

# Dancing with Glia: The Role of Astrocytes, Microglia and Oligodendrocytes and their Relation with Neurons in Neuroinflammation and Aging

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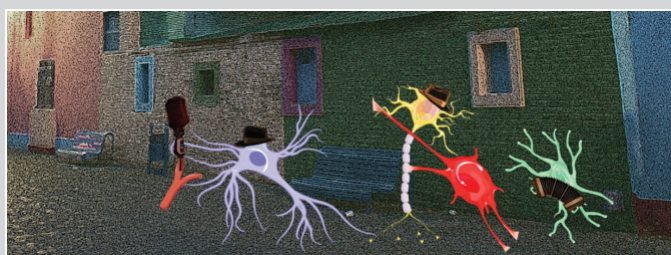
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## ABSTRACT

This review provides an original overview of glial cells functions on the central nervous system and their relationship with neuroinflammation. We decided to correlate astrocytes, microglia and oligodendrocytes functions with neurons interplay, and refer it to Tango genre and dance. Furthermore, this revision summarizes studies that support the roles of glial cells in neuroinflammation under different conditions, such as aging and main neurodegenerative diseases in particular, Parkinson's Disease and Alzheimer's Disease.

**KEYWORDS:** Neuroinflammation; Neurodegenerative diseases; Aging; Glia; Neuron

**ABBREVIATIONS:** A $\beta$ : Amyloid  $\beta$  peptide; AD: Alzheimer Disease; BrdU: Bromo-Deoxyuridine; CNS: Central Nervous System; CNTF: Ciliary Neurotrophic Factor; FGF-2: Fibroblast Growth Factor 2; GM-CSF: Granulocyte and Macrophage Colony Stimulating Factor; ICV: Intracerebroventricular; IL: Interleukin; iNOS: Inducible Nitric Oxide Synthase; LIF: Leukemia Inhibitory Factor; MAPK: Mitogen-Activated Protein Kinases; NFT Neurofibrillary Tangles; NF- $\kappa$ B: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; NMDA: N-Methyl-D-aspartate; NO: Nitric Oxide; NSCs: Neural Stem Cells; OPCs: Oligodendrocyte Precursor Cells; PD Parkinson's Disease; Rad: Recombinant Adenovirus; SASP: Senescence-Associated Secretory Phenotype; SNpc: Substantia Nigra Pars Compacta; TGF $\beta$ : Transforming Growth Factor-Beta; TNF $\alpha$ : Tumor Necrosis Factor-Alpha; VEGF: Vascular Endothelial Growth Factor



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## INTRODUCTION

Tango is a music genre and a dance, characteristic of Río de la Plata region and is indebted to multi-ethnic contributions, thanks to rioplatense colonial past (indigenous, African and creole) and the subsequent immigration contribution. Its etymology has been and continues being subject of multiple theories and strong controversies. In 1957, the historian Ricardo Rodríguez Molas investigated the languages of the slaves brought to Argentina and discovered that the word “tango” refer to “meeting places” or to “danceable meetings of the slaves”, used both in Africa and in colonial America [1]. In this sense, tango went through great stylistic stages in the evolution of the genre, from a primitive, anonymous, and popular stage, through the acquisition of its own identity, to the stage where it reached maturity, refinement, and international diffusion. Furthermore, this genre revolutionized the popular dance by introducing a sensual dance with an embraced couple that proposes a deep emotional relationship of each person with their own body, and the bodies of the dancers with one another. Tango is one of the rhythms which presence has become one of the most popular and familiar in the world.

This exquisite dance in the field of neurosciences, more precisely to the interaction of different neural populations where different types of neurons are surrounded by glia cells. Normal Central Nervous System (CNS) function requires proper assembly of numerous components, including both neurons and glia [2]. For years, neurobiology research specifically focused on the study of neuronal populations, while glia was considered only as a passive supplier of trophic support. In reference to the etymology of the word, the term “glia” means glue and it was first described by Virchow (1856) as “this connective substance forms in the brain, in the spinal cord, and in the higher sensory nerves a sort of putty” (Neurokitten = neuroglia), in which the It is possible to make an analogy of nervous elements are embedded” [3,4]. Since then, glial cells have been considered as the most abundant neural non-excitabile cells, essential in the architecture of the brain. Nevertheless, interest in glial cells and, therefore, the research grew exponentially when it was observed that these cells play an active role in regulating many aspects of neural function.

