengesi et al. 2018; Qu et al. 2017), deviations in the levels of nourishing factors or signaling substances, the presence of inflammatory agents (Castrogiovanni et al. 2021; del Pilar et al. 2021; Patterson et al. 2014; Wachter et al. 2016), and microvasculature modifications.

Understanding microvascular bed changes in neurodegenerative tissue helps predict therapy effectiveness and recovery challenges. Identifying alterations helps elucidate disease features and the impacts of local environments on recovery and neural plasticity. Vascular dementia, or cognitive impairment due to cerebrovascular issues, ranks second among dementia cases after NDDs. In this section, we will focus on the specific microvascular changes observed in certain neurodegenerative diseases.

1.6.1 Vascular changes in Alzheimer’s disease

During the era of Alois Alzheimer (1900s), the prevalent belief regarding dementia was that it was primarily caused by a condition known as "hardening of the arteries," often referred to as arteriosclerotic dementia (Bowler 2007; Jellinger 2006). Vascular factors were considered major players in dementia in the

20th century until the 1980s, when amyloid-beta (Aβ) peptide was identified as the main component of parenchymal (amyloid plaque) (Karran et al. 2011; Zlokovic 2011) and vascular (amyloid angiopathy) amyloid deposits (Glenner and Wong 1984; Kang et al. 1987), pathological hallmarks of AD. Furthermore, clinical studies and postmortem analysis suggest a significant interaction between Aβ deposition and microvascular pathology in a large majority (~ 90%) of patients with confirmed AD (Ellis et al. 1996; Kamara et al. 2018; Strozyk et al. 2010). Shortly thereafter, mutations in the amyloid precursor protein (APP) gene were identified in familial forms of Alzheimer disease (AD) (Bertram and Tanzi 2008).

Neurovascular changes appear to be closely associated with neuroinflammation caused by microglial activation and the release of proinflammatory cytokines in response to the deposition of insoluble Aβ proteins (Nichols et al. 2019; Streit et al. 2004). The potential supposed effects of Aβ, although not the direct cause of the disease, can result in a notable decrease in the number of neurons (Bouras et al. 2006; West et al. 2004). This decrease in neuron and synapse quantity, along with the presence of neurofibrillary tangles and senile plaques, is often observed alongside issues related to vascular pathology. There is also a reported increase in the occurrence of twisted, kinked, and string-like vessels, indicating a restructuring of the vascular extracellular matrix (Gama Sosa et al. 2010). Furthermore, a reduction in the length and number of vessels without any change in density (Kolinko et al.2015; Lee et al. 2005) might simply reflect an adaptive reaction of the capillary network to the decrease in energy demands associated with reduced neuronal activity in older individuals (Bouras et al. 2006).

There have also been reports of various degrees of vascular wall degeneration, with the loss of basal lumens and distorted, swollen nuclei found in endothelial cells, which promotes the formation of microhematomas up to 100 μm in diameter (Gama Sosa et al. 2010; Price et al. 2001; Winkler et al. 2013). In this context, small hemorrhages coincide with the buildup of Aβ deposits in the layers of blood vessel walls, such as the tunica media, smooth muscle cells, and adventitia (Charidimou et al. 2012; Charidimou et al. 2018; Di Marco et al. 2015). This accumulation hastens the development and advancement of amyloid angiopathy in the small blood vessels of the brain (de Wit et al. 2017). Such changes in the structure of vascular walls trigger a widespread increase in the production of proteins linked to the extracellular matrix (de Wit et al. 2017).

Microscope examinations have shown a strong correlation between the length of microvessels (capillaries) and the quantity of synaptic and neuronal mitochondria in the hippocampus (Chen et al. 2018; Smith and McMahon 2018).

Pericytes, which play a role in regulating the contraction of capillaries to maintain blood flow (Bergers and Song 2005; Hall et al. 2014), seem to undergo alterations due to the deposition of Aβ in blood vessels (Gama Sosa et al. 2010; Joo, et al. 2017; Kumar-Singh 2008; Lai, et al. 2015; Revesz et al. 2003; Sengillo et al. 2013).

Moreover, research indicates that the deposition of mutated Aβ in cell cultures could influence the maturation of neural stem cells (Fonseca et al. 2013b) and lead to irregularities in the functioning of glial cells (Voorhees et al. 2019). Finally, both premortem functional magnetic resonance imaging and postmortem studies on AD patients support the idea that degenerative changes in blood vessels contribute to impaired remodeling of blood vessels and/or angiogenesis (Desai et al. 2009; Kannurpatti et al. 2010).

In the initial stages of AD, hippocampal pericytes degrade, reducing platelet derived growth factor subunit B (PDGF-B) production (Halliday et al. 2016; Montagne et al. 2015; Tai et al. 2016). The disruption of endothelial/pericyte interactions via molecules such as PDGF-B, α-SMA (alpha smooth muscle actin), and CD13 (aminopeptidase N) leads to a reduced presence of vascular endothelial cadherin in BBB endothelial adherens junctions (Bell and Zlokovic 2009; Gertz et al. 2016), causing capillary diameter reduction and endothelial abnormalities (Hellstrom et al. 1999). This support of Aβ deposits (Dalkara and Alarcon-Martinez 2015; Dalkara et al. 2011; Yemisci et al. 2009) and accumulation of harmful substances, causing neurovascular unit dysfunction (Duncombe et al. 2017; Iadecola 2017). Amylin cell inclusions in the pericyte cytoplasm contribute to autophagy and reduced neuron-glial antigen expression (Molteni and Rossetti 2017). Consequently, this causes a leakage and buildup of harmful large molecules such as fibrin (Padel et al. 2016; Paul et al. 2007), thrombin (Chen et al. 2010; Mhatre et al. 2004), plasmin (Chen and Strickland 1997), and hemoglobin-derived hemosiderin, leading to the accumulation of iron and reactive oxygen species (Bell et al. 2012; Halliday et al. 2016; Zhong et al. 2008). This breakdown also contributes to the impairment of adhesion molecule production in pericytes, facilitating the entry of T-cells into the brain (Verbeek et al. 1995; Wevers and de Vries 2016). Such an occurrence is observed in neurodegenerative conditions such as multiple sclerosis.

The data from modern studies provide compelling evidence showing a 60% reduction in pericytes and a 33% decrease in mural vascular cells in the human cortex and hippocampus in patients with AD during the clinical stage (Sengillo et al. 2013). Changes in the structure of the vascular wall were correlated with an

increased production of extracellular matrix-related proteins. Studying capillary changes in AD revealed that endoplasmic-reticulum stress plays a vital role in reducing cerebral vascular density, increasing the number of apoptotic cerebral vascular cells, and boosting Aβ production (Fonseca et al. 2013a; Miao et al. 2005). The vascular changes in AD were described as degenerative, with the loss of the ability to perform vascular remodeling and/or angiogenesis (Desai et al. 2009; Kannurpatti et al. 2010). Nevertheless, the mechanisms underlying microvascular dysfunction are not fully understood.

From a clinical perspective, vascular changes observed in AD appear as cerebral amyloid angiitis (Chung et al. 2011) or more commonly, cerebral amyloid angiopathy (Charidimou et al. 2012; Illsley and Ramadan 2014). These conditions account for approximately 5–10% of instances involving spontaneous bleeding within the brain (Iadecola 2013; Montagne et al. 2017; Zlokovic 2011).

Additionally, AD and cerebrovascular conditions might be associated with overlapping risk factors, including hypertension, insulin resistance, diabetes, obesity, elevated homocysteine levels, and high cholesterol levels (Craft 2009; Fillit et al. 2008; Honjo et al. 2012; Purnell et al. 2009). The data indicate that individuals with early cognitive dysfunction experience brain capillary damage and BBB breakdown, independent of changes in Alzheimer's Aβ and tau biomarkers. BBB breakdown may serve as an early biomarker of human cognitive dysfunction, separate from Aβ and tau (Iadecola 2013; Iadecola 2017; Nation et al. 2019).

1.6.2 Vascular pathology associated with Parkinson’s disease

The second-most prevalent NDD in aging humans is Parkinson disease (PD) (de Lau and Breteler 2006). PD is a slowly progressing inflammatory condition affecting the nervous system. Symptoms such as slowed movements, stiffness, difficulty maintaining balance, and tremors while at rest are recognized. These symptoms stem from a considerable reduction in dopamine levels (Fahn 2003). PD tends to be more prevalent in men, particularly among those who have a history of smoking (Schwartz et al. 2012). The deterioration of neurons in PD patients primarily impacts areas such as the substantia nigra, basal ganglia nuclei, and the cerebral cortex, leading to a depletion of dopamine ing the nigro-striatal pathway (Poewe 2009).

One study examined the brain vessels of PD patients are reported a significant reduction in the number of capillaries, along a with shorter length and increased diameter (Guan et al. 2013). Evident damage to the capillary network was also evidenced by reduced branching (Guan et al. 2013). The vascular pathology included the formation of endothelial "clusters" and a damaged capillary network, possibly due to vessel fragmentation. Significant vessel degeneration was noticeable in various parts of the brain, including the substantia nigra, cerebral cortex, and brainstem nuclei, but not in the caudate nucleus (Guan et al. 2013). Comparable alterations were also observed in animal models (Sarkar et al. 2014).

These findings suggest that vascular degeneration may be a crucial additional factor contributing to PD progression and may even play a role in the initial pathology leading to neuronal degeneration. In support of this hypothesis, reports have indicated significantly increased levels of molecular markers, such as monocyte chemoattractant protein-1, vascular endothelial growth factor, and endothelin-1, indicating endothelial damage in PD patients (Hunt et al. 2020; Makarov et al. 2013). Notably, these changes were observed without alterations in the levels of monocarboxylates and glucose in animal models (Puchades et al. 2013).

Assessing the brain by employing immunostaining for integrin αvβ3, which signals the growth of new blood vessels and activated microglia, revealed an increase in the number and activation of microglia, specifically in the substantia nigra (Desai et al. 2009; Skaaraas et al. 2021). This finding the potential existence of newly formed vessels that might not possess the typical barrier features of the BBB.

1.6.3 Cerebrovascular alterations in Lewy body disease

The defining feature of Lewy body disease involves deteriorating neurons that contain abnormal accumulations of proteins such as α-synuclein (Kalaitzakis et al. 2008; Lin et al. 2009). These inclusions are known as Lewy bodies and are observed even before the clinical symptoms of PD appear, often during autopsy examinations (DelleDonne et al. 2008; Pifl et al. 2023). Surprisingly, research indicates a reverse link between Lewy body disease and established vascular conditions, such as a history of stroke (Ghebremedhin et al. 2010). However, specific vascular irregularities have been observed in the histological analysis of

individuals with Lewy body disease. Notably, small spherical accumulations of the TDP-43 protein have been observed near small blood vessels, but not near larger vessels (Lin et al. 2009). These accumulations tend to associate with capillaries and are enclosed by the vascular basal lamina, leading to the formation of new basal lamina that compresses and pinches off the endfeet of astrocytes. This finding suggested that the occurrence of microvasculopathy associated with the loss of BBB integrity. Furthermore, changes in the number of microglia and vessels, as well as increased angiogenesis, have also been documented in subjects with Lewy body disease, indicating that these changes may occur during the preclinical period of PD (Bradaric et al. 2012).

1.6.4 Altered vasculature in Huntington's disease

Huntington's disease (HD) commonly occurs in individuals between the ages of 35 and 50 and is inherited in an autosomal-dominant pattern (Montoya et al. 2006; Novak et al. 2012). This process involves the elongation of a polyglutamine segment in a specific protein. Magnetic resonance imaging has revealed notable reductions in blood flow within the brains of individuals with HD, particularly in areas of the cerebral cortex linked to increased neural activity (Chen et al. 2012). On the other hand, immunohistological studies in humans and mouse models have shown increased vessel density in the cortical and striatal regions, suggesting an intact and functional BBB (Franciosi et al. 2012; Lin et al. 2013). The chronic deposition of peripheral lipopolysaccharides, which is typical in presymptomatic HD, affects vessel integrity, but not vessel density or length (Franciosi et al. 2012).

The observed narrowing of vessel lumens was attributed to increased basal lamina thickness, reflecting augmented smooth-muscle cell proliferation and reduced protease activity involved in extracellular matrix turnover, leading to the accumulation of vessel wall components such as collagen IV (Franciosi et al. 2012). This process influences the expression and activity of endothelial nitric oxide synthase (Deckel et al. 1998; Duran-Vilaregut et al. 2011). However, the effects of the mutant Huntingtin protein on ECs have not been reported. Additionally, the vessel density in the cerebellum appeared similar between HD patients and healthy individuals (Maat-Schieman et al. 1999).

Several scientists have explored treating HD by transplanting intact fetal striatal tissue (Cisbani et al. 2013). However, these grafts exhibited fewer large

blood vessels and astrocytes, which possibly affected their survival. The blood supply seems to match the graft's size and how the fetal tissue is dissected (Freeman et al. 2011). Therefore, solid graft that include their own blood vessels from the donor might provoke a stronger immune response than transplants involving suspended cells (Cisbani et al. 2013; Freeman et al.` 2011).

1.6.5 The role of blood vessels in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) involves the slow progression of motor neuron dysfunction and degeneration of motor neurons in the brainstem nuclei, corticospinal tract, and ventral roots of the spinal cord and typically occurring after the age of 40 years (Evans et al. 2013; Garbuzova-Davis et al. 2011). It has both familial and sporadic causes, with mutations in more than twelve genes suspected to contribute to ALS (Su et al. 2014).

In ALS, abnormalities appear at the subcellular level. These defects include disrupted and deteriorating mitochondrial structures called cristae in both ECs and neuropil. Additionally, astrocytes lose the ability to remove water from neural tissue, causing swelling in the brainstem and spinal cord (Evans et al. 2013; Garbuzova-Davis et al. 2011). The condition involves swelling of the foot processes of astrocytes, decay of endothelial cells, and fluid buildup around astrocytes and motoneurons, which collectively disrupt the BBB (Garbuzova-Davis et al. 2011). Furthermore, ALS patients exhibit deposits around blood vessels, and these deposits consist of hemoglobin from red blood cells and hemosiderin, along with plasma proteins that leak outside the blood vessels (Winkler et al. 2013). The toxic effect of hemoglobin on neural cells suggests that microvessel ruptur plays a role in pathogenic neuronal degeneration. Additionally, vascular rupturing coincides with a reduction in the capillary pericyte population, which is critical for BBB function (Garbuzova-Davis et al. 2011; Winkler et al. 2013). Pericytes produce vasoactive neuropeptides; neurotransmitters; vasodilators; and regulators of perfusion, hypoxia, immune responses, and nociception (Staines et al. 2009). Hence, pericyte loss likely contributes to disease manifestation.

Moreover, research has suggested a reduction in capillary length, number, diameter, and blood flow in a mouse model of ALS (Miyazaki et al. 2011; Zygmunt et al. 2003). However, these findings were not derived from systematic

uniform random sampling (SURS), which might result in a biased selection of microscopic fields of view (FOVs).

