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Glial cells of the central and peripheral nervous systems: An overview of existing research

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Orientation: Until recently, most of that neural research was been directed at understanding the morphology and functions of the neuron. However, with advances in scanning and microscopy, the morphology and function of glia are attracting greater attention.

Research purpose: To many readers glia are often mysterious background players. This paper is an overview of existing literature was compiled to remove some of this mystery they may encounter when reading modern scientific neuroscience publications.

Motivation for the study: This study was motivated to increase understanding of the important roles played by glia cells in the efficient operation of the human nervous system.

Research approach or design and method: This study was compiled in the form of a literature review from freely accessible journal articles and common text books. Using key words ProQuest and Google Scholar databases were consulted for peer reviewed journal articles.

Main findings: Glia cells have a greater role than just 'glue' for neurons. Examples of their roles include maintaining the levels of essential extracellular cations such as calcium, the maintaining of the integrity of neural connectivity, the creation and release of communicating gliotransmitters, and the role of microglia as an integral part of the immune system.

Implications for practice: It is essential for anyone wanting to comprehend the mammalian nervous system as described in modern literature to have a broad understanding of the integration, signalling, and structural significance of glia. This overview provides a level of knowledge meeting this need.

Contribution or value-add: This overview has provided a basic, but comprehensive, low-cost launch-pad of knowledge to have a broad understanding of the integration, signalling, and structural significance of glia.

Keywords: glia; macroglia; microglia; astrocyte; oligodendrocyte; Schwann cell; radial glia.

Introduction

The human brain is made up of an exquisitely sculptured collection of cells that process all our body's sensations and experiences, interpret all our thoughts and emotions, and ultimately, direct and control our body's behaviour. To perform all these tasks our brain relies on the networks of our nervous systems for both the input of sensations and the output of responses. These neural networks, made up of neurons and glia cells, connect sensory and motor networks to a plethora of sensory cells and activate cells on muscles and glands as well as complex intra-brain connectivity that gives rise to higher executive processes. While many of the research reports centred on neurons, glial cells are now being included in the narrative more often so it is important to also have a working knowledge of these cells.

Much of what is known about human brain has been learned from animal studies in laboratories using animals such as rats, mice, and zebrafish, to name a few (Seeker & Williams, 2022). However, humans are distinctly different from animals in many ways. Importantly, it is the heterogeneity between the various types of brain cells that makes us distinctly human, and a deeper understanding of the cells that make the human brain is therefore imperative if effective treatments for neurodevelopmental disorders are to be discovered (Seeker & Williams, 2022).

Therefore, the purpose of this paper is to provide a working level of knowledge by shining the spotlight on the not-so-humble glia. We begin with a general description of glia, some of which are depicted in Figure 1.

Method

This literary review was accomplished by reference to ProQuest databases such as PsycArticles, Medline, EBSCO and Google Scholar. These are generally freely available to alumni of universities. Additionally, several seminal textbooks from undergraduate reading lists were consulted. Key words such as 'astrocyte and morphology and heterogeneity and function' were entered on database command bars and limited to peer-reviewed and full text articles. Books are not often peer-reviewed, so only texts considered seminal to the topic were selected. All articles, including diagrams, were freely available or released under open access protocols.

Because neuroscience is such a rapidly expanding discipline, only the most recent articles were selected; therefore, all referenced journal articles are post 2000 and one book 1999.

Historical background

Glial cells are non-neuronal cells that inhabit both the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS is comprised of the brain and the spinal cord, while the PNS refers to the rest of the organism's nervous system network. According to Pereira and Furlan (2009), glial cells are the most abundant cellular structures making up the human brain. There are an estimated 86 billion neuron cells compared with 85 billion non-neural glial cells that make up the volume of the human brain and spinal cord (Azevedo et al., 2009; Pereira & Furlan, 2010). However, this is controversial with researchers' suggesting ratios between 3:2 and parity dependant on the researcher's definition of glia and the region of the brain being assessed (Azevedo et al., 2009). The idea that glial cells only have a static role in the brain's operation has also been considerably revised as new knowledge is afforded by modern developments in research technology and methods (Miguel-Hidalgo, 2009). In general conversation, they are commonly referred to as neuroglia or more simply glia (plural of glial cells).