In this review, we summarize the emerging data regarding the importance of glial cells and how the interactions of astrocytes, microglia and oligodendrocytes, not only with neurons but also among themselves, mimics choreography that reflects the essential steps of tango. This novel approach outlines observations that strongly suggest the importance of glial cells in physiological and pathological conditions and how their inflammatory state could be the driven force of aging and multiple neurodegenerative diseases.

### Neural Tango

#### The origin

Neurons, astrocytes and oligodendrocytes have a common progenitor derived from the neuroepithelium [5]. Neural stem cells (NSCs) are multipotent cells with self-renewing capacity that generate neurons and glial cells of the CNS during embryonic development. Stem cells are characterized by their capacity to differentiate into multiple cell types such as neurons, astrocytes and oligodendrocytes [4]. They undergo symmetric or asymmetric cell division into two daughter cells. In symmetric cell division, both daughter cells are also stem cells. In asymmetric division, a stem cell produces one stem cell and one specialized cell [6]. On the other hand, microglia are resident, tissue-specific macrophages

that perform several critical roles in development and maintenance of the CNS [7]. These immune cells arise from primitive c-kit (+) erythromyeloid precursors in the very early stages of development. These precursors developed into CD45+CX3CR1- myeloid progenitors that differentiate to CD45+CX3CR1+ microglial progenitors and invade the developing brain before the emergence of definitive hematopoiesis [8,9]. In healthy conditions of intact blood-brain barrier in the adult mammalian brain, microglia persist as a self-sustained population that is not replenished by circulating bone marrow-derived cells [10].

### The Protagonists

#### Neurons: the “male” partner

Tango is more than a dance, is a life experience between two partners. It is a very personal and passionate dance based on rhythm, as opposed to music which is based on melody. Another unique feature of tango is that, when dancing tango, while the legs draw figures on the floor, the torso moves in another direction. We can observe a similar interaction between neurons and oligodendrocytes in close contact dancing to the rhythm of the music, played by microglia cells and singed by the greatest exponents of the genre, the astrocytes.

The main role of neurons is their capacity to transmit the electrical impulse throughout its axon. In 1888, Santiago Ramón y Cajal postulated the neuron doctrine, where he described that the nervous system is constituted of independent cells and that the basis of neurological function lies in neurons as discrete entities, whose interaction, mediated by synapses, leads to the appearance of complex responses [11]. These cells are specialized in receiving stimuli and driving the nerve impulse (action potential) among them or with other types of cells. Neurons have typical morphological characteristics that support their functions: a cell body, called soma; one or several short extensions that generally transmit impulses towards the cellular soma, called dendrites; and a long prolongation, called axon, that drives the impulses from the soma to another neuron or target organ. Consequently, neurons can be classified according to: i) shape and size: polyhedral, fusiform, starry, spherical, and pyramidal; ii) polarity: unipolar, bipolar, multipolar, monopolar, and anaxonic; iii) dendrites’ and axon’s characteristics: Golgi type I, Golgi type II, without defined axon, isodendritics, idi dendritics, alodendritics; iv) neurotransmitter: cholinergic, noradrenergic, dopaminergic, serotonergic, and GABAergic and v) function: motor, sensory, and interneurons, leading to a wide distribution of heterogeneous neuronal populations. The two last classifications are physically interconnected by three components of the nervous system: sensory, motor, and integrator. On the whole, a stimulus is captured in some sensory region, delivers information that is conducted through neurons, and is analyzed by the integrating component, which can elaborate a response, whose signal is conducted through the neurons. As a result, neurons form neural networks or circuits with glial components.

#### Oligodendrocytes: the “female” partner

When Virchow observed the fine structure of the brain tissue, he recognized that there were more entities within the “Nervenkitt” than astrocytes but they remained obscure and were only named the “third element” due to the imperfect staining methods. It was decades later that Pio del Río-Hortega (1921) applied a staining method shedding new light on the rest of the interstitial cells. These cells were found to contain numerous short processes and were named oligodendroglia and microglia [12]. In addition to

the function of support and union, oligodendrocytes play another essential role for the proper functioning of the neural network: they produce the myelin sheath in CNS. Regarding their morphology, they have small cell bodies filled with nuclei containing large amounts of chromatin, and their cellular extensions, that lacked fibres, are filled with cytoplasmic granules. By that time, Río-Hortega was able to distinguish four types of oligodendrocytes: i) type I cells generate many different myelin segments on small diameter axons in diverse orientations; ii) type II cells are similar to type I in size and number, but myelin segments run in parallel to each other; iii) type III oligodendrocytes unsheath fewer axons of larger diameter; and iv) type IV oligodendrocytes have a cell body closely opposed to a single very large axon similar to Schwann Cells. Nevertheless, nowadays oligodendrocytes are classified into two large groups: interfascicular -responsible for the production of the myelin sheath and isolation of the axon- and perineuronal satellite-whose function is not yet specified- Furthermore, in order to achieve their key function, the plasma membrane of oligodendrocytes is wrapped around the axon, like the woman to the man in a tango couple, shaping the myelin sheath. Myelinated axons are bundled together into white matter tracts that interconnect grey matter areas and are essential for rapid, integrated neuronal communication and cognitive functions.