1.6.6 Corticobasal degeneration and progressive supranuclear palsy

Both corticobasal degeneration and progressive supranuclear palsy fall under the category of Parkinson plus syndromes. Corticobasal degeneration is a progressive degenerative condition impacting both the cortical and subcortical systems, and typically emerges at approximately 60 years of age (Armstrong et al. 2013). A key part of the corticobasal degeneration involves the breakdown of the cerebellar dentate nucleus (Su et al. 2000). However, while this area is affected, the other cerebellar nuclei have not yet been thoroughly examined. This condition displays signs of phosphorylated tau in neurons and glial cells, showcasing various features such as pre-tangles, neurofibrillary tangles, astrocytic plaques, tufted astrocytes, coiled bodies, and argyrophilic threads (Katsuse et al. 2003).

PSP is characterized by supranuclear ophthalmoplegia, primarily affecting vertical gaze, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, and other less consistent cerebellar and pyramidal symptoms. Previously, this disease was considered arteriosclerotic parkinsonism (Critchley 1929), but this concept was later discarded. Progressive supranuclear palsy typically progresses more rapidly than PD and displays atypical clinical features (Steele et al. 2014). This rapid progression is associated with increased angiogenesis and a greater number of vessels in the affected areas (Bradaric et al. 2012).

Postmortem studies both corticobasal degeneration patients and patients with progressive supranuclear palsy frequently reveal the presence of astrocytic plaques and tuft-shaped astrocytes. A close proximity of the astrocytic plaques to the nearest blood vessel, which shows a reduced diameter, has been observed, suggesting the distal accumulation of phosphorylated tau associated with blood vessels (Shibuya et al. 2011). These findings imply a similarity in the pathogenic mechanisms of vascular injury in these diseases.

1.6.7 Small vessel disease, leukoaraiosis, and lacunar infarcts

Cerebral small vessel disease (CSVD) is a prevalent, chronic, and progressive vascular condition that primarily affects microvessels, 50–400 μm in diameter, that supply white matter and deep brain structures(Chojdak-Lukasiewicz et al. 2021). CSVD is frequently observed as an incidental finding on brain scans, particularly in individuals older then 80 years of age (Caruso et al. 2019; Yousufuddin 2019) and accounts for approximately 20% of dementia cases (Iadecola 2013). CSVD is commonly caused by various factors, including arteriosclerosis, cerebral amyloid angiopathy, genetic small vessel angiopathy, inflammation, immune-mediated small vessel diseases, and venous collagenosis. The disease presents with a wide range of clinical and radiological manifestations. It is primarily responsible for stroke incidents, gait disturbances, depression, cognitive impairment, and dementia in elderly individuals (Das et al. 2019; Rensma et al. 2018; van der Holst et al. 2015).

Confluent white matter lesions or leukoaraiosis, as well as lacunes (small white matter infarcts measuring less than 1.5 cm), are frequently observed in individuals with vascular cognitive impairment and are strongly linked to cardiovascular risk factors, particularly hypertension, diabetes, hyperlipidemia, and smoking (Gorelick et al. 2011; Iadecola 2013; Wardlaw et al. 2013a; Wardlaw et al. 2013b). These lesions result in various types of damage, including vacuolation, demyelination, axonal loss, and lacunar infarcts. The white matter lesions are typically visualized as hyperintensities on MRI scans, although they can also indicate other pathological conditions (Gouw et al. 2011). The vascular issues associated with these lesions involve several pathologies. These pathologies include atherosclerotic plaques affecting small blood vessels in the brain, the accumulation of a hyaline substance in the walls of these vessels (known as lipohyalinosis), fibrotic changes causing a stiffening and distortion of vessel walls (arteriolosclerosis), and a complete breakdown of vascular wall integrity (fibrinoid necrosis) (Blevins et al. 2021; Thal et al. 2012). Arterioles can become twisted, with thicker basement membranes, and they are often surrounded by enlarged perivascular spaces (Brown and Thore 2011). Additionally, there is a reduction in the number of capillaries, and some nonfunctional capillaries, referred to as "string vessels," are present; these lack endothelial cells and consist solely of a basement membrane (Brown and Thore 2011). Venules exhibit collagen deposits (with venous collagenosis) (Black et al. 2009; Brown and Thore 2011).

1.6.8 Vasculature changes in Niemann–Pick disease

Niemann–Pick disease is associated with different levels of lipid storage and foam cell infiltration in tissues, and affected young age patients exhibit shared clinical features such as hepatosplenomegaly, pulmonary insufficiency, and/or CNS involvement (Schuchman and Desnick 2017). Recent advancements have led to the understanding that Niemann–Pick disease can be attributed to two separate metabolic abnormalities. The first abnormality arises from the deficient activity of the enzyme acid sphingomyelinase, leading to "types A & B" (Brady et al. 1966). The second abnormality is related to defective cholesterol transport, resulting in the condition known as type C disease. Neurodegenerative signs are observed mainly in type A and type C of Niemann–Pick disease patients (Schuchman and Desnick 2017). The disease is distinguished by a rapidly advancing neurodegenerative course, with profound hypotonia and failure to reach milestones.

Although the primary cause of the disease is A4/beta protein, it is not detected in the form of plaques or in the walls of blood vessels (Love et al. 1995), which might be associated with early atherosclerotic heart disease (McGovern et al. 2004). However, in type C, there is a significant reduction in cholesterol absorption and plasma cholesterol levels, providing nearly complete protection from the development of atherosclerosis (Blevins et al. 2021; Davis et al. 2007). Despite the availability of animal models for Niemann–Pick disease, there is a lack of research on the pathological changes in the brain microvasculature.

1.7 Influence of the vascular network on graft survival and integration

The vascular network plays a significant role in influencing the survival and integration of grafts within the brain (Ballabh et al. 2004; Cisbani et al. 2013; Vorbrodt and Dobrogowska 2003). The success of grafts, such as transplanted cells or tissues, relies on their ability to establish proper vascular connections with the host tissue. The vascular system provides the essential supply of oxygen,

nutrients, and other vital factors necessary for cell survival and function (Abbott et al. 2010; del Pilar et al. 2021).

When grafts are introduced into the brain, their survival and integration largely depend on their ability to quickly establish a connection with existing blood vessels (Cendelin 2016; Cvetanovic et al. 2017). The host vascular network provides the necessary resources for the graft and facilitates the removal of waste products and toxins produced by the graft.

Moreover, a well-functioning vascular network is crucial for maintaining the appropriate microenvironment around the graft, as it helps regulate temperature, pH levels, and overall tissue homeostasis, and immune activities, all of which are essential for the survival of grafted cells or tissues (Abbott et al. 2010; Cendelin et al. 2022; Cendelín et al. 2006; del Pilar et al. 2021).

Conversely, inadequate vascularization can lead to graft failure. An insufficient blood supply can result in ischemia, where the graft tissue is deprived of oxygen and nutrients, leading to cell death. Poor vascular integration can also hinder the exchange of signaling molecules between the graft and the host tissue, limiting the ability of the graft to communicate and integrate effectively (McFarland et al. 2007; Vogel et al. 2001; Winkler et al. 2014).

On the other hand, hematopoietic cells capable of influencing angiogenesis and neurovascular repair in certain areas of the brain can be used for grafting (Garbuzova-Davis et al. 2019).

1.8 Models of neurodegenerative diseases

NDDs often involve changes in very small blood vessels within affected tissues. Sometimes, these changes are secondary effects, while in other cases, they directly contribute to the degeneration process (Kolinko et al. 2015). Additionally, abnormal microvessel density can either promote or hinder tissue regeneration and might affect treatment efficacy. The level of vascularization in tissue is crucial, especially for issues such as the development and proper integration of neural and stem cell grafts into the affected areas (Cendelin 2016). However, there is limited knowledge about vascular changes specific to cerebellar degeneration. Hereditary cerebellar ataxias, a diverse and uncommon group of NDDs, significantly impact

motor abilities, cognition, and emotional functions in patients (Manto 2005).

Many studies have focused on understanding how exercise affects the number of small blood vessels in the motor cortex and the cerebellum (Isaacs et al. 1992; Kleim et al. 2002; Swain et al. 2003). Prolonged physical activity prompts significant capillary growth in the motor regions of the cortex as an effective response. However, a previous detailed quantitative analysis specifically examining of the extent of blood vessel growth in various histological sections of the cerebellum had not been conducted prior to our research.

The frequently used models of cerebellar NDDs are Lurcher and Purkinje cell degenerated mutant mice. To highlight the importance of studying the microcirculation in the cerebellum, consider the following examples: In Lurcher mutant mice, unlike in wild-type mice, cerebellar grafts struggl to integrate into the host cerebellar tissue (Babuska et al. 2015; Cendelin et al. 2018; Purkartova et al. 2019). However, this integration issue was not observed in Purkinje cell degeneration pcd mutant mice (Purkartova et al. 2019).

This difference could be linked to abnormal numbers of very small blood vessels, potentially influencing graft development. However, it is unclear whether the change in the absolute number of capillaries results from less active blood vessel formation during rapid neurodegeneration in the developing cerebellum (Swain et al. 2003), or from a secondary decrease in capillaries that have already formed (Rhyu et al. 2010). It is also plausible that both mechanisms are at play. To answer this question, a more comprehensive study of various developmental stages is necessary.

Over the last twenty years, transgenic (Tg) mouse models of AD have revealed the vascular consequences associated with human AD mutations and the accumulation of amyloid-beta peptides (Fonseca et al. 2013b; Gama Sosa et al 2010; Kumar-Singh 2008; Lai et al. 2015; Lee et al. 2005; Sasaguri et al. 2017). However, there is growing interest in using rats that overexpress mutations linked to familial AD (Cohen et al. 2013; Jankowsky et al. 2001; Koulousakis et al. 2020). This is because rats share a closer evolutionary connection with humans and exhibit greater behavioral complexity compared than mice (Yang et al. 2004), thus offering additional advantages for studying AD-related mutations in this model. This prompted us to extend the scope of the results obtained from the study of the aforementioned mouse models and assess their relevance for the specific pathology. Consequently, we conducted a parallel investigation of hippocampal vascularization utilizing a well-established rat model of Alzheimer's disease.

1.8.1 Lurcher mice

Mutant or transgenic mouse models have been crucial for studying the characteristics and progression of, as well as potential treatments for, hereditary cerebellar ataxias (Cendelin 2014). One well-known spontaneous mutant model is the Lurcher mouse (Lc) model, which mimics olivocerebellar degeneration (Phillips 1960; Porras-Garcia et al. 2013). This condition arises from a mutation (Grid2Lc) in the gene encoding responsible for the delta 2 glutamate receptor (GluRδ2), which is mainly found in Purkinje cell dendrites and certain hindbrain neurons.(Araki et al. 1993; Lomeli et al. 1993; Takayama et al. 1995). Mice heterozygous for the Grid2Lc mutation experience a complete loss of Purkinje cells within three months due to prolonged cell membrane depolarization (Zuo et al. 1997). This triggers intracellular enzymes that promote neural degeneration, leading to tissue protease activation (Lu and Tsirka 2002) and subsequent secondary degeneration of granule cells, inferior olive neurons (Caddy and Biscoe 1979; Doughty et al. 2000; Heckroth and Eisenman 1991; Wetts and Herrup 1982a; Wetts and Herrup 1982b; Wullner et al. 1995), and inhibitory interneurons in the cerebellar cortex (Zanjani et al. 2006). Although the cerebellar nuclei undergo milder degeneration (Heckroth 1994), the loss of neurons sparks an unusually persistent inflammatory response in the cerebellum of Lc mutant mice (Vernet-der Garabedian et al. 2013). This degeneration causes ataxia (Fortier et al. 1987), cognitive issues, and behavioral abnormalities in these mice (Cendelin et al. 2014; Hilber et al. 2004; Lalonde et al. 1988; Lorivel et al. 2014). Supporting the damaged tissue through the host vascular system has emerged as a straightforward method to counter and reduce the effects of this degeneration (Cendelin 2016).

The Grid2Lc mutation, when present in a homozygous, results in extensive loss of hindbrain neurons during the embryo development (Cheng and Heintz 1997). After birth, these large neurons are entirely absent (Cheng and Heintz 1997). This severe degeneration causes early death (Cheng and Heintz 1997; Resibois et al. 1997), making homozygous homozygous for the Grid2Lc mutation unsuitable for long-term experiments. In contrast, the wild-type (WT) littermates of Lc mutants mice remain entirely healthy and are ideal as control subjects for experiments.

1.8.2 pcd mice

Purkinje cell degeneration (pcd) mice represent another commonly used cerebellar mutant mouse model. These mice are homozygous for Agtpbp1pcd/J mutations found in the gene encoding responsible for cytosolic ATP/GTP binding protein 1, also known as cytosolic carboxypeptidase-like protein (CCP1 or Nna1) (Baltanas et al. 2011; Fernandez-Gonzalez et al. 2002). This protein is notably active in cerebellar Purkinje cells (Baltanas et al. 2011; Fernandez-Gonzalez et al. 2002), olfactory bulb mitral cells (Greer and Shepherd 1982), and retinal photoreceptors (LaVail et al. 1982). The mutation triggers a swift and almost complete degeneration of Purkinje cells through either apoptotic (Kyuhou et al. 2006) or autophagic (Chakrabarti et al. 2009) mechanisms. Degeneration initiates around Postnatal Day 20 (Baltanas et al. 2013), and by Day 28, it is nearly total in most parts of the cerebellum (Mullen et al. 1976). The decrease in cerebellar granule cells follows the loss of Purkinje neurons and escalates progressively (Ghetti et al. 1987; Triarhou 2010). Cerebellar nuclei exhibit a slight reduction in size (Triarhou et al. 1987), while inferior olivary neurons begin disappearing between Postnatal Days 17 and 23, with a 49% decrease reached by Day 300 (Ghetti et al. 1987). Pcd mice additionally undergo a gradual degeneration of the retina, olfactory bulb mitral cells (Blanks et al. 1982; Blanks and Spee 1992; LaVail et al. 1982; Mullen et al. 1976), and thalamus (Ogorman 1985; Ogorman and Sidman 1985). They serve as a model for neurodegeneration, showcasing the selective death of specific neuron groups across different brain regions over a well-defined period (Mullen et al. 1976; Wang and Morgan 2007). The organization of the microcirculatory network in the pcd mouse cerebellum closely aligns with previously described principles (Kleiter and Lametschwandtner 1995; Kolinko et al. 2016; Rhyu et al. 2010).

1.8.3 Transgenic rat model of AD

Transgenic Fischer 344 Alzheimer's Disease (TgF344-AD) rats express human APP with the Swedish mutation and human PSEN1 with the Δexon 9 mutation. Both of these transgenes are controlled by the mouse prion promoter

(Cohen et al. 2013). Compared to those of endogenous rats, the brains of TgF344-AD rats exhibit more then than twofold greater expression of human APP and sixfold-fold greater expression of human PSEN1 (Cohen et al. 2013). Over time, TgF344-AD rats exhibit increasing levels of both detergent-soluble and detergent-insoluble amyloid-beta (Aβ) between 6 and 26 months (Cohen et al. 2013).