In 1858, Rudolph Virchow first described the substance between the neurons as a type of neural putty (Nervenkitt) or neural glue, that he believed to be in the form of a fibrous mass, from which the term glia emerged (Şovrea & Boşca, 2013). During the latter part of the 19th century, scientists were drawing astrocytes as stellate or star shaped cells; however, it was Camillo Golgi in 1878 using his silver-chromate staining process who first described glial cells in detail (Şovrea & Boşca, 2013). Golgi on observing how some glia cells displayed endfeet that were enveloping blood vessels and interconnecting with the adjacent cells postulated that glia was not simply 'neuronal glue' but was actually playing an important role in the metabolism of the CNS (Şovrea & Boşca, 2013). In 1893, Von Lenhossék introduced the term 'astrocyte' as a reflective descriptor of the ubiquitous stellate glia cells. Glia may be further classified as

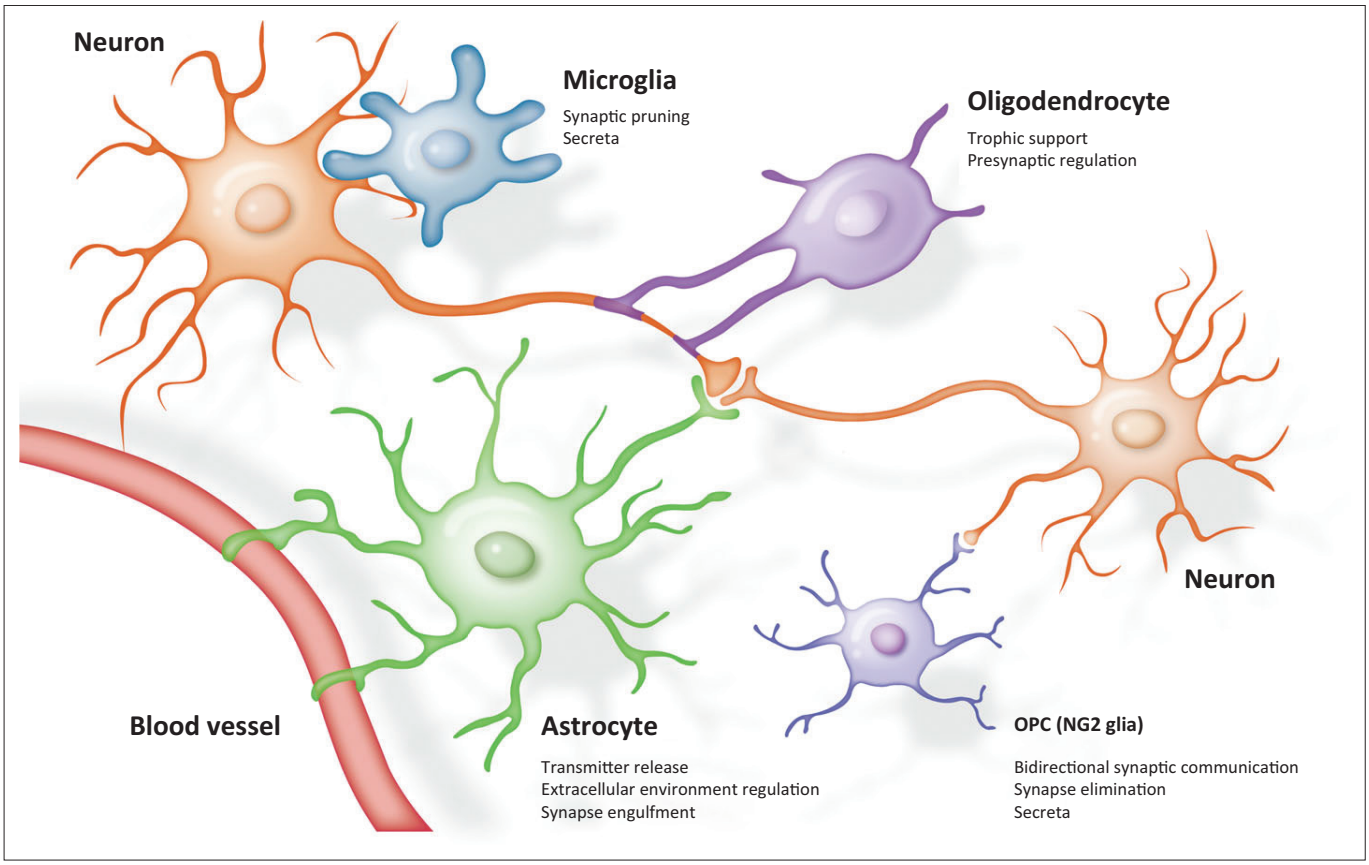

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FIGURE 1: Common cells of the human central nervous system.

protoplasmic or fibrous, terms that are reflective of their localised morphological functionality within grey or white matter, respectively (Şovrea & Boşca, 2013). Modern research studies have continued to build upon this early research, and we now have a far greater understanding of the pivotal and dynamic role played by glial cells.

Notwithstanding the aforementioned, glia are typical cells and, like neurons, contain protoplasmic organelles such as structural protofilaments of protein tubulin and microfilaments of twisted actin filaments for structural stability, lysosomes for the removal and recycling of cellular waste, isolated endoplasmic reticulum for gliotransmitter manufacture, small Golgi apparatus to package and deliver neuroactive molecules, and mitochondria to mediate the synthesis of energy (Raine, 1999). Furthermore, most glia and neurons originate from the same common pool of neuroepithelial cells from which the embryonic nervous system emerges (Kandel et al., 2013). Microglia originate from bone marrow and migrate to all parts of the nervous system early in foetal development and are an active part of the immune system (Kandel et al., 2013).