### **Astrocytes: the stars of the brain**

The phenomenon of tango could not have been possible if had it not been for its maximum referents such as Carlos Gardel, Astor Piazzolla, Anibal Troilo and Enrique Discépolo, among others. In the brain, the stars are the astrocytes, not only because of its shape and its etymology, but also for their multiple vital functions in the maintenance of the CNS.

Astrocytes were first described in 1891 by Lenhossek and later by Santiago Ramón y Cajal [13,14]. These cells constitute the most abundant glial cell type in CNS (20-50% of brain volume) with a specific distribution among different brain structures. This distribution led to the use of astrocyte/neuron ratio which is region and sex-dependent, e.g. in the cerebral cortex, astrocytes outnumber neurons, while in the cerebellum neurons are the dominant population [15]. Regarding their morphology, astrocytes have small bodies with processes that branch and extend in all directions making contact with neuronal synapses and other brain components. Historically, astrocytes have been classified into 2 subtypes: i) protoplasmic astrocytes, located mainly in the gray matter with complex arborization that are in contact with blood vessels and surrounding synapses, and ii) fibrous astrocytes, located mainly in the white matter, with longer and less complex processes oriented in such a way that they form bundles of fibrils [16-18]. However, thanks to new technologies, such as single-cell RNA sequencing and fluorescence-activated cell sorting-based strategy, several astrocyte subtypes could be identified resulting in a large heterogeneous population [19,20].

During the development of CNS, these cells contribute to neuronal survival, guide axonal growth, stimulate angiogenesis and contribute to the refinement of synapses by eliminating weak synapses and axons via MEGF10 and MERKT receptors [21]. In the adult CNS, astrocytes fulfill important functions of support, maintenance and protection of neurons. Thus, they form the "tripartite synapsis". Moreover, thanks to their close contact with blood vessels, astrocytes provide metabolic support to neurons [22] and are able to increase blood flow in brain regions with higher neuronal activity [23]. Furthermore, astrocytes are also responsible for regulating glutamate and glucose metabolism in

the synaptic cleft and may have neuroprotective functions against oxidative stress releasing glutathione precursors [24,25], removing potassium excess in the synaptic cleft [26] and capturing the excess of free iron [27].

### **Microglia: the immune orchestra**

Classically, tango is performed by a typical orchestra or sextet and recognizes the bandoneon as one of the essential instruments. Bandoneon gave tango its complex characteristic, integrating the melody on a simultaneously rhythmic and harmonic basis. This melodic-rhythmic-harmonic complexity was further deepened with the incorporation of the piano and the development of a technique of execution especially tango, based on rhythmic percussion. This complexity may resemble to the functions of immune cells in the brain.

Microglia cells are well-known from their immune role in the CNS. They were first described in 1919 by Pio del Río-Hortega [28] and, as we mentioned before, they have an origin in the blood monocytes that invade the brain during the early development, constituting 20% of the population of glial cells. Among their key functions, microglia cells are in charge of assuring the immune defense of the brain and the maintenance of homeostasis through a balance between their degenerative and protective roles. An interesting characteristic of microglia cells is that they alter their morphology according to their reactivity: i) resting (quiescent) microglia present a small cellular body with ramified long branches that survey the environment looking for harmful stimuli; ii) activated non-phagocytic microglia have an hypertrophied cellular body with shorter numerous branches; iii) activated phagocytic microglia present an amoeboid morphology. Furthermore, these cells also change their secretory phenotype depending on the sum of stimuli they sense and polarized into a pro-inflammatory or an anti-inflammatory phenotype, known as M1 and M2 activation states, respectively [29]. Pro-inflammatory M1 state is characterized by increased expression of induced nitric oxide synthase (iNOS) and secretion of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , promoting degeneration [29,30]. On the contrary, anti-inflammatory M2 state present an increased expression of Arginase 1 enzyme and production of the anti-inflammatory cytokines IL-4, IL-10, TGF $\beta$ , IGF1, VEGF, and play an important role in tissue repairing and wound healing [29-33]. Taking into the aforementioned, microglia activity and reactivity must be under tight regulation in order to assure the elimination of harmful elements without threatening healthy components.