Amyloid plaques progressively accumulate in the hippocampus and cortex of these rats. These plaques also appear in the striatum and cerebellum. Cerebral amyloid angiopathy emerges in the cortex, hippocampus, striatum, and cerebellum. Neuritic dystrophies are associated with these plaques (Cohen et al. 2013).

Signs of microgliosis and astrogliosis become noticeable by 6 months (Cohen et al.2013). While the neuron numbers in the hippocampus and cortex of TgF344-AD rats resemble those in wild-type animals at 6 months of age, approximately 40% neuron loss is observed by 16 months (Cohen et al. 2013). At 16 months, the presence of Hirano bodies and spongiform vacuolar pathology are evident (Cohen et al. 2013). Cerebrovascular dysfunction is linked to vascular amyloid deposition, leading to the loss of normal increases in blood flow in cortical penetrating arterioles in response to hypercapnia (Joo et al. 2017). Until now, only a limited number of studies have focused on examining the intricate network of very small blood vessels in these and other transgenic rat models of AD (Ahmad et al. 2002; Corbett et al. 2013; Fitting et al. 2010; Heggland et al. 2015; Madhavadas and Subramanian 2017; Wang et al. 2014).

Tau pathology has also been identified in TgF344-AD rats. Antibodies targeting specific phospho-tau epitopes and conformation-selective tau antibodies can be used to stain neurons in the hippocampus and cortex (Anderson et al. 2023; Morrone et al. 2022). The locus coeruleus was postulated to be one of the initial brain regions to display tau pathology during AD development, prompting an inquiry into locus coeruleus pathology and noradrenergic markers in TgF344-AD rats (Rorabaugh et al. 2017). Hyperphosphorylated tau is detected in the locus coeruleus at 6 months of age, preceding its appearance in the medial entorhinal cortex or hippocampus. Although no neurofibrillary tangles, amyloid plaques, astrogliosis, or neuron loss are observed in the locus coeruleus in rats up to 16 months of age, the norepinephrine content in the hippocampus is lower in TgF344-AD rats than in wild-type rats at 16 months of age. Similarly, in comparison to wild-type rats, 19-month-old TgF344-AD rats exhibit decreased visual acuity but increased contrast sensitivity (Tsai et al. 2014).

2 Objectives and hypothesis

The basic aim of this work was to investigate various aspects of brain microcirculation, and cerebellar disorders, and to perform histological quantification in different mouse models to gain a comprehensive understanding of their roles in neurodegenerative diseases and potential therapeutic interventions.

The specific and complementary objectives are as follows:

2.1. To explore the role of brain microcirculation in the pathogenesis of various neurodegenerative diseases, focusing on the processes of angiogenesis and changes in the brain microcirculation.

Hypothesis: The brain microcirculation plays a significant role in the development of neurodegenerative diseases, and these vascular changes may have both secondary consequences and direct involvement in the pathogenesis of these diseases, contributing to neuronal degeneration based on their quantitative characteristics. The review should also discuss stereological methods commonly used to assess qualitative and quantitative changes in the brain microvascular bed (more in 10.1).

2.2. To compare spatial navigation, learning, and memory in three-month-old mice using two commonly used cerebellar mutant mouse models, pcd and Lc mice, to better understand the functions and mechanisms of cerebellar disorders related to motor coordination, cognitive processes, and affective behaviors. The focus is on the quantitative differences in the retina receptors of the mice.

Hypothesis: Both pcd and Lc mice would exhibit deficits in spatial navigation, learning, and memory due to their cerebellar mutations. These mutations could contribute to retinal degeneration, especially in middle-aged and older mice, affecting the results of behavioral studies. However, the extent to which retinal degeneration affects behavioral disorders in mice in this age group is unclear. We expected to observe differences in their exploration behavior, motivation, and performance in various tests, with Lc mice showing better overall performance than pcd mutant mice. We believed that these results will not be attributed to differences in the

number of retinal receptors (more in 10.2).

2.3. To investigate the influence of cerebellar-related stress response abnormalities on spatial learning and memory in cerebellar-deficient Lurcher mice. The focus is on the quantitative differences in the mouse adrenal gland, which produces stress hormones.

Hypothesis: Additionally, we expected that, compared with wild-type (WT) mice, Lc mice would exhibit an enhanced stress response, as evidenced by increased levels of corticosterone in their urine and increased volumes of adrenal gland components. This should be reflected in a change in the volume, first and foremost, of the glomerular zone of the adrenal glands. However, despite the stress response, we predicted that Lc mice would still retain some capacity for spatial learning (more in 10.3).

2.4. To investigate and compare the vascularity of the individual cerebellar components in WT, pcd and Lc mice, which serve as models of hereditary olivocerebellar degeneration.

Hypothesis: The cerebellar components of Lc mutant mice would exhibit changes in the total number of microvessels compared to those of WT mice, with reductions in vascular density in the cortex due to a reduction in cerebellar volume. Additionally, we expected to observe differences in the relative density of microvessels in the cerebellar cortex and nuclei between Lc mutant and WT mice, potentially providing insights into the vascular changes associated with hereditary cerebellar degeneration (more in 10.4.1).

Hypothesis: In pcd mutant mice, there would be a significant reduction in the microvascular network in the cerebellum, proportional to the cerebellar volume reduction, especially in the cerebellar gray matter compared to that in WT mice (more in 10.4.2).

2.5. To assess the total volume and general morphology of embryonic cerebellar grafts injected in the form of embryonic Purkinje cell suspensions in Lc and pcd mutant mice, as well as in their WT counterparts.

Hypothesis: We believed that the intensity of microvascularization would affect trophic support and have an impact on the quality of graft survival, which may be evident in changes in the graft total volume and/or the general morphology of transplanted cells. Additionally, such a study would allow the assessment of the efficacy of treating Lc degeneration through embryonic cell transplantation (more in 10.5.1).

Hypothesis: Graft survival in pcd and Lc mice may differ due to variations in cerebellar microvascularization. Thus, we hypothesized that in the group with a higher capillary density, transplant-derived Purkinje cells would colonize the host cerebellum more efficiently (more in 10.5.2).

2.6. To assess microvascular structure differences between Tg rats and non-Tg littermates of rats using rigorous stereological methods. The focus is on the number and length of microvessels in various hippocampal subregions.

Hypothesis: There would be significant microvascular differences in the total hippocampus and specific hippocampal cell layers between Tg and non-Tg rats. Additionally, within each group, differences in microvascular parameters were expected across different hippocampal subregions. (more in 10.6).

2.7. To review and unify the existing understanding of how brain pericytes work in normal body functions, their role in causing neurodegenerative diseases, and their connections with different parts of the neurovascular system.

Hypothesis: We hypothesized that brain pericytes would play crucial roles in normal brain physiology and be involved in the pathogenesis of neurodegenerative diseases and tumorigenesis. The interaction between pericytes and other components of the neurovascular unit was expected to be essential for maintaining proper brain function. By gaining a comprehensive understanding of brain pericyte function, we could uncover new insights into the mechanisms of various brain disorders and develop novel therapeutic strategies. (more in 10.7).

2.8. To explore the use of virtual microscopy in developing sampling strategies for the quantification of FOVs via histology, covering various histological examples.

Hypothesis: We hypothesized that virtual microscopy and whole slide scans of histological sections would enable efficient and unbiased sampling of FOVs for quantitative histology, providing practical implications for various histological studies (more in 10.8).

3 Description of the experimental materials and methods used

3.1 Animals and ethical statements

The following types of rodents were used in the experimental part of this study:

- Three-month-old (± 1 week) B6CBA and C3C mice with clinical signs of cerebellar ataxia and healthy WT mice (clinically healthy individuals, i.e., mutation noncarriers or heterozygotes) from identical litters of the strain were used. Males and females were tested at an approximately 1:1 ratio. These mice were kindly provided by Prof. A. Resibois from the Université Libre de Bruxelles, and the mice for the experiments were then generated by crossing wild-type females and heterozygous Lurcher males in the breeding facility of the Faculty of Medicine in Pilsen.

- Three-month-old (± 1 week) B6.BR-Agtpbp1^{pcd}/J strain pcd mice with clinical signs of cerebellar ataxia and strain-matched WT mice. Males and females were used in approximately a 1:1 ratio.

- Twelve-month-old (± 1 week) male rats from TgF344-AD (Tg) litters and non-Tg littermates were used. The DNA of the Tg rats included both the APPsw and Δ exon 9 mutant human presenilin-1 (PS1ΔE9) genes, while the non-Tg rats were negative for either or both of these human mutations.

The animals were kept in plastic cages (22 × 25 × 14 cm), with 2–4 mice per cage, all within the same room in the breeding facility. The animals were maintained under consistent conditions, with controlled temperature (22–23 °C) and humidity (30–60%), following a 12-hour light/dark cycle (from 6 am to 6 pm). Food (standard commercial pellet diet) and water were provided without restriction.

Animal care and breeding were carried out in the Central Animal Facility of the Faculty of Medicine in Pilsen, which possesses the necessary licenses for animal use and for breeding and supplying experimental animals. The institution

was also certified for genetically modified organism manipulations. The experiments reported here were conducted in full compliance with the European Union guidelines for scientific experimentation on animals and with the permission of the Faculty Committee for the Prevention of Cruelty to Animals. The samples were collected at the Department of Pathophysiology, Faculty of Medicine in Pilsen, in laboratories accredited for experimentation on animals by researchers with certification for experimentation on laboratory animals. All animal manipulations were approved and performed in compliance with Act № 246/1992 of the Czech Republic Coll., on the Protection of Animals against Cruelty, as amended.

3.2 Tissue processing

Specific details or experimental procedures, including the multilevel sampling of tissue, tissue blocks, and FOVs, as well as IHC protocols, are provided in the corresponding papers (*see 10.2-10.6*). The sampling strategy was previously optimized in a pilot study by Kolinko et al. 2015 & 2022 (s*ee 10.1 and 10.8*).

Briefly, the animals earmarked for the study of brain vascularization were euthanized by flushing 0.1 M phosphate-buffered saline (PBS; pH 7.4) followed by 4% paraformaldehyde through the heart. The brains were then preserved in 70% alcohol at 4 °C for 24 hours and subsequently transferred to 10% phosphate-buffered formalin for 30 days before being embedded in paraffin blocks for subsequent procedures.

Paraffin blocks were sectioned into 18-μm thick serial sections using a Leica RM 2145 microtome (Germany). Every 30th horizontal section was placed onto glass slides and subjected to immunostaining using a polyclonal rabbit anti-laminin antibody (dilution 1:1000; Dako, Glostrup, Denmark). The staining was visualized using diaminobenzidine (Dako, DAB Chromogen) and the sections were further counterstained with hematoxylin.

Graft-treated mice were euthanized after the transplantation by an overdose of thiopental (0.2 ml of 10% solution intraperitoneally) and then transcardially perfused with Ringer's solution followed by 4% phosphate-buffered paraformaldehyde. The brains were then immersed in the formaldehyde solution for 2 hours. After incubating in 15, 20, and 30% sucrose, the brains were frozen

and stored at – 80 °C until further processing. Subsequently, 40 µm frontal frozen sections were cut. The graft was identified using enhanced green fluorescent protein in native specimens.

3.3 Immunohistochemistry

The microvessels within brain sections were observed by employing a polyclonal rabbit anti-laminin antibody (dilution 1:50; Dako, Glostrup, Denmark; No. Z009701). To ensure accuracy, negative immunohistochemistry controls were used following the manufacturer's guidelines. Additionally, the mouse colon was utilized as a positive control in this analysis.

The sections were dewaxed in xylene, rehydrated and successively incubated in 1) cooled acetone for 10 minutes; 2) 1% normal goat serum for 10 minutes at room temperature; 3) primary antibody solution for 12 hours at 4 °C; 4) N-Histofine Simple Stain MAX PO (Multi, Nichirei biosciences, Inc.) for 30 minutes at room temperature; and 5) a Liquid DAB+ Substrate Chromogen System (Dako, DAB Chromogen) for 1-4 minutes for visualization. Finally, after standard staining with Goll's hematoxylin for visualization of nuclei, the sections were dehydrated with alcohol, cleared with xylene, mounted on slides with Solakryl mounting medium, and coverslipped.

The presence of graft-derived Purkinje cells was verified through the colocalization of enhanced green fluorescent protein (EGFP) and anti-calbindin fluorescence.

3.4 Quantitative histological analysis

Stereological analyses were performed on sections from each unit without prior knowledge of their genotype. The analysis was conducted using Stereologer software (v11.0) from SRC Biosciences (Tampa, Florida, USA). This software was operated on a PC that was set up with a Nikon Eclipse Ti-U microscope, standard optical lenses, a high-resolution digital imaging camera (Promicra 3-

3CC), and a ProScan III motorized 3-axis step motor from Prior Electronics, UK, to carry out the analyses. Microscopic fields of view were taken automatically in an SURS manner. The stereology data were collected for the total region volume (V) of interest and for the specified histological layers of the cerebellum (ML, GL, WM, N) or hippocampus (CA 1-2, CA 3, DG). The details related to the specific quantitative technique and histological staining used for the data collection are outlined in *Table 2*.

The estimated volumes of each reference space were determined using the Cavalieri principle by counting points (Mouton 2002; Mouton 2011) using standard low-magnification lenses (Plan Fluor, NA 0.13-0.45). Briefly, the V of each region was quantified from the sum of points (∑P) hitting each subregion in a grid of equidistant, calibrated points superimposed on the slide according to the following (Equation 1:

(Equation 1)

$$\boldsymbol{V = k \cdot \left(\sum A \cdot h\right) = \left(\sum P \cdot A_P \cdot t\right) \cdot k}$$

where k is a constant interval between the sampled sections; ΣA is the sum of the areas of all sections of the sample, given as a function of the sum of points (∑ P) that intersect an anatomically defined reference area of interest, multiplied by the area per point (A_P); and h is the height of these sections, measured after the completion of tissue processing (t), which has been validated using theoretical arguments (Gundersen and Jensen 1987) and by practical demonstration using the Archimedes principle of volume displacement (Subbiah et al. 1996).