Like other mammalian eukaryote cells glial cells have a surrounding membrane, or plasmalemma, comprised of an asymmetrically constructed bilayer of phospholipids and proteins that form a hydrophobic barrier to most water-soluble substances (Vanderah & Gould, 2016). Enclosed within this membrane is the cell body containing a nucleus surrounded by cytoplasm that is made up of cytosol and membranous organelles similar to neurons (Kandel et al., 2013).

Glia cannot create action potentials and do not have axons or dendrites like neurons and maybe this explains why they were considered to only play a supportive but essentially passive role in the functioning of the brain (Araque & Navarrete, 2010). However, subsequent research has discovered that they are not just passive supporters but perform and influence many critical functions. For example, ependymal cells, most likely the cells associated with their original concept of being glue, delineate and impose structural constraints of the extracellular space surrounding the neurons (Araque & Navarrete, 2010). Endothelial glia cells form a large part of the barrier that exists between the blood systems and the brain tissue. This allows the transportation of nutrients and fuel to the neurons while isolating the brain from unwanted imports such as pathogens (Şovrea & Boşca, 2013). Glial cells insulate the neurons with myelin to improve conductivity and synaptic connection (Sigaard et al., 2014). Microglia mediate phagocytosis of cellular debris resulting from apoptosis and normal cell death and neural injury (Lull & Block, 2010). Glial cells have an important role in programming the metabolization of glutamate, the regulation of glutamatergic transmission, and the maintenance and stimulation of synaptic expression (Miguel-Hidalgo, 2009).