In addition to their surveillance role, microglia can influence synaptogenesis and synaptic plasticity. It has been demonstrated that microglia are key regulators of synaptic formation, remodelling and elimination during development and in the adult brain, in order to have an appropriate brain connectivity [34-36]. During development, neurons form excessive synaptic connections. Many of these connections will soon be removed during synaptic pruning, a process by which microglia eliminate immature and incorrect neural circuits in order to have an appropriate brain connectivity [37,38].

Moreover, when deciding which synapse must be eliminated, microglia are able to detect and selectively eliminate low activity synapses rather than highly active ones [39]. Furthermore, in the adult brain, neuronal circuits are also highly dynamic and undergo synaptic remodelling, a process known as synaptic plasticity, in charge of microglia [36]. Changes in neuronal activity can strengthen or weaken synapses, which is sensed by microglia thus

inhibiting or promoting synapse removal, respectively. Thus, once again, synapse's activity conditions its own survival [34-40].

### Let's Dance

Tango is built on four basic components: hug "el abrazo", walk "la caminata", cut "el corte" and break "la quebrada", being these last two classic terms the axis of improvisation and the choreographic figures that decorate the dance and that are known under the generic name of "firulete". Above all, tango must be danced with body language through which personal emotions of the couple are transmitted. In this section, we are going to describe the mechanisms by which the four neural components mentioned above interact and perform specific choreographic figures.

#### Neurons & Oligodendrocytes: the perfect couple

To start the dance, the man and the woman meet; the man extends his hand and she places hers on his. The man surrounds the woman's body with the other arm. The woman lays her arm on his shoulder or around his neck. As a greeting, they tune their movements, turning with their bodies in a semicircle or also making a swing, passing the weight of the body from one leg to another.

Oligodendrocytes produce and maintain the myelin sheath that isolates and supports neuronal axons. These cells undergo a morphological differentiation characterized by elaborated branched processes to enwrap neuronal axons, where dynein cofactor NDE1 could be a possible mediator [41]. Axon myelination is essential for the efficient and rapid conduction of action potentials in the CNS [42] but also is important for neuronal survival, which is attributed to metabolic transfer from oligodendrocytes to neuronal axons through myelin [43]. Nevertheless, oligodendrocytes can also respond to axonal signals [44]. For example, one of the neuronal signals for myelination is electrical activity, which can regulate oligodendrocyte proliferation and differentiation [45]. Axons are necessary for the maintenance of normal myelin protein gene expression within oligodendrocytes [41]. As a result, myelination is highly regulated, in a dependent manner, by oligodendrocyte-neuron signaling that regulates oligodendrocyte proliferation, differentiation and myelin formation by the Notch signaling pathway [46]. Some neuronal factors involved in this regulation have been identified as ligands expressed by axons, e.g. neuregulin-1 [47], jagged1 [46], PSA-NCAM [48] and LINGO-1 [49,50]. This activity-dependent selection of axons by oligodendrocyte is essential for higher brain function through modification of neural information processing. Communication in this "tango couple" is vital due to glial support of axonal integrity where oligodendrocytes are metabolically active and functionally connected to the subjacent axon via cytoplasmic-rich myelinic channels for movement of macromolecules to and from the internodal periaxonal space under the myelin sheath [12].

#### Let the music sound

Communication between the immune system and CNS is exemplified by cross talk between glia and neurons, which is essential for maintaining homeostasis [51]. The interaction between neurons and microglia occurs in a ligand-dependent way, involving many ligand and receptors. Three main signaling pathways (CD200/CD200R, CX3CL1/CX3CR1 and Cq1-C3/C3R pathways) have been well described [52]. In all cases, neurons express specific ligands that, by binding to their receptors localized on the microglia, act as a pro-survival stimulus and modulate microglia activation, keeping them in a quiescent state [53]. On the other hand, any insult that

affects neuronal integrity and interrupts these signals, or even the lack of expression of these ligands in neurons is recognized by the microglia as a "eat me" signal and, therefore, triggers the activation of the microglia and promoting phagocytosis of neurons [54-56]. Thus, depending on the balance of signals in the cross talk between neurons and microglia, these last ones can receive a "help me" or "eat me" signal from neurons.