The coefficient of error (CE) is estimated to assess the data reliability and precision. It measures the variability in sampling results and ensures accuracy in estimating tissue characteristics. The method (Gundersen et al. 1999) involves calculating three sums of section areas as the first step:

Table 2 - *Utilized methods of histological staining and the quantitative parameters obtained from them*

Staining	Quantitative parameter (unit)	Approach	Evaluated areas	Used objective
HE	Total region volume (V)	Cavalieri estimator	Adrenal gland; entire medulla	4x
			zona glomerulosa; zona fasciculata; zona reticularis; medullary tissue	10x
			Retina	4x
			Outer nuclear layer	20x
	Total number (N)	Optical disector probe	Nuclei of retinal receptor cells	60x oil
Anti-laminin (Dako)	Total V	Cavalieri estimator	Entire cerebellum or hippocampus	4x
			Cerebellar histological layers (ML, GL, WM, N)	4x
			Hippocampal principal cells sublayers (DG, CA1, CA2/3)	10x
	Total microvascular number (N_{cap})	Optical disector probe	Histological layers of the cerebellum or hippocampal principal cell sublayers	60x oil
	Total microvascular length (L_{cap})	Optical space ball probe	Histological layers of the cerebellum or hippocampal principal cell sublayers	60x oil
Native EGFP fluorescence	Total region volume (V)	The Cavalieri estimator	Embryonic Purkinje cell suspension	20x
non	Parameters based on the above indicators	Mathematically in postprocessing	Total N_{cap} or L_{cap} of cerebellum	-
	Average densities of capillaries (N_{Vcap}) and/or their length (L_{Vcap})	Mathematically in postprocessing	Histological layers of the cerebellum or hippocampal principal cell sublayers	-
	Potential diffusion distance (DD)	Mathematically in postprocessing	Histological layers of the cerebellum or hippocampal principal cell sublayers	-

(Equation 2)

$\boldsymbol{A = \sum a_i^2}$ - taking into account all sections selected from the first ($\boldsymbol{a_1}$) to the last ($\boldsymbol{a_n}$);

$\boldsymbol{B = \sum a_i \cdot a_{i+1}}$ - taking into account all sections selected from $\boldsymbol{a_1}$ to $\boldsymbol{a_{n-1}}$;

$\boldsymbol{C = \sum a_i \cdot a_{i+2}}$ - taking into account all sections selected from $\boldsymbol{a_1}$ to $\boldsymbol{a_{n-1}}$.

Then, the CE was calculated using the following relationship:

(Equation 3)

$$\boldsymbol{CE = \frac{\sqrt{\frac{3A + C - 4B}{12}}}{\sum a_i}}$$

The sampling strategy was adjusted to achieve the desired accuracy levels of CE ~ 0.10 across the study.

According to the theories on capillary growth and overall capillary structure (Ausprunk and Folkman 1977; Patan et al. 1992), the capillary network can be seen as a node-segment setup. Each node or saddle point represents where a blood vessel branches out, while a capillary is formed as a loop connecting two nodes in the vascular network. To count the number of loops/segments, it is crucial to assess how the capillary network is interconnected at microvascular endpoints. The estimation of capillary numbers, endpoint counts, and lengths was carried out using a 60× oil objective (CFI, Plan Apo Lambda, Na 1.4), with the exclusion of 1-µm guard zones at the top and bottom surfaces of each section.

The total number of microvascular segments (N_{cap}) and the total microvascular length (L_{cap}) were estimated using an optical disector probe (Gundersen 1986; Sterio 1984; West et al. 1991). Briefly, we counted structures within small reference samples, and based on those counts, we determined the values for the total object volume. If the chosen regions of interest (ROIs) had multiple layers, each part of the cerebellum was counted within the appropriate

ROI using the point grid method (Glaser et al. 2007; Mouton 2002).

The total number of microvascular endpoints was estimated by counting the saddle points of the capillary branch nodes +1(Gundersen et al. 1993; Nyengaard and Marcussen 1993). N_{cap} is double (2x) the number of nodes (Lee et al. 2005; Mouton 2002; Nyengaard and Marcussen 1993).

Estimates of L_{cap} were made using the Space Balls probe (Mouton 2002; West 2018). In this technique, small spherical probes, called space balls, are virtually embedded in the tissue, and their intersections with microvessel profiles are counted to obtain unbiased estimates. L_{cap} was equal to double the number of cross-sections between the sphere and vessel profiles.

The average capillary segment density (N_{Vcap}) and/or length density (L_{Vcap}) were calculated as N_{cap} or L_{cap} divided by the total volume. The mean length of a single capillary segment could be determined by dividing L_{cap} by $N_{cap.}$

Finally, the potential diffusion distance (D_D) of the capillaries was determined during postprocessing using using the following equation:

(Equation 4)

$$\boldsymbol{D_D = \frac{\Gamma(1+\frac{1}{2})}{\pi {L_D}^{1/2}}}$$

The gamma function (Γ) is used to account for the nonuniform contour of vascular diffusion relative to the center of the vessel (Isaacs et al. 1992). This indicates that the ability of nutrients to spread is inversely proportional to the square root of the density of the blood vessels.

3.5 Statistical analysis

Calculations were performed using the software Statistica 13 (StatSoft, Inc., Tulsa, OK, USA). Given that a considerable portion of the data were not normally

distributed, all the methods used were nonparametric. We used a two-sample Mann–Whitney U test to compare the effects between two groups (WT vs. pcd). To assess the effects within each group, we used Friedman ANOVA and Kendall's coefficient of concordance (F_{ANOVA}). Relationships between two parameters were assessed using Spearman's rank correlation coefficient. The data are presented as the mean ± SD, and $P < 0.05$ indicated statistical significance.

3.6 Literature reviews preparation

After defining the focus and specific research question within the field of interest, a comprehensive search was conducted using databases such as Scopus, PubMed, and Web of Science. Keywords, Boolean operators, and filters were employed to gather articles relevant to the scope of the review.

Initially, review-type articles were assessed, followed by a detailed examination of the original research articles. Emphasis was placed on studies using stereological approaches for tissue analysis. Consideration was given to the publication year and venue.

Key information extracted from the selected articles was meticulously organized, categorized, and supplemented by pertinent data from other literature sources. The primary objective was to identify common patterns, controversies, and gaps in the literature, as well as to compare and contrast findings across various studies.

The referencing of selected articles throughout the manuscript adhered to the appropriate citation style guidelines.

4 Results

4.1 The role of microvascularization in the pathogenesis of various neurodegenerative diseases

We review the processes of angiogenesis and the alterations that occur in brain microvessels within the context of the most prevalent NDDs. Notably, there is no consistent pattern of vascular alterations among these diseases. Sometimes, vascular changes occur as a result of the primary disease, while in other cases, they might contribute to the disease origin and progression by impacting nerve cell degeneration, depending on their severity and quantity. Furthermore, we discuss stereological methods commonly employed to obtain both qualitative and quantitative data for evaluating changes in the brain microvascular network.

4.2 A trend toward a reduction in the density of retinal receptors in pcd and Lc mice

The mean volume of the control mouse retina was 1.916 ± 0.334 mm^3. The retina V of B6.BR mice were 22% larger than those of B6CBA mice (*Figure 4A*). Additionally, the mean retinal volume was 13% greater in males than in females. The volume of the outer nuclear layer in males was 0.534 ± 0.1214 mm^3, whereas that in females was 0.442 ± 0.1171 mm^3. The total number of photoreceptor nuclei located in the outer nuclear layer was 2,542,595 ± 860,915 on average in the control mice, and the density of the nuclei in females was 7.6% greater than that in males (*Figure 4B*). Nonsignificant reductions in the total volume (Lc, 11.5%; pcd, 16.6%), total number of photoreceptors (Lc, 8.3%; pcd, 27.7%), and density were observed in both the pcd and Lc mutant mice. In females, the loss of photoreceptors per unit of outer nuclear layer volume progressed more quickly due to their initially denser distribution (*see section 10.2*).

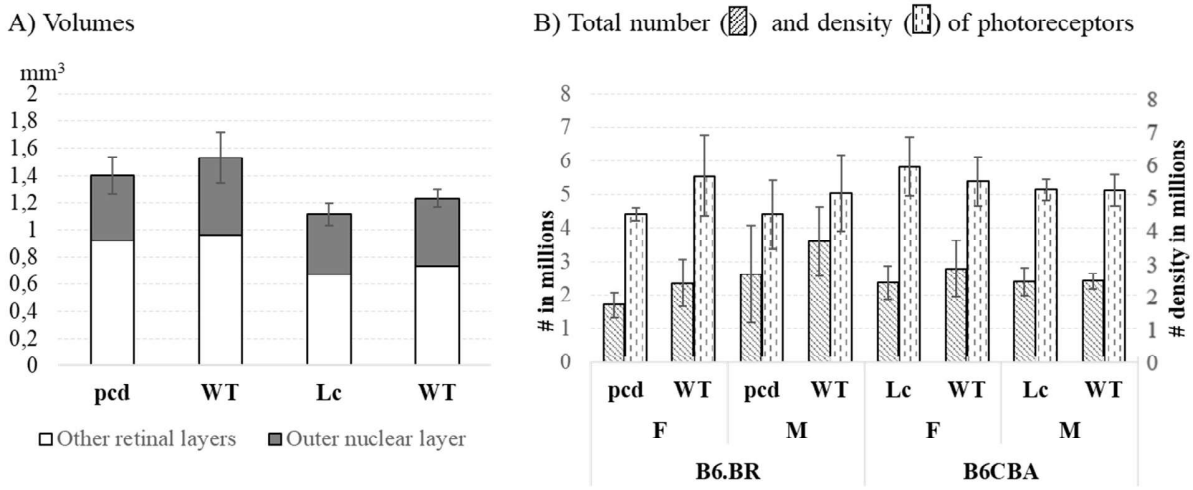

Figure 4 - *The results of the stereological investigation of the retinas in B6.BR (WT and pcd) and B6CBA (WT and Lc) mice*

4.3 Adrenal gland morphology in Lurcher mice

In this part of the study, Lc mice exhibited increased corticosterone levels following exposure to the Morris water maze and maintained consistently higher levels than did wild-type mice throughout the water maze trials (Tuma et al. 2017). Notably, the sustained increase in stress in the mutant mice was not consistent with the decrease in stressor impact due to adaptation to the water maze (*see section 10.3*).

Stereological analysis revealed (*Figure 5*) that the entire adrenal glands of Lc mice were notably larger than those of WT mice (2.153 ± 0.03 in Lc vs. 1.847 ± 0.222 in WT). When analyzing cortical zones individually, the zona glomerulosa exhibited no significant difference, while the zona fasciculata and zona reticularis were relatively larger in the Lc mutant mice than in the WT mice. Interestingly, despite serving as sources of corticosterone, these latter two zones did not exhibit significant correlations between their volumes and either basal or stress-induced hormone levels. Furthermore, both the absolute and relative volumes of the adrenal medulla were greater in Lc mice. The mass of the medulla, excluding the large vessels, was also larger both in absolute terms and in proportion to the overall size in Lc mice (*Figure* **5** *A,B*). Remarkably, the detailed histological structure of individual components within the adrenal gland of Lc mutant mice did not appear to be altered (*Figure 5C*).

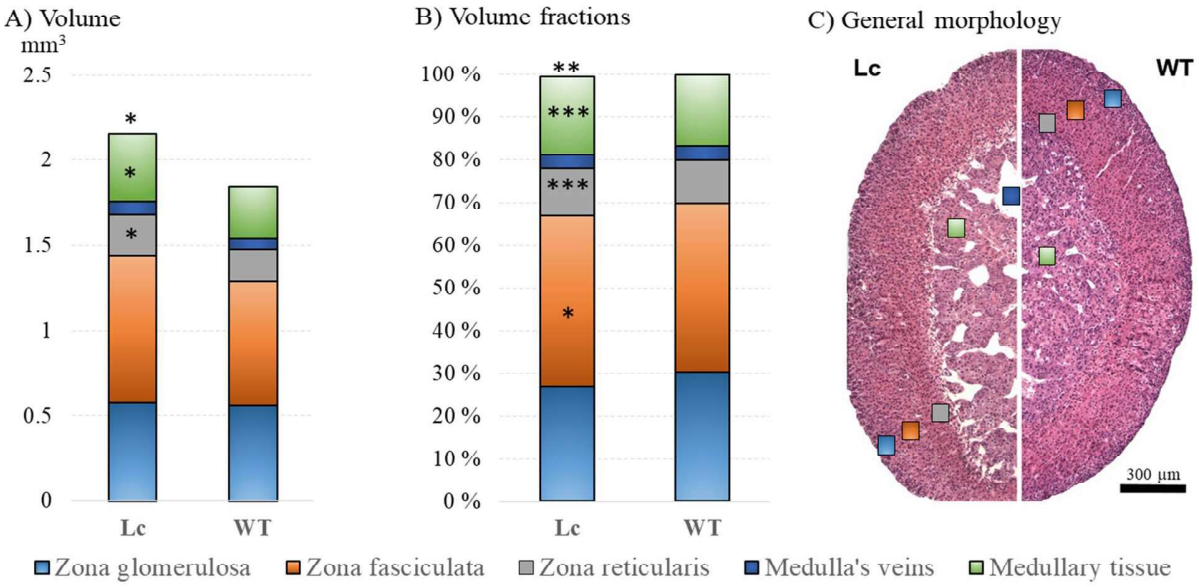

Figure 5 - *Graphical comparison of acquired quantitative data (A, B) and general morphology (C) of the adrenal gland in Lurcher (Lc) and wild-type (WT) mice. * P <0.05; ** P <0.01; *** P <0.001. C – stained with hematoxylin and eosin*

4.4 Morphometric analysis and microvascular characteristics of cerebellar degeneration

In this part of the study, we investigated the differences in the microvascular bed organization between healthy *(Figure 6A)* and ataxic mice *(Figure 6B-D)*, particularly focusing on Lc and pcd mutant mice.

We examined healthy mice and observed no significant differences in the volume of their cerebellum. However, mice with ataxia exhibited distinct alterations. First, compared with pcd mice, Lc mice showed a more substantial reduction in cerebellar volume (Lc, ~71%; pcd, ~43%), with the cortex being primarily affected in both cases *(Figure 6F)*. Second, the decrease in the microvessel N_{cap} *(Figure 6E)* in Lc mice was disproportionate to the decrease in cerebellar volume (~53% reduction in Lc versus ~40% in pcd). Remarkably, the N_{Vcap} doubled in Lc mice but remained relatively stable in pcd mice.