There are a variety of terms that have been used to describe glia and many of these emanated from the 19th century scientists as they recognised the differentiated morphology of the cells (Rakic, 2003). For example, Virchow (nervenkitt), Golgi and Ramón y Cajal (epithelial cells), Retzius (foetal ependymal cells), and Von Lenhossék (spongioblast). Other terms such as tanycytes, faserglia, Muller cells, and Bergman glia have also persisted in modern usage to denote glia modified by specific spatial environments (Rakic, 2003). However, the modern electron microscopic and immunohistochemical methods have confirmed a consistent biomarker of glia by the identification of glial fibrillary acidic protein (GFAP) in primates and humans allowing detection of glia from as early as corticogenesis (Rakic, 2003).

There are exciting times ahead in neuroscience for those uncovering the secrets of glial cells. For example, the recent research that uncovered the presence of monoamine transporter proteins expressed by some neurons and astrocytes has vastly increased our knowledge of how glia actively modified the extracellular concentrations of neurotransmitters (Andrews et al., 2022). The discovery of monoamine transporter proteins in astrocytes as well as neurons may contribute valuable information in understanding how selective serotonin reuptake inhibitors (SSRIs) relieve the symptoms of depression (Andrews et al., 2022). SSRIs are presently the most prescribed antidepressants used to treat depression but, how they reduce the symptoms is not fully understood (Andrews et al., 2022).

Research into glia is informing psychiatry in providing understanding of the mechanisms that may underpin disorders. For example, the uptake of glutamate from the synaptic cleft after neural activity and recycling it back to the presynaptic neuron are mainly achieved by a specific astrocyte transporter (Wang et al., 2017). Malfunction of this recycling by astrocytes is associated with glutamate toxicity, neuronal death and, in the pre-frontal area of the frontal lobe, with emotional processing disorders and depression (Wang et al., 2017).

Glia cells will also be in the spotlight with research into neurodegenerative diseases such as Alzheimer's disease in which astrocytes play a role in the control and maintenance of neurons while microglia are implicated in the buildup of β amyloid plaques and tau tangles in neurons (Siracusa et al., 2019). Additionally, research into the myelination diseases such as Parkinson's disease, Huntington's disease, and Multiple Sclerosis (MS) in the CNS can be expected to implicate glial cells (Seeker & Williams, 2022).

Types of glia

Glia may initially be segregated into two general categories, macroglia and microglia according to their relative physical size and origin (Sun, 2018). However, this simple discrimination is too broad to adequately describe glia as we now know them. A more recent differentiation that includes gliogenesis may be more appropriate. In this description of gliogenesis the first group of macroglia to be identified as future astrocytes and oligodendrocytes arise from neural

tube stem cells, or spongioblasts, emerging from the ectoderm (Raine, 1999). A second group to emerge of mesodermal origin are identified as the microglia (Raine, 1999). Finally, a third sub-group, the ependymal cells, of similar ectodermal origin as the first group, are identified (Raine, 1999). The ependymal cells are further reduced into other smaller groups of specialised discrete cell types, most of which are included in Table 1.

Macroglia, the larger glial cells, play a regulatory and supportive role and are found throughout the CNS and PNS as well as the enteric nervous system (ENS) in the gut. Macroglia include radial glia, oligodendrocytes, Schwann cells (SCs), astrocytes, ependymal cells, satellite cells, and enteric glia (Sun, 2018). Macroglia are responsible for separating neurons to maintain insulation and the integrity of synapses, the regulation of extracellular potassium (K) to maintain efficient neural signalling, enhancement of the uptake of surplus neurotransmitters and glutamate from synapses, as well as nourishing nearby neurons by the release of various growth factors (Kandel, et al., 2013). Astrocytes are known to modulate neural synaptic activity by processing and releasing gliotransmitters such as glutamate, serine, and adenine triphosphate (ATP) (Araque & Navarrete, 2010).

Finally, not all neurons, or parts of neurons survive, with a number programmed to die as part of normal neurodevelopmental stages, while others may die from injury or disease. It is essential that all dead cells must be removed along with any debris if the neural environment is to be maintained in a healthy state (Konishi et al., 2022). Neurons that die are said to be apoptotic cells and the act of removal by recycling is known as phagocytosis and is carried out by phagocytes (Konishi et al., 2022). Phagocyte is a term that has been commonly associated with microglia, about to be mentioned; however, astrocytes are also capable of phagocytosis, and along with advances in glial research, this activity is also being attributed to astrocytes (Konishi et al., 2022).