Oligodendrocytes express a wide variety of innate immune receptors and produce and respond to chemokines and cytokines that modulate immune responses in the CNS. Crosstalk between oligodendrocytes and microglia shows a delicate balance between activated microglia being harmful to the myelin-producing cells and being necessary for their repair and regeneration. On the other hand, oligodendrocytes can regulate microglial activity through the production of chemokines, cytokines and chaperokines [51]. Emerging data suggests that extracellular nucleotides play important roles in glial activation in the CNS via purinergic receptors. Likewise, oligodendrocytes also use purinergic receptor signaling for their development and for myelination [57].

Activated microglia may also have important roles in glutamate release by increasing glutamate-cystine exchange transporter expression. Although this neurotransmitter is essential for synaptic transmission, high levels of glutamate results in  $Ca^{2+}$  mediated excitotoxicity leading to pathological conditions [58,59]. Related to this, oligodendrocytes express AMPA and NMDA receptor subtypes and, consequently, glutamate excitotoxicity could trigger apoptosis, or cell death through the release of TNF- $\alpha$  and IL-1b by microglia, which might lead to myelin damage [59]. These pro-inflammatory cytokines can also contribute to oligodendrocyte damage via iNOS gene activation, making oligodendrocytes extremely susceptible to oxidative damage [51]. To sum up, neuron and oligodendrocyte couple dances to the rhythm of microglia music, due to their influence on synaptogenesis and synaptic plasticity, and taking into account that many products of activated microglia cells may be potentially detrimental to oligodendrocytes.

#### Let the stars shine

Until now, we have presented the couple and the music, but to talk about the arrabal, we need the presence of famous tango stars. What would Tango be without its singer? Somehow, astrocytes have a similar vital importance in the interaction of neural components.

In the last decades, emerging data suggest an important modulatory role of astrocytes in brain homeostasis [20]. Among the many functions of astrocytes, we can name: control of CNS blood circulation and extracellular ion homeostasis, release of energy substrates, production of growth factors, and recycling of neurotransmitters. All these functions allow astrocytes to actively modulate the dynamic of neurons by regulating and organizing local or distant (extrasynaptic) synaptic activity, excitability, transmission, and plasticity at the cellular and system levels [60]. Astrocytes are commonly referred as housekeeping cells due to their role in energy metabolism homeostasis [61], their continuous flow of molecules through their gap junctions [62], and by transporting neurotransmitters (D-serine, ATP, GABA and glutamate) [63]. A constant feedback is observed between neurons and astrocytes: both types of cells response to each other's signals [64]. For example, during tripartite synaptic neurotransmission, astrocytes have the capacity to regulate both the neuronal presynaptic bottom and postsynaptic neuron through the  $Ca^{2+}$  dependent release of gliotransmitters [65]. Among these neurotransmitters, the

excitation of neurons caused by glutamate can be modulated by inhibition through release of GABA induced by glutamate uptake from astrocytes [65,66]. These modulatory mechanisms are vital for neural network activity and dynamics.

Apart from the complexity of astrocyte-neuron cross talk, glial interactions are becoming a potential target of study in order to understand many demyelinating CNS diseases [60]. Ishibashi et al. reported a connection between myelination, astrocytes, and electrical impulse activity in axons, mediated by the cytokine leukemia inhibitory factor (LIF). LIF, which promotes myelination, is secreted from astrocytes in response to ATP released from active axons [67]. Furthermore, it was observed that astrocytes produce ciliary neurotrophic factor (CNTF) to stimulate cytokines, neurotrophic factors and growth factors release, including fibroblast growth factor 2 (FGF-2), a stimulator of oligodendrocyte precursor cells (OPCs) proliferation, that favors remyelination [68,69]. Moreover, IL-1 $\beta$  can promote astrocytic LIF release [70], which has been shown to promote oligodendrocytes' survival and differentiation [71]. *In vitro* studies demonstrated that conditioned medium collected from primary cell culture of astrocytes and then incubated with cultures of OPCs, promotes the proliferation of OPCs and protects them against stress [72, 73].