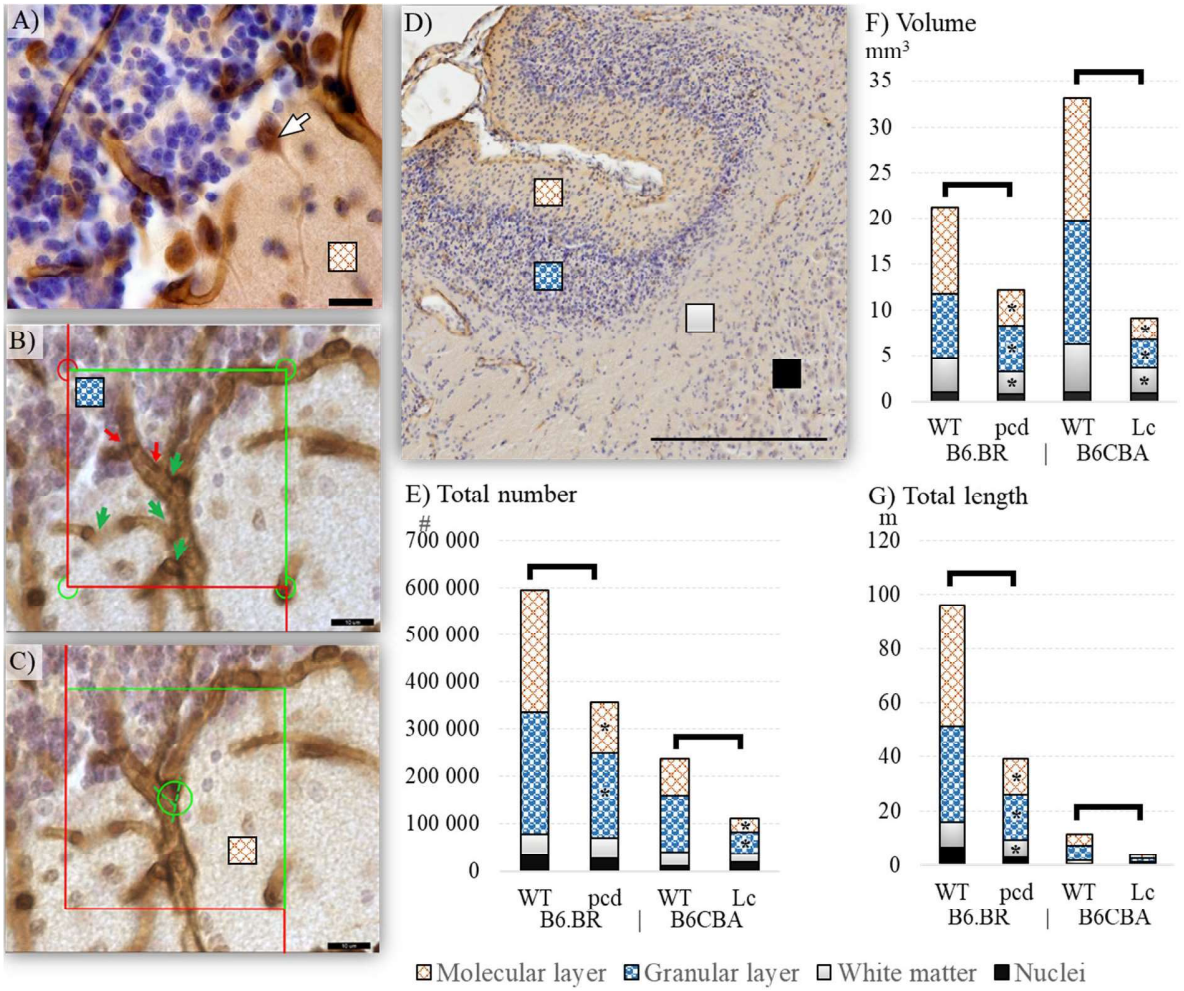

Figure 6 - *Photomicrographs of control (A) and ataxic (B-D) mouse microvessels labeled with an anti-laminin antibody and box plots (E-G) illustrating selected quantitative parameters of the microvascular network in the cerebellar histological subregions*

A) Purkinje cell labeled with a white arrow. B) The optical disector frame was used for the quantification of "capillary saddle points" (green arrows for the molecular layer and red arrows for the granular layer) at branch points or nodes. Labels for the frame corners were used to distinguish the respective regions of interest (red and green circles) during the analysis. C) The capillary length was determined using the space ball method by counting the number of intersections between the surface of the spherical probe and a spline through the center of each capillary (green dotted line). E-G) Significant differences ($p \leq 0.05$) identified using the Wilcoxon matched-pair rank test are indicated by the error bars between adjacent data bars for differences between groups and by * for the respective compartments.
Space bars: A–C –10 µm; D – 200 µm

Furthermore, analyses of L_{cap} revealed significant differences *(Figure 6G)*. In asymptomatic B6CBA mice, L was considerably lower in all gray matter layers than in asymptomatic B6.BR mice. In particular, a significant reduction in L was observed in the granular layer of Lc mice. Interestingly, the vessel density in the ML was lower than that in the GL in asymptomatic mice. In pcd mice, the N_{Vcap} and L_{Vcap} increased solely in WM. However, in Lc mice, the capillary density increased in the cortex layers.

Our study highlights the complex alterations in microvascular bed organization in cerebellar ataxia mice (*see sections 10.4*). Notably, ataxia mice exhibited distinct changes in cerebellar V, N_{cap}, and N_{Vcap}, particularly in the cortex layers. These findings provide valuable insights into the vascular dynamics associated with ataxia, shedding light on potential mechanisms underlying cerebellar dysfunction in these murine models.

4.5 Graft survival and microvessel supply in the mouse cerebellum

Generally, the grafts exhibited bilateral survival in most mice, with occasional instances of unilateral or complete graft extinction. Consequently, no significant differences in graft survival were observed (*see section 10.5*).

The presence of a clear demarcation between the graft and the host tissue was strongly associated with Lc cerebellar degeneration due to greater clustering of the graft-derived Purkinje cells (*see section 10.5.1*). Overall, there were only isolated cases of EGFP-positive sprouting fibers or dispersed Purkinje cell-like cells that migrated beyond the bulk of the graft into the host tissue (*Figure 7A*). In WT mice of the same strain, the cerebellum was colonized by numerous enlarged Purkinje-like cells, albeit with disorganized dendritic trees.

In contrast to those in Lc mice, both WT and pcd mutant mice exhibited enhanced fiber sprouting from the graft into the host cerebellum and/or colonization of the host cerebellar cortex by EGFP-positive cells (*see section 10.5.2*). Sprouting of fibers from the graft into the host cerebellum was less frequently observed in both WT and Lc mice of the B6CBA strain, as well as in wild-type B6.BR mice. In contrast, this phenomenon was consistently noted in pcd mice with graft–cerebellar contact. The fibers extended from the graft mass into the white matter or were oriented toward the cerebellar nuclei in pcd mutant mice (*Figure 7B*).

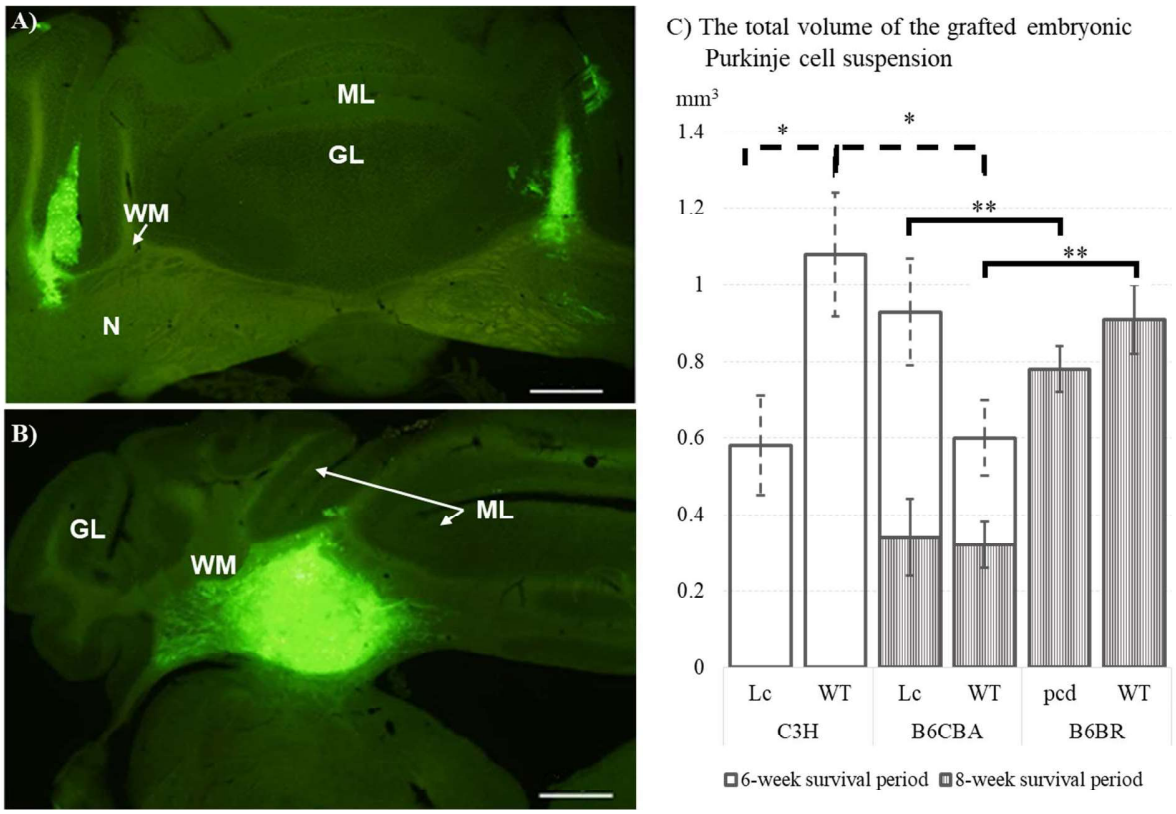

Figure 7 - *Features of the placement of the embryonic Purkinje cell suspension in the cerebellum of Lc (A) and pcd (B) mutant mice and the results of total volumesvolume measurement (C)*

A,B) Native EGFP fluorescence: grafted tissues glow bright green. Space bars–500 μm. C) Error bars represent the standard error of the mean (SEM). The dotted line represents the comparison for the 6-week survival period, and the solid line represents the comparison for the 8-week survival period. Significant differences between adjacent data bars are indicated by the error bars: * P <0.05; ** P <0.01

Graft volume was significantly greater in C3H wild-type mice than in C3H Lc mutant mice (*Figure 7C*). In B6CBA mice, no significant difference was observed between Lc and WT mice. It is important to note that a strain difference was observed in wild-type mice, with C3H wild-type mice having larger grafts than their B6CBA counterparts.

The B6CBA mice exhibited a gradual reduction in graft volume as time progressed. Consequently, over the 6- to 8-week survival period, the graft volume

decreased by approximately half in both Lc and WT mice. The graft volume in the B6CBA mice was consistently smaller than that in the B6.BR mice, whether they were wild type or carried the mutation causing Purkinje cell death. On the other hand, no significant differences were observed between pcd mice and their WT littermates.

4.6 Reduction in microvascular length in the hippocampus in an Alzheimer's disease rat model

Hippocampal sections from Tg rats showed plaques with clear contours and prominent findings of abnormal hair-like capillaries in the vicinity of Aβ plaques (*Figure 8 A,B*). The findings from the study (*Figure 8 C-E; Section 10.6*) demonstrated significant decreases in V, Ncap, and Lcap in the hippocampal PCL of the transgenic rats compared to those in the hippocampal PCL of their nontransgenic littermates. In particular, the overall length of capillaries within the DG was affected in Tg rats. This reduction was accompanied by a clear tendency toward a decrease in the total number of capillary segments. Interestingly, the mean capillary length was notably greater in the transgenic rats than in the nontransgenic rats ($p=0.036$). This trend was particularly pronounced in the CA1 region of the hippocampus. Notably, a similar trend toward increased occurrence of kinked, twisted, and string-like vessels has been observed in transgenic mouse models of AD. However, our results diverge from those of studies conducted on transgenic mouse AD models, as the total number of capillaries in the white matter, specifically the corpus callosum, was significantly lower. This disparity warrants further investigation into potential species-specific differences in capillary remodeling processes.

4.7 Brain pericyte function

In this study, we consolidate the existing information on the role of brain pericytes in both normal brain function and their involvement in the development of neurodegenerative diseases and tumorigenesis. The findings reveal the essential requirement for enhancing the understanding of the mechanisms by which pericytes lead to alterations in overall brain metabolism. The lack of standardized

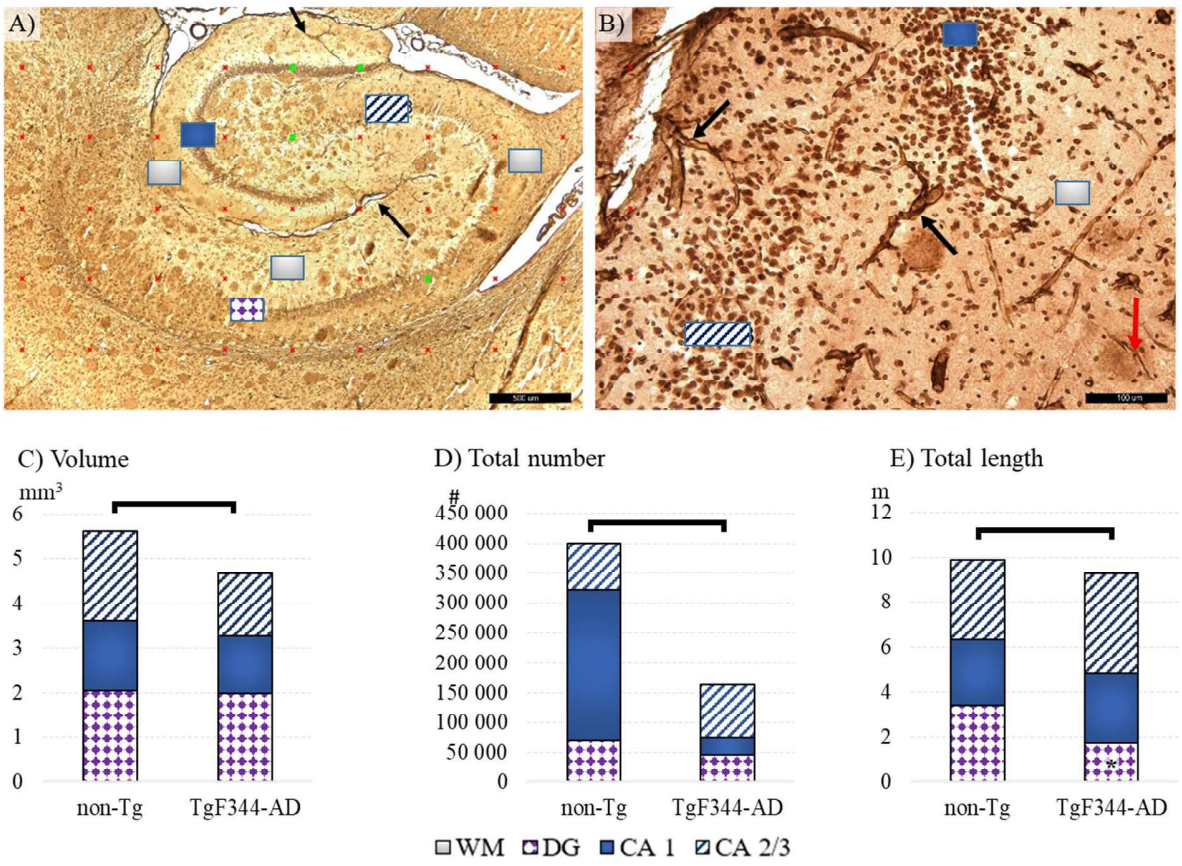

Figure 8 - *Examples of anti-laminin antibody-labeled microvessels (A,B) and box plots (C-E) illustrating selected quantitative parameters in the hippocampal principal cell layers of control (non-Tg) and transgenic (TgF344-AD) rats*

A) A randomly positioned systematic-uniform grid of equidistant points (red) was generated by the software over each outlined region of interest. The green points represent interesting objects. B) The vessels serve as the main source of hippocampal blood supply as shown by black arrows. Thinner hair-like capillaries (red arrows) are common in transgenic rats. C-E) Significant differences ($p \leq 0.05$) identified using the Wilcoxon matched-pairs ranks test are indicated by the error bars between adjacent data bars. Space bars: A, B – 100 µm

mechanisms by which pericytes lead to alterations in overall brain metabolism. The lack of standardized methodologies and the limited quantitative data in existing studies hinder a comprehensive and precise understanding of pericyte changes in neurodegenerative diseases and tumorigenesis. Variability in methodologies across studies contributes to conflicting outcomes, emphasizing the necessity for consistent

approaches. Despite the considerable volume of related research, substantial gaps persist, particularly in understanding pericyte effects on perivascular glial cells, since the effectiveness of pericyte signaling has emerged as crucial for understanding the regenerative mechanisms of brain tissue following injury and plays a role in brain plasticity.