TABLE 1: List of glial cell types, system location and higher levels of functioning.

Cell name	System	Function
Macroglia		
Radial glia	-	Developmental support structure at neurogenesis
Astrocytes	CNS	Communication – interneuron, interglial – neuron to blood Associated with formation of blood/brain barrier
Oligodendrocyte	CNS	Myelination
Ependymal cells	CNS	Line ventricles/spinal cord, retain spinal fluid
Tanycytes	CNS	Homeostasis of CSF
Bergmann cells	CNS	Interconnecting cells in cerebellum
Schwann cells	PNS	Myelination and repair of PNS neurons.
Satellite cells	PNS	Communication
Enteric glial cells	PNS	Support and communication of enteric neural network
Microglia		
Macrophages	CNS	Phagocytosis
Amoeboid	CNS	Inflammation
Ramified	CNS	Communication

Nervous system abbreviations: CNS, central nervous system; PNS, peripheral nervous system; ENS, enteric nervous system; CSF, cerebrospinal fluid.

Amoeboid and ramified are functional body states of microglia.

Microglia, the smaller glial cells, are mostly found in the CNS; however, there is evidence of them temporarily migrating into the PNS to carry out their roles (Sun, 2018). The role of microglia is to maintain the neural environment by moderating inflammation and the immune system responses and, in coordination with macroglia, influencing the neurotransmitter responses of neurons (Konishi et al., 2022). Microglia promote healthy neural functioning by the removal of neural debris and unused synapses by ingestion, phagocytosis, when in their amoeboid state (Konishi, 2022).

Glial cells are ubiquitous and variable in their morphology and functionality dependent on their spatial and temporal location at any time of development. In describing glial cells this paper will begin with macroglia, microglia and then some of the prominent specialised glial cells. Table 1 lists the main glial cells, their location and some of their functions.

Macroglia

Macroglia originate from the stem cells, neuroblasts and glioblasts, precursors of neurons and glial cells respectively, that emerge from the ectodermal material forming the neural crest by about 21 days post-conception (Johnson & De Hann, 2015; Raine, 1999; Vanderah & Gould, 2016). Most of the cells that form the human brain emanate within the so-called proliferation zones of the neural tube bulges in the vicinity of what is to become the future fluid-filled ventricles (Johnson & deHann, 2015). During the first few weeks after conception, the cells of the developing brain are born, they migrate and then they differentiate into the many specialised cells that form the human brain (Johnson & De Hann, 2015; Raine, 1999; Vanderah & Gould, 2016).

Radial glial cells

During very early embryonic development, radial glial cells, as well as being the primary neural cells are also multipotent, capable of developing not only into neurons, but also glia cells such as astrocytes, microglia cells, ependymal cells, and oligodendrocytes (Jessen, & Mirsky, 2019; Taverna et al., 2014). Radial glial cells are the earliest morphologically distinct cell type to emerge from the progenitor cells secreted from the neural plate in the developing embryo (Jessell & Sanes, 2013). Radial glial cells are the beginning of the process of neural cellular population and specialisation of the neural architecture of the telencephalon. Radial glial cells emerge from the epithelium adjacent to the future ventricular zone in the developing brainstem (Jessell & Sanes, 2013). Radial glial cells are distinctly different from all other cells morphologically, biochemically, and functionally (Rakic, 2003; Vanderah & Gould, 2016). An elongated fibrous structure projects to the cerebral extremity from the radial glial cell body, or soma, providing structural support and guidance for the pioneer neurons as they begin to populate the lamina structure of the cerebral cortex (Rakic, 2003). There was considerable controversy over what became of the radial glial cells after the structure of the brain was accomplished. Most theories centred around the fate of the