Regarding astrocytes-microglia interaction, it was observed that during CNS development, both cell types influence each other in order to promote their own development and maturation. As a matter of fact, proliferation and differentiation of microglia occur in parallel to that of astrocytes within the same regions [74]. It has been demonstrated that microglia can stimulate astrocytes proliferation and differentiation through release of interleukins (such as IL-1 and IL-6); [75,76] and nitric oxide (NO) [77]. Furthermore, astrocytes can stimulate microglial proliferation and maturation by release of soluble factors such as interleukin 3 (IL-3) [78] and granulocyte and macrophage colony stimulating factor (GM-CSF) [79]. In the adult brain, astrocytes and microglia cross talk through soluble factors and cytokines to modulate each other [80]. One of these factors is S100B, a protein that is constitutively secreted by astrocytes under normal conditions, acting as a neurotrophic factor. Nevertheless, in response to damage, an overproduction of S100B occurs, fact that could mediate microglial activation, leading to the exacerbation of neuroinflammation [81]. Furthermore, in a rat model of hippocampal excitotoxic injury with NMDA, S100B was found to be key for the modulation of microglia phenotype [82]. On the other hand, when microglia sense a damage, they release IL-1 $\beta$  which can cause astrocytic activation [83]. In summary, neuron-glia crosstalk is essential for normal brain homeostasis, while miscommunication between them could lead to pathological conditions. Thus, a better understanding of neuron-glia interactions will allow us to deepen our knowledge about the inflammatory mechanisms of the most prevalent neurodegenerative diseases of CNS.

## TANGO TOPICS

Tango 'songs and melodies cover certain emotional and social topics such as the feeling of belonging to the arrabal, love disappointment, death, sexual desire and sadness, gender issues, and passage of time.

### Aging

Reflection on time is a very special feature of tango lyrics. Generally, all tangos contain a torn look about the destructive effect of time on relationships, things, and life itself. Aging is a biological process that leads to a progressive loss of brain functional integrity

due to i) increased oxidative stress with damage in nuclear DNA [84] and in cellular proteins [85]; ii) protein misfolding and aggregation [86]; iii) disturbances in calcium homeostasis [87], and iv) mitochondrial dysfunction and energy deficiency [88]. Aging is associated with structural and cellular damage that has a direct consequence on cognitive, motor and behavioral impairment, and increase susceptibility to neurodegenerative disorders [89].

Age-related neuronal dysfunction is often associated with ultrastructural changes in neurons and glia. For example, it has been observed that neurons may develop intracellular and extracellular plaques and tangles [90], which could promote neuronal cell death aging. Moreover, neurons may also present decreased synaptic density, synaptic plasticity, and reduced neurotransmitter production [91,92]. Regarding glial cells, it is well known that the aged brain is characterized by a chronic inflammation established by both microglia and astroglia [93-95]. As for oligodendrocytes, studies in human brain demonstrated that their number decrease about 27% from 18 to 93 years old [96]. Moreover, oligodendrocyte morphology changes toward a swelled one, with inclusion bodies inside. These alterations correlate with a progressive demyelination of neurons [97]. Studies in rodents have shown that the number of OPCs maintains stable during life, but it has been observed a decrease in remyelination efficiency due to a decreased in OPCs migration and the consequent impaired differentiation to oligodendrocytes [98,99] and at a diminished self-renewal rate [100].

Regarding astrocytes, it has been shown that they present senescence-associated secretory phenotype (SASP): i) increased GFAP and vimentin levels, and hypertrophy; ii) increased cytokines expression; and iii) increased toxic protein aggregates. Moreover, isolated astrocytes from aged brain display a pro-inflammatory phenotype, thus suggesting a role of astrocytes in age-related neuroinflammation and neural degeneration. Taking into account the many functions of astrocytes, it is evident that age-related senescence of astrocytes enhances the decline in functional capacity of the brain [101-104]. Reactive astrogliosis and astrocytic loss of function contribute to loss of homeostasis in the brain and represent a risk factor for neurodegenerative diseases. It has been demonstrated in animal models of Alzheimer's disease that astrocytes go through a degeneration process and atrophy during early stages of the disease, while in later stages reactive astrocytes are found directly associated to neurite plaques [105].

Numerous studies described the alterations that make microglia become during aging and disease [106, 107] polarized towards a pro-inflammatory phenotype [108], expressing increased levels of pro-inflammatory cytokines such as IL 1 $\beta$ , IL 6 and TNF $\alpha$ , and reduced levels of anti-inflammatory cytokines such as IL 10 and IL 4 [107]. Moreover, senescent microglia undergo an age-dependent degeneration and loss of their neuroprotective function thus contributing to age-related diseases onset [108,109]. These microglia carry out the process known as "microglia priming", an exaggerated or exacerbated microglial response to inflammatory stimuli. Such excessive and prolonged response causes neuroinflammation, resulting in synaptic damage, neuronal death during aging and several age-associated diseases [110]. In fact, the progression of many neurodegenerative diseases is dependent on microglial activation [111-114].