This study underscores the urgency of further comprehensive research on brain pericytes, considering the multifaceted roles of the BBB and the complexities of disease development. Future investigations should delineate changes in pericytes within diseased tissue and preferably track the progression of these changes throughout the disease course. Additionally, employing unbiased quantification methods, such as automatic stereology systems, is advocated for accurate pericyte assessment. These comprehensive studies are pivotal for advancing clinical applications in diagnosing and treating neurodegenerative and mental disorders. For more details, see 10.7.

4.8 Sampling in quantitative histology and stereology

When planning a stereological assessment, determining the method of sampling FOVs is a pivotal consideration. The choice lies between analyzing the entire slide (whole-slide analysis, which requires a scanner) or focusing solely on a representative section. In studies with limited sample sizes or small sample sizes, assessing complete preparations is suitable. However, for larger preparation areas, it is crucial to select a sufficient number of FOVs to minimize variable deviation. This error increases as the number of FOVs decreases, although it remains acceptably low for homogeneous samples. Therefore, for heterogeneous samples, conducting a pilot study is advisable to determine the appropriate number of FOVs for a specific study. Occasionally, samples with different absolute sizes, despite having an equal number of sampled FOVs, result in varying sampling densities. In cases of low biological variability, this discrepancy typically does not introduce significant errors.

5 Discussion

The study of the brain microvasculature, especially in the cerebellum, holds pivotal importance for both theoretical science and clinical applications. Understanding these microcirculatory processes provides insights into potential interventions that can enhance the neuronal environment. By focusing on drugs affecting the brain microvasculature/microcirculation, opportunities arise for surgical and therapeutic strategies aimed at optimizing the conditions for individual neurons, thereby potentially improving neurological outcomes and treatments.

5.1 Unveiling the significance of microvascular changes in neurodegenerative diseases

The review presented in section *10.1* allowed us to delve into the intricacies of microvascular research within neurodegenerative diseases. This exploration serves as a foundational step toward broadening the research scope of our laboratory in this domain. It was imperative for us to establish this starting point to guide our future studies in this critical area. A separate task was to become more familiar with the methods of quantitative histological analysis of brain capillaries and critically analyze the data obtained by other scientists in this area.

Despite numerous studies on microvascular changes, our investigation uncovered substantial gaps in understanding the state of microvessels within spinocerebellar ataxias, a heterogeneous group of diseases. Moreover, conducting quantitative analyses of brain region perfusion in individuals with conditions such as mental illness, chronic alcoholism, or multiple sclerosis holds significant interest. Based on our findings, it became evident that there is an extensive dearth of information concerning the microvessel topography in the human brain. Existing studies predominantly focus on mapping arger and medium-sized vessels (Delion et al. 2017; Marco et al. 2019) within the human brain, leaving a significant gap in understanding microcirculatory channels, primarily through extrapolation from animal model research.

On the other hand, this part of the work shows that in-depth studies on alterations in brain blood supply occurring in NDDs will affect therapeutic effectiveness. Understanding the role of microvascular abnormalities in the pathogenesis of NDDs is vital for clinical applications. If vascular pathology actively contributes to disease progression rather than being solely a secondary phenomenon, therapeutic targeting may be warranted (Gama Sosa et al. 2010; Iglesias-Gamarra et al. 2007).

5.2 Spatial disturbances in Lurcher and pcd mice

This and other sections of the work represent a continuation of numerous projects dedicated to investigating cerebellar neurodegeneration, which have been ongoing in the laboratories of the Faculty of Medicine in Pilsen, Charles University (Babuska et al. 2015; Cendelin et al. 2012; Cendelín et al. 2006; Vozeh et al. 1997).

Cerebellar disorders can cause significant sensory problems in two ways—by affecting the processes involved in perception and by causing abnormalities in eye movement control. When the cerebellum is affected by lesions, it disrupts systems related to perception, such as vision, proprioception, and self-motion awareness (Baumann et al. 2015). This disruption leads to various sensory impairments. Additionally, controlling eye movements, especially for maintaining sight fixation and tracking moving objects, is crucial. Studies have reported abnormalities in optokinetic and vestibuloocular reflexes in Lc mice (Van Alphen et al. 2002). Similar eye movement issues could be expected in pcd mice (Killian and Baker 2002), in which vestibuloocular reflexes remain nearly normal (Yakusheva et al. 2007).

Vision profoundly impacts spatial navigation, and retinal degeneration significantly influences behavior, especially spatial performance in pcd mice. Although retinal degeneration progresses slowly in these mice (Blanks et al. 1982; Blanks and Spee 1992; LaVail et al. 1982; Marchena et al. 2011), we noted only a slight decrease in photoreceptor density during spatial orientation testing. However, even before a noticeable reduction in photoreceptors occurs, vision issues could affect behavior due to the early functional decline of the degenerating retina (Marchena et al. 2011).

Given these factors, sensory issues are expected to significantly contribute to navigation challenges in mice with cerebellar degeneration. In tasks involving a visible goal, these issues might be less prominent than in tasks with hidden goals. This difference arises because the visible goal represents a single object within the maze, while locating a hidden goal requires the identification of multiple external landmarks. This distinction notably contributes to the increased stress experienced by experimental animals with neurodegeneration compared to that experienced by healthy subjects by affecting their capillary network through the secretion of significant amounts of stress hormones.

5.3 Spatial performance and abnormal stress response in Lurcher mice

In the next step of the study (Tuma et al. 2017), we explored the intricate connection between levels of corticosterone, a classic stress marker (Hilber et al. 2004; Lorivel et al. 2014), and spatial impairments (Maras et al. 2014; Sandi et al. 1997) in Lc mutant mice (*more in 10.3*). The findings, based on basal corticosterone levels in the urine of Lc and WT mice, revealed that stress induced by the testing mazes remains consistent throughout the procedure in both healthy and neurodegenerative mice, challenging assumptions regarding habituation and stress hormone secretion.

However, the stereological investigation of the adrenal glands revealed specific enlargement of the zona fasciculata and zona reticularis, both of which are involved in corticosterone production, consistent with the heightened stress-induced corticosterone levels observed in Lc mice. This expansion could be attributed to heightened stimulation by adrenocorticotropic hormone (ACTH) and subsequent hypertrophy. Although basal corticosterone levels did not correlate with these volumes, the enlarged adrenal cortex suggested a capacity for greater corticosterone production. This could be attributed to the prolonged activation of the stress axis in Lc mice, implying possible hypersensitivity to stress at the central level.

In summary, these findings shed light on the intricate interplay of corticosterone levels, the stress response, and spatial impairments in cerebellar Lc mice. The observed alterations in corticosterone levels and adrenal morphology

provide valuable insights into the complex mechanisms underlying stress sensitivity and its potential impact on cognitive performance.

5.4 Alterations in cerebellar vascularization in degenerative mice

The results presented in sections *4.4 and 10.4* (Kolinko et al. 2016; Kolinko et al. 2023) revealed that the mouse cerebellar cortex constitutes more than 80% of the total volume of the cerebellum. Approximately half of this volume is attributed to the GL, while the other half comprises the ML and Purkinje cell layers. The cerebellar cortex contains the highest number and length of blood vessels, notably within the GL. Neuron-rich regions such as the GL and cerebellar nuclei display dense vessel networks due to high metabolic demands (Rhyu et al. 2010). In contrast, white matter possesses lower vascular density and longer diffusion distances. Unfortunately, detailed studies on human cerebellar microcirculation are lacking, yet comparisons indicate variations in vessel density between humans and mice, especially in gray and white matter (Cassot et al. 2006; Kubikova et al. 2018; Tonar et al. 2011). Although the distribution of vessels differs, the overall trends in vascularization are similar between human brains and mouse cerebellum, except for varying rates of blood flow in specific areas (van Raaij et al. 2012).

At three months of age, the total volume of the cerebellum was significantly lower (by approximately two-thirds) in the Lc mice than in the WT mice due to cortical degeneration, with the granular and molecular layers being particularly affected. This was attributed to the degeneration of Purkinje, basket, and stellate cells, which caused a decrease in the number of axons coming from the GL (Baltanas et al. 2013; Caddy and Biscoe 1979; Fernandez-Gonzalez et al. 2002; Triarhou 2010). The reduction in granule cell volume resulted from secondary target-related death. While white matter showed a decreased in volume, there was a notable disappearance of Purkinje cell axons and degeneration of climbing fibers. Vascular changes were largely observed in the cerebellar cortex after substantial degeneration, indicating a relationship between neural degeneration and vascular alterations. The increased capillary density in the cerebellar cortex of Lc mice correlated with reduced tissue space, potentially enhancing nutrient availability and the transport of regulatory factors. However, it might also

intensify the exposure of tissues to proinflammatory cytokines (Cvetanovic et al. 2017; Vernet-der Garabedian et al. 2013; Vernet-der Garabedian et al. 1998). We speculate that this could influence the pathogenesis and therapeutic strategies for cerebellar degeneration. However, the underlying relationship between vascular changes and neuronal degeneration needs further exploration, especially given the temporal relationship of these changes during ontogenesis.

The features of the microvascular bed in pcd mice differed from our earlier findings in Lc mutant mice. First, it is crucial to note that the cerebellar volume reduction was more pronounced in Lc mice than in pcd mice (~71% in Lc versus ~43% in pcd mice). Second, the N_{cap} was lower in Lc mice but this reduction was not proportional to the reduction in cerebellar volume, unlike in pcd mice (~53% reduction in Lc versus ~40% in pcd mice). Consequently, capillary density almost doubled in Lc mice but remained nearly unchanged in the cerebellar gray matter of pcd mice. Additionally, the average length of a capillary did not change in pcd mice.

Purkinje cell degeneration commences approximately Postnatal Days 8-10 in Lc mice (Caddy and Biscoe 1979), but begins at Postnatal Day 20 in pcd mice (Baltanas et al. 2013). This discrepancy potentially explains the more severe degeneration of granule cells, which leads to a significant volume reduction and consequently, a secondary increase in relative capillary density. Thus, these differences in the timeline of neuronal degeneration between Lc and pcd mice may explain the distinct differences in the distribution of the cerebellar microvascular network. For more details *see section 10.4.2*.

In summary, both Lc and pcd mice exhibited cerebellar volume and microvascular network changes. Reduced capillary numbers did not alter the density of capillaries in pcd mice, unlike in Lc mutant mice. Despite the reduced absolute quantity of capillaries in pcd mutant mice, their nearly normal microvessel density at 3 months led to a comparable diffusion distance, which was critical for maintaining extracellular homeostasis. Early vascular shifts might occur during degeneration. The findings support structural implications.

5.5 Interplay between graft survival and vascularization quality in the cerebellum of mutant mice

Although the primary focus of this chapter is not on the transplantation process, providing context here contributes to a more holistic understanding of the interplay between graft survival and regional vascularization quality. This is important because the potential success of tissue transplantation for therapeutic purposes is directly related to the quality of blood supply to the recipient tissue. In addition, tissue with a higher vascular density may serve as the better recipient for a transplant, even before its own vascular network is established. Embryonic cerebellar grafts were chosen for treatment due to their reliability as a source of Purkinje cells (Babuska et al. 2015; Cendelin et al. 2012; Purkartova et al. 2014; Sotelo and Alvaradomallart 1987), the primary cell type experiencing degeneration in both Lurcher and pcd mice.

The study showed that graft volume was significantly influenced by degeneration/strain factors but not by single factors. The qualitative graft morphology varied significantly between Lc and WT mice, and this distinction was not strain-specific (*see 10.5.1*). The most pronounced distinction emerged in graft integration into the host cerebellum. While WT mice exhibited graft-derived cell dispersion from the main graft mass, Lc mice often exhibited distinct graft-host borders, even on the surface of the cerebellum of mutant mice.

Alternatively, higher capillary density and reduced diffusion distance might expose the graft to more proinflammatory cytokines (del Pilar et al. 2021; Vernet-der Garabedian et al. 1998). This could potentially restrict the movement of transplanted cells and the sprouting of axons into the host tissue.

In contrast to Lc mice, which primarily display delimited grafts, pcd mice exhibited a greater frequency of fiber sprouting from the graft than did WT mice, with Purkinje cells migrating and colonizing the host cerebellum (*see 10.5.2*). Notably, the strict delimitation of grafts is not an issue in pcd mutant mice. These observations indicate that graft integration challenges in Lc mice differ from those in pcd mice and highlight the distinct influence of the local tissue niche on graft cells.

The results revealed that factors such as increased neurotrophic levels (Babuska et al. 2015), increased release of stress hormones and microvascular

density (Kolinko et al. 2023; Tuma et al. 2017) at the site of implantation of the brain graft can play key roles in the therapeutic effect of successful tissue implantation.

In conclusion, these studies enhance our understanding of cerebellar graft development and its interaction with degenerated tissue. While graft survival is attainable in the cerebellum of mutant mice, graft integration varies significantly. This study underscores the necessity of tailored neurotransplantation therapeutic approaches for various cerebellar pathologies.

5.6 Capillary network modifications in AD-TgF344 rats

As part of an effort to deepen our understanding of morphological changes in microvessels in NDDs, this study delved into the morphological changes in microvessels within a rat model of Alzheimer's disease (AD), aiming to quantitatively assess the microvascular system in the hippocampus—a key region affected in AD. An investigation of 12-month-old TgF344-AD rats highlighted a substantial reduction (49%) in the L_{cap} in the DG, accompanied by increased mean microvessel diffusion distance. This reduction, coupled with a decrease in N_{cap} and DG volume, potentially underpins the reported neurodegeneration, electrophysiological disturbances, and cognitive decline in early AD stages (Zhang et al. 2019). Here, we found that the presence of a number of delicate capillaries near amyloid plaques in Tg rats aligns with observations in murine AD models (Bailey et al. 2004; Gama Sosa et al. 2010), indicating similarities with the cerebral amyloid angiopathy observed in postmortem AD patients (Bailey et al. 2004; Lai et al. 2015). Based on these findings, we believe that the TgF344-AD mouse model demonstrates a histological representation of secondary capillary network degeneration due to neurodegeneration.