cell created by mytosis with one 'daughter cell' becoming a neuron within the new bundle and the other cell remaining in the proliferation zone as a progenitor radial glial cell for the next molecular cycle (Rakic, 2003). However, more recent research using modern histological staining techniques and genetic markers such as GFAP identification and electron microscopes indicated that the radial glial cell transformed into a form of astrocyte correlating with the disappearance of radial glia early in the foetal development (Jessell & Sanes, 2013; Rakic, 2003). How the progenitor cells in the ventral epithelium decide to propagate as radial glial cells, neurons, or astrocytes is mediated by an evolutionary conserved cell-surface protein signalling system called Notch Signalling that uses a trans-membrane ligand and receptor to influence the genetic transcription (Jessell & Sanes, 2013).

Astrocytes

Astrocytes were named for the stellar, or star shape, noted by early investigators looking at protoplasmic astrocytes (Pereira & Furlan, 2010).

Wang et al. (2017) described astrocytes as influencing almost every function and activity of the human brain, including both the maintenance of other neuronal cells and the functionality of neuronal processes. A single astrocyte has been reported as influencing up to 100 000 synapses (Tabata, 2015). It is estimated that an individual astrocyte can be in communication, directly or indirectly, with around 2 million other cells at any time, making them major players in normal and pathological mental health conditions (Wang et al., 2017).

With the advent of modern histological microscopy and immunofluorescence markers, such as GFAP for white matter fibrous and reactive astrocytes, and S100ß, a marker protein to visualise grey matter protoplasmic astrocytes, many morphologically different forms of astrocyte have now been recognised and described (Clavreul et al., 2023). Additionally, new techniques such as multicolour cytoplasm staining that allows simultaneous tracking of newly cloned or proliferating astrocytes combined with our greater knowledge of the transcription factors affecting the expression of RNA have greatly added to our knowledge of astrogenesis and morphology (Clavreul et al., 2023).

Morphology

Astrocytes initially differentiate in early embryotic life from neural progenitor cells emerging from the ventricular zone of the newly formed neural tube under the influence of cell-surface signalling (described in radial glial cells), followed by rapid proliferation because of cell division (Schwartz et al., 2013). Neural progenitor cells from the ventricular area may produce neurons, radial glial or astrocytes depending on the influence of genetic transcription factors (Schwartz et al., 2013).

In the frontal cortex, these cells can be morphologically distinguished into four types, namely fibrous astroglia, protoplasmic, varicose, and interlaminar projections and all can be found in the white matter cortical tracts and the cerebral cortex neural columns (Vasile et al., 2017).

However, two broader classifications are often used describing astrocytes: fibrous and protoplasmic astrocytes (Kandel et al., 2013). Protoplasmic astrocytes have many branches with endfeet and are the astrocytes that create the blood-brain barrier (BBB) (Tabata, 2015).

Contrastingly, fibrous astrocytes have long, straight processes that are specialised to suit their function and location within the neural bundles (Tabata, 2015). Fibrous astrocytes express much more GFAP than protoplasmic astrocytes that only code this protein on their endfeet when they are in contact with blood vessels (Tabata, 2015). Fibrous astrocytes are more populous than protoplasmic astrocytes in white matter, and protoplasmic astrocytes are more populous than fibrous astrocytes in grey matter (Clavreul et al., 2023). Furthermore, both types of astrocytes have cells with similar functions and morphology such as associating with blood vessels or having multiple branches, thus the white matter/grey matter differentiation is a very general categorisation at best.

Function

Astrocytes are associated with many important roles in the human nervous system such as neural development, functionality, and neurotransmission. Astrocytes are associated with the formation of the BBB (Castañeyra-Ruiz et al., 2022). In addition to connecting to other astrocytes, they facilitate many intercellular communications (Wang et al., 2017). For example, they interconnect neurons and endothelial cells (Castañeyra-Ruiz et al., 2022), and neurons to blood vessels (Wang et al., 2017).