Aged brain integrity is also affected by the decrease in the production of neuroprotective molecules. Among these, IGF1 and its signaling pathway have been widely investigated [115-117]. This

growth factor is essential for the correct development of the CNS as it influences proliferation and survival of all the components of the CNS. Moreover, IGF1 participates of neurogenesis, myelination, and synaptic plasticity in the adult brain [118,119], demonstrating the importance of this growth factor. Notwithstanding, IGF1 level declines during aging, correlating with learning and memory abilities, motor performance, and synaptic plasticity impairments [120,121]. Indeed, all major disorders commonly found in the aged brain, including cell dysfunction, metabolic impairment, and altered brain functions can be attributed to reduced brain IGF1 input, a condition that is inherently linked to the aging process [122]. Therapeutic approaches administrating IGF1 have corroborated these observations: Intracerebroventricular (ICV) infusion of IGF1 increased in the number of BrdU-labeled cells in the proliferative sub-granular zone, the granular cell layer and hilus in old rats [123]; intrahypothalamic injection of recombinant adenovirus carrying the IGF1 gene (rAd-IGF1) reversed hyperprolactinemia and increased the number of dopaminergic neurons in the hypothalamus of aged rats [124]; transgenic overexpression of IGF1 increased neural stem cells proliferation as well as differentiation of neuronal stem cells into neurons in the sub-granular and subventricular zones of adult mice brains [125]. Moreover, ICV gene therapy with rAd-IGF1 improved both motor and cognitive performance in senile rats [126,127].

### Sexual Dimorphism

In the traditional male-female couple, gender roles are sexually defined. This means that the man creates and directs the dance and the woman follows him, although with an autonomous choreography. However, at the beginning of 19<sup>th</sup> century, the tango was danced between men. Moreover, tango choreography also admits that occasionally, is the woman who leads. Finally, by the end of 2000, a movement emerged in Germany, called tango queer, which proposes dancing tango without the roles being fixed to biological sex.

Regarding biology, it is also possible to find sex differences in the brain. Sexual dimorphism is controlled, mainly, by androgen and estrogen, the steroid hormones from the gonads. In the classic perspective on sexual differentiation of the brain (Organizational hypothesis) [128], these gonadal hormones act on the brain during a sensitive perinatal period to organize the male or female phenotype. In fact, it has been observed in rodents that the early appearance of estrogen in the brain, as a result of testosterone aromatization, generates a masculinized/male brain. During this period, the brain presents sexual differences in apoptosis, synaptogenesis, and neurogenesis. Following this differentiation, androgen and estrogen act on the female or male brain throughout life, to produce sex-specific behaviors [129]. However, not all sexual differences are a result of hormonal action. A great contribution is given by sex chromosomes due to differential expression of several genes during development. Among these genes is the SRY gene of the Y chromosome, which is not only known for its participation in testicular development but also in the regulation of the synthesis of some neurotransmitters [130]. During early stages of brain development, males have a greater number of microglia in several regions of the brain, such as the hippocampus, amygdala and paraventricular nucleus [131]. In addition, male rats present not only a higher number in the preoptic area, where the dimorphic nucleus is found, but also a greater activation of microglia, promoting thus a formation of a synaptic pattern that results in a typical masculine sexual behavior [132]. This difference is reversed in adulthood, where females have more activated microglia and

higher levels of pro-inflammatory cytokines in the brain [131-133]. In the posterodorsal medial amygdala, hemispheric-dependent sex differences were observed in the number and complexity of the astrocytes and it is believed that androgen receptors could be critical in establishing these differences [134]. *In vitro* cultures of astrocytes showed sexual differences in the response to pro-inflammatory stimulus, which could be determined by perinatal exposure to testosterone [135]. It has been demonstrated that the number of oligodendrocyte progenitors and myelination are regulated by sex hormones, probably contributing to sexual differences in the repair of nerve damage [136].

## NEURODEGENERATIVE DISEASES

The term 'neuroinflammation' refers to any inflammatory process, whether acute or chronic, involving the nervous system. It remains unknown if neuroinflammation is a simply reaction to tissue damage or if it has an active role promoting neuronal and synaptic damage, and its importance in pathogenesis. In the following section, we will summarize the importance of glia cells in the modulation of neuroinflammation in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD).

### Alzheimer's Disease

Alzheimer's disease (AD), firstly described by Dr. Alzheimer in 1906 as a "pre-senile dementia", has two major pathological processes: amyloid beta (A $\beta$ ) and Tau protein deposition [137]. Nowadays, AD is the most common neurodegenerative disease worldwide, where aging constitutes the major risk factor and constitutes the most common cause of dementia in the elderly [138].