The study also noted decreasing volumes across principal cell sublayers in Tg rats, consistent with previous findings and suggesting degeneration (Cohen et al. 2013; Jankowsky et al. 2001; Koulousakis et al. 2020). Notably, the PCL displayed a denser capillary network than the entire hippocampus in Tg rats, possibly indicating microcirculatory remodeling in response to Aß deposition (Ardalan et al. 2016; Pearson-Leary et al. 2017). However, discrepancies with previous reports in Tg rodent AD models were evident, suggesting potential

differences in vulnerability and temporal changes in the microvascular system between species(Gama Sosa et al. 2010; Lee et al. 2005; Zhang et al. 2019). Further investigation into the chronological development of these changes may elucidate similarities and differences between rodent AD models and human (Ardalan et al. 2016; Chen et al. 2018; Gama Sosa et al. 2010; Lee et al. 2005).

5.7 The impact of pericytes on the brain during neurodegeneration

The curiosity surrounding brain pericytes has grown as their impact on neuronal function has become more apparent. Despite numerous studies exploring the properties and functions of these proteins, we often lack a comprehensive understanding of their functional histology. In *section 10.7* (Kolinko et al. 2018) of this work, we conducted a review to consolidate the current understanding of brain pericyte function in normal body functions, their involvement in NDDs, and tumor development. We focused on how these proteins interact with other elements in the neurovascular unit. Additionally, we discussed the techniques used to identify brain pericytes and the methods for obtaining both qualitative and quantitative data to evaluate changes in pericytes.

Understanding how brain microvascular pericytes influence brain metabolism could pave the way for diagnostic and therapeutic breakthroughs in NDDs and mental disorders. However, the methods used in studies and the scarcity of quantitative data in published research pose challenges in clearly describing and quantifying pericyte alterations in NDDs and tumor growth. Conflicting findings arise from the use of diverse methods, leading to a lack of consensus even within studies of the same disease. Despite extensive research on pericyte changes, there is still a significant knowledge gap. Investigating pericyte quantity across different brain regions during viral infections, mental health conditions, chronic alcohol use, and neurodegenerative illnesses could offer valuable insights. The efficiency of pericyte signaling is critical for natural healing mechanisms in brain tissue postinjury and for brain adaptability. Hence, comprehensive studies on brain pericytes, considering the multifaceted functions of the BBB and the complexities in disease development, are crucial for clinical applications. These studies should outline pericyte alterations in diseased tissue and, if possible, their evolution during disease progression. Additionally,

employing unbiased quantification techniques, such as automatic stereology systems, would be beneficial.

5.8 Using virtual microscopy for sampling strategies in quantitative histology

Effective quantification demands two criteria: clear staining for structure identification and well-defined reference space boundaries (Howard and Reed 2004; Mouton 2002). It is important to note that the illustrated FOV sampling represents a fraction of the quantitative histology. Other sampling levels—subjects per group, tissue probes, and slide sampling—are equally important (Gundersen and Osterby 1981; West et al. 1991).

In the examples provided, we aimed to distribute sampling evenly across the regions of interest and specimens. This SURS strategy, illustrated above, surpasses simple random sampling by uniformly covering all relevant areas (Mayhew and Lucocq 2015). Although not exhaustive, these examples offer insights into 2D FOV sampling for quantitative histology. We included optimized pilot studies and challenging cases.

Pilot studies, in which sample power analysis is calculated from typical samples, help manage sampling error (CE estimates) combined with biological variance (Tschanz et al. 2014). Descriptive pilot statistics (mean, standard deviation) aid in sample power analysis (Chow et al. 2017), guiding required sample sizes for group comparisons.

In summary, combining virtual slide scanning and unbiased sampling aligns with quantitative microscopy principles (Gundersen et al. 1999). Virtual microscopy aids slide-level sampling. The principles of SURS benefit validity, efficiency, and repeatability. Virtual slide scanners should support the scientific use of SURS.

6 Conclusions

Our presented series of research, which focuses on quantitative histological analysis of microvascular changes in neurodegenerative rodent models, holds significant importance. Providing detailed quantitative data on microvascular alterations, will contribute to a better understanding of how structural changes in blood vessel networks may impact neural health and function. This knowledge can have far-reaching implications, from explaining cognitive and motor deficits to potentially guiding therapeutic interventions targeting vascular-related aspects of neurodegeneration. Moreover, this work highlights the necessity of precise quantitative methods for interpreting complex biological changes, emphasizing the synergy among histology, neuroscience, and broader scientific inquiries.

The experience gained from addressing the aforementioned studies leads us to several common understandings:

6.1. Vascular changes in common neurodegenerative diseases vary widely. They can either be secondary effects or actively contribute to neuronal degeneration. Our discussion also covers the common stereological methods used to assess these changes in the brain microvascular network.

6.2. Although retinal degeneration might impact behavioral disorders in younger subjects, we observed noticeable differences in behavior and test performance between Lc and pcd mutant mice. These distinctions are not thought to be connected to variations in the number of retinal receptors.

6.3. This research explored stress responses in mutant mice during maze testing and revealed consistent stress levels despite assumptions about habituation. Enlarged adrenal gland sections related to stress hormone production suggest continuous stimulation of the capillary network, especially brain microvessels, by stress hormones. These findings offer insights into the complex relationship among stress, corticosterone levels, and microvasculature status in this neurodegenerative model.

6.4. The cerebellar cortex and nuclei contain a significant portion of the cerebellar microvascular network, particularly in mice, with variations in vascular density across its layers. In Lc mice, severe cerebellar degeneration correlates with reduced capillary numbers but increased capillary density, impacting

nutrient availability and potential inflammation. Conversely, pcd mice exhibit a different timeline of degeneration, leading to distinct microvascular changes. Despite capillary reductions, their maintained densities suggest crucial implications for tissue homeostasis. These findings emphasize the interplay between neuronal degeneration and cerebellar microvascular alterations, warranting further exploration of therapeutic strategies.

6.5. This study reveals that degeneration significantly influences graft distribution. Graft integration differs notably between mutant mice, revealing the impact of the tissue environment. Factors such as neurotrophic levels and local microvascular density are crucial for successful tissue implantation. These findings advance our understanding of cerebellar graft development and its interaction with degenerated tissue, highlighting the need for tailored transplantation approaches in cerebellar pathologies.

6.6. We detected microvascular alterations in the transgenic Alzheimer's disease rat model, highlighting considerable reductions in the number of hippocampal microvessels. These changes appeared largely secondary and exhibited partial histological similarities to the observed alterations in pcd mice but differed in nature from the microvascular changes observed in Lc mice. Furthermore, disparities from earlier rodent models suggest varying vulnerabilities and temporal shifts in microvasculature, underscoring the importance of further investigations to delineate similarities and differences between rodent AD models and human AD.

6.7. This review highlights the significance of brain pericytes in neurophysiology, neurodegenerative diseases, and tumorigenesis. It demonstrates that pericytes play a crucial role in brain tissue local niches, warranting further research. This pursuit holds promise for potential advancements in neurological disorder diagnostics and therapeutics, underscoring the need for comprehensive studies utilizing standardized quantification methods across various pathological contexts.

6.8. Effective quantification via histology relies on clear staining, well-defined boundaries, and uniform quantification rules. Our focus on FOV sampling illustrates one facet of quantitative histology, emphasizing the importance of evenly distributed sampling across regions of interest. Pilot studies and sample power analyses help manage sampling errors and guide sample size determination for group comparisons. The integration of virtual slide scanning and unbiased sampling aligns with quantitative microscopy

principles, enhancing validity, efficiency, and repeatability in scientific endeavors.

In summary, quantitative histology serves as a powerful tool for comprehensively investigating and interpreting structural changes, functional consequences, and potential therapeutic interventions in various research contexts. The integration of quantitative histology with other disciplines underscores its significance and the critical role it plays in advancing our understanding of complex biological systems and driving scientific progress. This research exemplifies the essential connection between quantitative histology and broader scientific endeavors, making it a valuable contribution to the field.

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9 The author's published work catalog

9.1 In journals with impact factors

1. **KOLINKO, Y.,** M. KRALICKOVA AND J. CENDELIN Reduction of microvessel number and length in the cerebellum of purkinje cell degeneration mice. *Cerebellum*, 2023, 1-8. https://doi.org/10.1007/s12311-023-01556-y; PMID: 37071329; $IF_{JCR2022}$ = 3.5; Q2 (Neurosciences).

2. BEROUNSKY, K., I. VACKOVÁ, L. VISTEJNOVÁ, A. MALECKOVÁ, et al. Autologous mesenchymal stromal cells immobilized in plasma-based hydrogel for the repair of articular cartilage defects in a large animal model. *Physiological Research*, 2023, 72(4), 485-495. https://doi.org/10.33549/physiolres.935098; $IF_{JCR2022}$ = 2.1; Q3 (Physiology).

3. FENCLOVÁ, T., M. CHEMEK, J. HAVRÁNKOVÁ, **Y. KOLINKO**, et al. Effect of bisphenol S on testicular tissue after low-dose lactation exposure. *Environmental Pollution*, 2022, 315. https://doi.org/10.1016/j.envpol.2022.120114; PMID: 36096261; IFJCR2022 = 8.9; Q1 (Environmental Sciences).

4. DAVE, P., D. GOLDGOF, L. O. HALL, **Y. KOLINKO**, et al. A disector-based framework for the automatic optical fractionator. *Journal of Chemical Neuroanatomy*, 2022, 124. https://doi.org/10.1016/j.jchemneu.2022.102134; PMID: 35839940; $IF_{JCR2022}$ = 2.8; Q3 (Neurosciences).

5. **KOLINKO, Y**., A. MALECKOVA, P. KOCHOVA, M. GRAJCIAROVA, et al. Using virtual microscopy for the development of sampling strategies in quantitative histology and design-based stereology. *Anatomia Histologia Embryologia*, 2022, 51(1), 3-22. https://doi.org/10.1111/ahe.12765. PMID: 34806204; $IF_{JCR2019}$ = 1.114; Q4 (Anatomy & Morphology).

6. SUCHY, T., L. VISTEJNOVA, M. SUPOVA, P. KLEIN, et al. Vancomycin-loaded collagen/hydroxyapatite layers electrospun on 3D printed titanium implants prevent bone destruction associated with S. epidermidis infection and enhance osseointegration. *Biomedicines*, 2021, 9(5).

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7. VISTEJNOVA, L., V. LISKA, A. KUMAR, J. KRECKOVA, et al. Mesenchymal stromal cell therapy in novel porcine model of diffuse liver damage induced by repeated biliary obstruction. *International Journal of Molecular Sciences*, 2021, 22(9). https://doi.org/10.3390/ijms22094304; PMID: 33919123; $IF_{JCR2019}$ = 6.2; Q1 (Biochemistry & Molecular Biology).

8. NEVORAL, J., J. HAVRANKOVA, Y. KOLINKO, S. PROKESOVA, et al. Exposure to alternative bisphenols BPS and BPF through breast milk: Noxious heritage effect during nursing associated with idiopathic infertility. *Toxicology and Applied Pharmacology*, 2021, 413. https://doi.org/10.1016/j.taap.2021.115409; PMID: 33476676; $IF_{JCR2019}$ = 4; Q2 (Pharmacology & Pharmacy).

9. **KOLINKO, Y**., L. MARSALOVA, S. P. PENA, M. KRALICKOVA, et al. Stereological changes in microvascular parameters in hippocampus of a transgenic rat model of Alzheimer's disease. *Journal of Alzheimers Disease*, 2021, 84(1), 249-260. https://doi.org/10.3233/JAD-210738; PMID: 34542078; $IF_{JCR2019}$ = 4.9; Q2 (Neurosciences).

10. RIMNACOVA, H., M. STIAVNICKA, J. MORAVEC, M. CHEMEK, et al. Low doses of Bisphenol S affect post-translational modifications of sperm proteins in male mice. *Reproductive Biology and Endocrinology*, 2020, 18(1). https://doi.org/10.1186/s12958-020-00596-x; PMID: 32466766; $IF_{JCR2019}$ = 5.3; Q1 (Reproductive Biology).

11. PURKARTOVA, Z., F. TICHANEK, **Y. KOLINKO** AND J. CENDELIN Embryonic cerebellar graft morphology differs in two mouse models of cerebellar degeneration. *Cerebellum*, 2019, 18(5), 855-865. https://doi.org/10.1007/s12311-019-01067-9; PMID: 31418135; $IF_{JCR2019}$ = 3.7; Q2 (Neurosciences).

12. SCHOLTZOVA, H., A. G. PATEL, H. K. LYO, E. L. CHO, et al. P4-044: Therapeutic potential of innate immunity stimulation by class B CPG ODN in a tauopathy mouse model, RTG4510. *Alzheimer's & Dementia*, 2019, 15,

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13. **KOLINKO, Y.**, M. KRALICKOVA AND Z. TONAR The impact of pericytes on the brain and approaches for their morphological analysis. *Journal of Chemical Neuroanatomy*, 2018, 91, 35-45. https://doi.org/10.1016/j.jchemneu.2018.04.003; PMID: 29678665; $IF_{JCR2019}$ = 2.7; Q3 (Neurosciences).

14. CENDELIN, J., Z. PURKARTOVA, J. KUBIK, E. ULBRICHT, et al. Long-term development of embryonic cerebellar grafts in two strains of Lurcher mice. *Cerebellum*, 2018, 17(4), 428-437. https://doi.org/10.1007/s12311-018-0928-3; PMID: 29450804; $IF_{JCR2019}$ = 3.7; Q2 (Neurosciences).

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16. EAST, B., M. PLENCNER, M. KRALOVIC, M. RAMPICHOVA, et al. A polypropylene mesh modified with polye-epsilon-caprolactone nanofibers in hernia repair: large animal experiment. *International Journal of Nanomedicine*, 2018, 13, 3129-3143. https://doi.org/10.2147/IJN.S159480; PMID: 29881270; $IF_{JCR2019}$ = 8.1; Q1 (Pharmacology & Pharmacy).

17. TUMA, J., **Y. KOLINKO**, D. JELINKOVA, P. HILBER, et al. Impaired spatial performance in cerebellar-deficient Lurcher mice is not associated with their abnormal stress response. *Neurobiology of Learning and Memory*, 2017, 140, 62-70. https://doi.org/10.1016/j.nlm.2017.02.009; PMID: 28213063; $IF_{JCR2019}$ = 2.8; Q3 (Neurosciences).

18. **KOLINKO, Y.**, J. CENDELIN, M. KRALICKOVA AND Z. TONAR Smaller absolute quantities but greater relative densities of microvessels are associated with cerebellar degeneration in Lurcher mice. *Frontiers in Neuroanatomy*, 2016, 10. https://doi.org/10.3389/fnana.2016.00035; PMID: 27147979; $IF_{JCR2019}$ = 3.9; Q1 (Anatomy & Morphology).

19. TUMA, J., **Y. KOLINKO**, F. VOZEH AND J. CENDELIN Mutation-related differences in exploratory, spatial, and depressive-like behavior in pcd and Lurcher cerebellar mutant mice. *Frontiers in Behavioral Neuroscience*, May 2015, 9. https://doi.org/10.3389/fnbeh.2015.00116; PMID: 26029065; $IF_{JCR2019}$ = 3.6; Q3 (Neurosciences).