By monitoring neural activity, they are able to be involved in the maintenance of neural homeostasis by assisting in the modification of blood flow in response to neural activity (Tabata 2015), the control of water, amino acids, and neurotransmitter intake by neurons (Castañeyra-Ruiz et al. 2022), and the clearance of glutamate from synapses (Tabata 2015). Astrocytes are also highly permeable to K^+ and are therefore able to modulate exoplasmic K^+ expelled by activated neurons (Schwartz et al., 2013).

Additionally, astrocytes form the outer layer of the cortex membrane adjacent to the pial surface creating the cellular limitation of the brain (Tabata, 2015).

Astrocytes, like neurons, can metabolise and express fibroblast growth factor 2 (FGF2), brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF) (Kajitani et al., 2012). In animal studies, the release of these cytokines has been seen to be positively associated with anti-depressant agents (Kajitani et al., 2012).

Reactive astrocytes

Some fibrous astrocytes respond to neural insults, and when activated in, increase the secretion of the signalling protein Tenascin-C, (TN-C), thereby regulating inflammatory cytokines and mediating neural survival (Gotoh et al., 2023). This type of fibrous astrocyte is referred to as a reactive astrocyte.

Reactive astrocytes can be further classed into two general categories: neurotoxic (A1), activated by neuroinflammation-induced injury and neuroprotective (A2), activated by ischaemia-induced injury. The phenotype of the reacting astrocyte will be dependent on the nature of the injury it is responding to (Goto et al., 2023).

Type A1 astrocytes can also respond to signalling from microglia activated by the injury (to be discussed later) to secrete interleukin-1 (IL-1), or tumour necrosis factor (TNF) (Gotoh et al., 2023). This response after traumatic injury, neurodegenerative disease or infection is known by several names including *astrocyte reactivation*, *reactive gliosis*, and *astrocyte reaction* (Gotoh et al., 2023).

Astrocytes and glucose

Glucose is the cellular fuel source for most human cells and is stored in the form of glycogen, a substance that can easily be metabolised. Most glycogen is stored in the astrocyte's cytoplasm (Falkowska et al., 2015). Glucose enters protoplasmic astrocytes from blood vessels through a GLUT1 cross membrane transporter protein expressed in their endfeet that they wrap around nearby blood vessels (Falkowska et al., 2015). These astrocytes may have many branches with endfeet forming non-overlapping, tight junctions as they envelop blood vessels helping create the BBB (Tabata, 2015).

The greatest demand for glycogen comes from the big muscles and organs of the PNS and accordingly, the greatest reserves are found in the astrocytes serving the liver and muscles (Brown et al., 2012). The CNS is also served by cytoplasmic glycogen in astrocytes but additionally has a strategic reserve in the form of lactate that has been produced and released into the extracellular plasma by astrocytes to provide 'energy substrate buffering' that can be called upon by cells in times of abnormally high neural activity (Brown et al., 2012).

Communication

Astrocytes communicate indirectly by releasing 'waves' of calcium ions that stimulate gliotransmitter compounds to be released by other affected glial cells (Wang et al., 2017). Astrocytes express many types of G protein coupled receptors (GPCRs) that respond to neurotransmitters and neuromodulators that are released during neural activity (Kofuji & Araque, 2021). Astrocytes respond by elevating calcium (Ca^{+2}) levels which are seen as waves through connexons to adjoining cells that stimulate gliotransmitter compounds to be released by other affected glial cells (Wang et al., 2017).

Connexons

Astrocytes can communicate with other cells directly using a form of chemical synapse known as a gap junction (Bear et al., 2016). Gap junctions or connexons (Cx) are formed by hemichannels, one in each adjoining cell membrane, that will align to cojoin the cytoplasm of two adjoining cells providing inter-cytoplasmic communication (Philips & Rothstein, 2017; Wang et al., 2017). A connexon channel is formed from an expressed membrane protein that creates an interconnecting channel. Each connexon consists of six sub-units known as *connexins* that, as a molecular unit, form one half of an interconnecting channel between adjoining astrocytes (Jeanson et al., 2015). Connexon-mediated communication also applies to most other types of glia and some neurons (Philips & Rothstein, 2017). There are 21 identified Cx in humans and their numerical identification refers to their molecular weight (Ayad et al., 2006).