In the last decades, it became evident that glia cells interaction plays a key role in the pathophysiology of AD, where both A $\beta$  plaques and neurofibrillary tangles (NFTs) may be cause and consequence of neuroinflammation. In general terms, A $\beta$  regulates synaptic and neuronal activities, and its accumulation in the brain leads to synaptic depression and aberrant network activity [139]. This aggregation is frequently associated with the activation of microglia and astrocytes, since A $\beta$  induces the expression of inflammatory enzymes such as COX-2 and iNOS, and inflammatory cytokines (e.g. TNF $\alpha$  and IL-1 $\beta$ ), which enhance APP production and stimulate NF- $\kappa$ B and MAPK signaling pathways [50]. A $\beta$  can also disrupt gliotransmitter release and astrocytic calcium signaling, interfering with synaptic plasticity in the astrocyte-neuron communication [140]. In addition, Tau protein aggregates play an important role in the stabilization and assembly of microtubules, which are crucial for normal cellular morphology and trafficking. Oligomeric Tau release synaptotoxic species that may contribute to synapse degeneration closely correlated with cognitive decline in AD [141] and to oligodendrocyte dysfunctions through inflammation and oxidative stress. An impairment in the OPCs repair might possibly enhance the progression of the disease under decreased self-healing ability from aging process and pathological factors including A $\beta$  pathology and/or NFTs [142]. As we mentioned before, neurodegeneration is concomitant not only with microgliosis and oligodendrocytes dysfunction but also with microvascular remodeling and astrogliosis. Astrocytes mediates CNS inflammation of AD by releasing cytokines and chemokines to influence effector cells [138], modulating the BBB and forming glial scars [143]. Understanding the heterogeneity of inflammatory mechanisms involved in the pathology of AD will prompt the research of a personalized treatment for this dementia.

## Parkinson's Disease

In 1817, James Parkinson published *An Essay on the Shaking Palsy* where he first described the neurological disorder that today bears his name [144]. Parkinson's disease (PD) has become the second most common neurodegenerative disorder after AD. It is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) projecting to the putamen and caudate nucleus brain areas [145].

Neuroinflammatory processes in PD are rather involved in self-perpetuating deleterious events that lead to protracted neuronal degeneration. These processes occur alongside the loss of dopaminergic neurons and is associated with alterations to many cell types, most notably microglia [146]. Thus, T-cell infiltration accompanies activated microglial and astrocytic accumulation in and surrounding the SNpc [147], contributing to neurodegeneration. Neuronal death further activates inflammatory mechanisms, resulting in a vicious cycle of inflammation and neuronal loss. An increased microglial activation was observed in the SNpc of patients indicated by increased expression of CR3/43 and EBM11, markers for activated microglia [148]. Dopaminergic neurons of the nigrostriatal pathway are particularly vulnerable to microglial mediated neurotoxicity and neurodegeneration [149]. Moreover, post-mortem studies demonstrated that  $\alpha$ -synuclein is present in different brain regions where microglial activation is also known to be present, shifting microglial morphology to an amoeboid shape thus causing dopaminergic neurotoxicity [150].

On the other hand, astrocytes play direct, important, active, and critical roles in mediating neuronal survival and function in PD. These cells are more susceptible and recognize multiple soluble signals from activated microglia such as chemokines and cytokines, and function differentially in response to oxidative stress. It is important to know that astroglial-mediated inflammatory and oxidative stress mechanism may be more important than the microglial or neuron, since they are the most abundant cell type in the brain and are extensively involved in the nourishment of the neurons [151]. A small change in the surrounding astroglial cells may effectively cause neuronal cell death compared to any other cell type in the brain [152]. The mechanisms underlying the progressive neurodegenerative inflammation in PD are still elusive, and the discovery of the active or main driving force is of paramount importance in the search of effective therapeutic strategies.

## CONCLUSION

This review shows that glial cells are key regulators of neuroinflammation and in the natural process of aging. They act together and with neurons forming an interneural matrix for a proper maintenance of physiological conditions. Immune system and its reactions have been always characterized using a battlefield analogy. This study provides a new approach, a dance to refer homeostatic conditions. Glial cells roles, and their dual effects, could be detrimental or beneficial depending on the age, gender or pathological conditions. Given the important regulatory roles of these cells, they are appealing targets for treatment of neurodegenerative diseases. However, due to the complex scenario, it is clear that more research is needed to identify individual pathways or genes that modulate glial phenotype to develop targeting specific therapies.

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