20. **KOLINKO, Y.**, K. KRAKOROVA, J. CENDELIN, Z. TONAR, et al. Microcirculation of the brain: morphological assessment in degenerative diseases and restoration processes. *Reviews in the Neurosciences*, 2015, 26(1), 75-93. https://doi.org/10.1515/revneuro-2014-0049; PMID: 25337818; $IF_{JCR2019}$ = 4.7; Q2 (Neurosciences).

21. OSTASOV, P., M. KRALICKOVA, J. CENDELIN, J. TUMA, et al. Hereditary cerebellar degeneration and stem-cell based therapy. *EPMA Journal*, 2014, 5, 1-2. $IF_{JCR2019}$ = 5.3; Q1 (Medicine, Research & Experimental).

9.2 Other articles published in peer-reviewed journals

22. MORERA, H., P. DAVE, S. ALAHMARI, **Y. KOLINKO**, et al. MIMO YOLO – A Multiple Input Multiple Output Model for Automatic Cell Counting. *In 36th IEEE International Symposium on Computer-Based Medical Systems (CBMS).* LAquila, ITALY, 2023, p. 827-831. DOI: 10.1109/CBMS58004.2023.00327

23. DAVE, P., **Y. KOLINKO**, H. MORERA, K. ALLEN, et al. MIMO U-Net: Efficient Cell Segmentation and Counting in Microscopy Image Sequences. *In Conference on Medical Imaging – Digital and Computational Pathology.* San Diego, CA, 2023, vol. 12471. https://doi.org/10.1117/12.2655627

24. MORERA, H., P. DAVE, **Y. KOLINKO**, K. ALLEN, et al. Classification of Global Microglia Proliferation Based on Deep Learning with Local Images. *In Conference on Medical Imaging – Image Processing.* Electr Network, 2022, vol. 12032. https://doi.org/10.1117/12.2611581.

25. ROMASH, I. B., V. H. MISHCHUK, I. R. ROMASH, I. O. KRASILYCH, et al. Manifestations of excessive daytime sleepiness and ghrelin level in case of

gastroesophageal reflux disease in patients with undifferentiated connective tissue disease. *Wiad Lek*, 2022, 75(2), 344-350. PMID: 35307656.

26. KOTYK, T., N. TOKARUK, V. BEDEJ, M. HRYSHCHUK, et al. Multi-step clustering approach of myelinated nerve fibers in experimental neuromorphology. *International Journal of Ambient Computing and Intelligence*, 2021, 12(2), 73-91. https://doi.org/10.4018/IJACI.2021040105; Q2 (Computer Science, Theory & Methods).

27. **KOLINKO, Y. O.** The state of the conduction apparatus and microcirculatory bed of the sciatic nerve of rats on the seventh day after general deep hypothermia. *Ukrainian Morphological Almanac*, 2010, 8(2), 91-93. (Published in Ukrainian).

28. LEVITSKY, V. A. AND **Y. O. KOLINKO**. Ultrastructural changes in nerve fibers of the rat sciatic nerve after the influence of general deep hypothermia. *Bulletin of Morphology*, 2010, 1(16), 139-142. (Published in Ukrainian).

29. **KOLINKO, Y. O.** Histo- and ultrastructural changes in the conduction apparatus of the rat sciatic nerve after the influence of general deep hypothermia. *Current Problems in Modern Medicine: Bulletin of the Ukrainian Medical Dental Academy*, 2009, 9(4-3 (28)), 53-56. (Published in Ukrainian).

30. **KOLINKO, Y. O**. Morphometric benchmarks of myelinated fibers of the rat sciatic nerve under normal conditions. *Galician Medical Bulletin,* 2009, 1, 42-43. (Published in Ukrainian).

31. **KOLINKO, Y. O**. The state of the conduction apparatus and microcirculatory bed of the rat *sciatic* nerve immediately after the influence of general deep hypothermia. *Galician Medical Bulletin*, 2009, 4, 55-58. (Published in Ukrainian).

9.3 Ph.D. Thesis

32. **KOLINKO, Y. O.** Morphofunctional features of the conduction apparatus and blood vessels of the rat sciatic nerve under normal conditions and after the influence of general deep hypothermia. Ph.D. Thesis, 2011, I. Horbachevsky Ternopil National Medical University, Ternopil. (Published in Ukrainian).

10 Annotated work result compilation

10.1 **KOLINKO, Y.,** K. KRAKOROVA, J. CENDELIN, Z. TONAR, M. KRALICKOVA. Microcirculation of the brain: morphological assessment in degenerative diseases and restoration processes. *Reviews in the Neurosciences*, Feb 2015, 26(1), 75-93.

$IF_{JCR2019}$ - 4.7

Quartile (WOS, 2019): Neurosciences - Q2

Available in: WOS:000350396700006
DOI: 10.1515/revneuro-2014-0049
PMID: 25337818

Commentary: In this work, we provide a concise overview of the critical role brain microcirculation plays in various brain diseases, highlighting specific characteristics and functions of brain vessels. This paper focuses on reviewing angiogenesis processes and microcirculation changes in prevalent neurodegenerative diseases, noting the absence of uniform vascular changes across these conditions. Overall, this paper serves as a foundational glimpse into the complex interplay between brain microcirculation and neurodegenerative diseases, covering essential aspects and methodologies in this field of study.

Author's Contribution: First and corresponding author. The author conducted the literature search and composed, and prepared the manuscript for publication.

10.2 TUMA, J., **Y. KOLINKO,** F. VOZEH AND J. CENDELIN Mutation-related differences in exploratory, spatial, and depressive-like behavior in pcd and Lurcher cerebellar mutant mice. *Frontiers in Behavioral Neuroscience*, May 2015, 9.

$IF_{JCR2019}$ - 3.6

Quartile (WOS, 2019): Neurosciences – Q3
Behavioral Sciences – Q2

Available in: WOS:000354572300001
DOI: 10.3389/fnbeh.2015.00116
PMID: 26029065

Commentary: In this publication, we compared spatial navigation, learning, and memory in two prevalent cerebellar mutant mouse models, pcd and Lurcher, shedding light on their behavioral differences. To ensure the accuracy of our assessments, it was important to confirm that retinal degeneration may not impact the outcomes of our behavioral tests.

Author's Contribution: Coauthorship. The author performed the stereology analyses of the retina, and the data analysis and contributed to the literature searches and the design and writing of the manuscript.

10.3 TUMA, J., **Y. KOLINKO**, D. JELINKOVA, P. HILBER, AND J. CENDELIN Impaired spatial performance in cerebellar-deficient Lurcher mice is not associated with their abnormal stress response. *Neurobiology of Learning and Memory*, Apr 2017, 140, 62-70.

IF$_{JCR2019}$ - 2.8

Quartile (WOS, 2019): Neurosciences – Q3
Behavioral Sciences; Psychology; Multidisciplinary – Q2

Available in: WOS:000398646700008
DOI: 10.1016/j.nlm.2017.02.009
PMID: 28213063

Commentary: This study delved into how cerebellar-related stress responses affect spatial learning and memory in Lurcher mutant mice. These mice exhibited an increased stress response, reflected by elevated corticosterone levels and adrenal gland changes. Increased levels of stress hormones potentially trigger vascular spasms, including those in brain vessels, impacting local metabolism.

Author's Contribution: Coauthorship. The author performed the stereology analyses of the adrenal glands and the data analysis and contributed to the literature searches and the design and writing of the manuscript.

10.4 Stereology investigations of microvessels in mouse models associated with cerebellar degeneration

10.4.1 **KOLINKO, Y.,** J. CENDELIN, M. KRALICKOVA AND Z. TONAR Smaller absolute quantities but greater relative densities of microvessels are associated with cerebellar degeneration in lurcher mice. *Frontiers in Neuroanatomy,* Apr 2016, 10.

$IF_{JCR2019}$ - 3.9

Quartile (WOS, 2019): Anatomy & Morphology – Q1
Neurosciences – Q2

Available in: WOS:000374307000001
DOI: 10.3389/fnana.2016.00035
PMID: 27147979

Commentary: This study compared vascular differences in the cerebellar components and midbrain of WT and Lc mutant mice, highlighting distinct patterns. Lc mice exhibit reduced vascularity in the cortex with lower overall microvessel density. This detailed mapping approach offers valuable insights into neurodegeneration in mouse models, aiding future studies on similar conditions.

Author's Contribution: First and corresponding author. The author performed the stereology investigation and data analysis, conducted the literature search and composed and prepared the manuscript for publication.

10.4.2 **KOLINKO, Y.,** M. KRALICKOVA AND J. CENDELIN Reduction of microvessel number and length in the cerebellum of Purkinje cell degeneration mice. *Cerebellum*, Apr 2023, 1-8.

IF$_{JCR2019}$ - 3.7;

Quartile (WOS, 2019): Neurosciences – Q2.

Available in: ://WOS:000971502100001; DOI: 10.1007/s12311-023-01556-y; PMID: 37071329.

Commentary: In this study, we investigated vascular changes in the cerebellum of WT and Purkinje cell degeneration (pcd) mutant mice. Additionally, this work is similar to the previous one but was carried out on a different model of hereditary cerebellar degeneration. The findings indicate substantial reductions in cerebellar volume and microvessel parameters in pcd mice compared to those in control mice. This specific correlation between cerebellar degeneration and a diminished microvascular network differs from the relationship observed in Lc mice.

Author's Contribution: First and corresponding author. The author performed the stereology investigation and data analysis, conducted the literature search and composed and prepared the manuscript for publication.

10.5 Embryonic graft morphology and distribution in selected models of cerebellar degeneration

10.5.1 CENDELIN, J., Z. PURKARTOVA, J. KUBIK, E. ULBRICHT, F. TICHANEK, AND **Y. KOLINKO** Long-term development of embryonic cerebellar grafts in two strains of Lurcher mice. *Cerebellum*, Aug 2018, 17(4), 428-437.

$IF_{JCR2019}$ - 3.7

Quartile (WOS, 2019): Neurosciences – Q2.

Available in: WOS:000437113000005
DOI: 10.1007/s12311-018-0928-3
PMID: 29450804

Commentary: In this study, we delve into the potential of neurotransplantation as a therapeutic avenue for degenerative cerebellar diseases. The findings reveal intriguing insights: while graft survival was successful, challenges in graft integration in the cerebellum occurred in Lurcher mutant mice compared with wild-type mice. This limitation hindered significant functional improvements. Therefore, we believe that the peculiarities of local microvascular systems and their correction can play a key role in therapeutic techniques in the future.

Author's Contribution: Last author. The author was responsible for the stereology analysis, participated in the design and writing of the manuscript.

10.5.2 PURKARTOVA, Z., F. TICHANEK, **Y. KOLINKO** AND J. CENDELIN Embryonic cerebellar graft morphology differs in two mouse models of cerebellar degeneration. *Cerebellum*, Oct 2019, 18(5), 855-865.

$IF_{JCR2019}$ - 3.7

Quartile (WOS, 2019): Neurosciences – Q2

Available in: WOS:000487811100004
DOI: 10.1007/s12311-019-01067-9
PMID: 31418135

Commentary: In this paper, we continued our exploration of neurotransplantation therapy for cerebellar diseases, emphasizing the complexities of graft integration in mice with various types of cerebellar degeneration. Although graft survival was successful in both mutant and wild-type mice, the distinctive patterns of graft integration, particularly in pcd mice, highlighted a direct correlation between capillary network density and fiber sprouting intensity during graft germination. This finding underscores the impact of disease-specific factors on graft fate.

Author's Contribution: Co-authorship. The author was responsible for the stereology analysis, participated in the design and writing of the manuscript.

10.6 **KOLINKO, Y.,** L. MARSALOVA, S. P. PENA, M. KRALICKOVA, AND P. R. MOUTON Stereological changes in microvascular parameters in hippocampus of a transgenic rat model of Alzheimer's disease. *Journal of Alzheimers Disease*, 2021, 84(1), 249-260.

$IF_{JCR2019}$ - 4.9

Quartile (WOS, 2019): Neurosciences – Q2

Available in: WOS:000722639900020
DOI: 10.3233/JAD-210738
PMID: 34542078

Commentary: This study delves into quantifying microvessel changes in the hippocampus of transgenic (Tg) rats modeling Alzheimer's disease (AD) compared to non-Tg littermates. Notably, compared with non-Tg rats, Tg rats exhibit unique microvascular alterations near Aβ plaques, indicating a disruption in microanatomy. These findings reveal significant changes in microvessel parameters, emphasizing the potential for stereology-based analyses to pave the way for innovative AD protection and therapeutic strategies.

An added contribution of this research lies in comparing the secondary microvascular changes observed in the AD model mice with the alterations observed in microvessels in pcd and Lc mice. These indirect comparisons imply that changes in the microvascular bed of PCD mice are more akin to secondary changes, while alterations in the capillary network in Lc mice are likely to be primary.

Author's Contribution: First and corresponding author. The author performed the stereology investigation and data analysis, conducted the literature search and composed and prepared the manuscript for publication.

10.7 **KOLINKO, Y.**, M. KRALICKOVA AND Z. TONAR The impact of pericytes on the brain and approaches for their morphological analysis. *Journal of Chemical Neuroanatomy*, Sep 2018, 91, 35-45.

IF$_{JCR2019}$ - 2.7

Quartile (WOS, 2019): Neurosciences – Q3
Biochemistry & Molecular Biology – Q3

Available in: WOS:000439400700005
DOI: 10.1016/j.jchemneu.2018.04.003
PMID: 29678665

Commentary: This paper focuses on the roles of brain pericytes in normal brain function, neurodegenerative diseases, and tumorigenesis. The findings of these studies emphasize the intricate involvement of pericytes in the neurovascular unit and outline methods for studying pericyte changes qualitatively and quantitatively. The work performed in this article contributes to a better interpretation of the conclusions of previous studies and defines potential directions for further research.

Author's Contribution: First and corresponding author. The author conducted the literature search and composed and prepared the manuscript for publication.

10.8 **KOLINKO, Y.,** A. MALECKOVA, P. KOCHOVA, M. GRAJCIAROVA, T. BLASSOVA, T. KURAL, A. TRAILIN, L. CERVENKOVA, J. HAVRANKOVA, L, VISTEJNOVA, P. TONAROVA, V. MOULISOVA, M. JIRIK, A. ZAVADAKOVA, F. TICHANEK, V. LISKA, M. KRALICKOVA, K. WITTER AND Z. TONAR Using virtual microscopy for the development of sampling strategies in quantitative histology and design-based stereology. *Anatomia Histologia Embryologia*, Jan 2022, 51(1), 3-22.

$IF_{JCR2019}$ - 1.114

Quartile (WOS, 2019): Veterinary Sciences – Q3
Anatomy & Morphology – Q4

Available in: WOS:000720838900001
DOI: 10.1111/ahe.12765
PMID: 34806204

Commentary: This study explores unbiased sampling strategies in histology and the use of virtual microscopy for quantification methods. The author covers practical examples across various histological fields, showcasing techniques from tissue structure assessment to cellular quantification. Emphasizing the importance of systematic uniform random sampling, this paper discusses the pros and cons of using virtual sections for accurate analysis.

Author Contribution: First author. The author provided technical support consulted other co-authors, and participated in the design and writing of the manuscript.