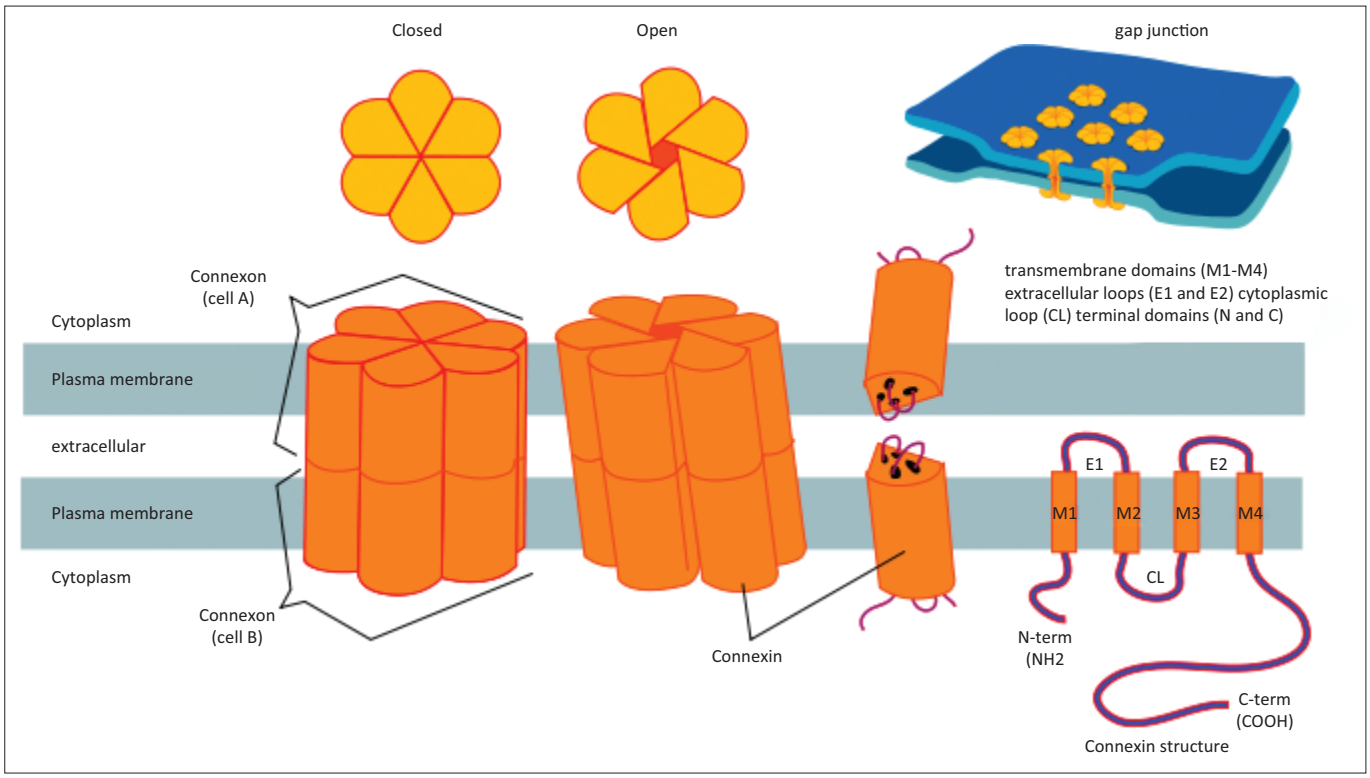
Connexons, and therefore astrocytes, have frequently been associated with neurodegenerative diseases and have recently become the focus of research into depressive disorders (Ayad et al., 2006). Post-mortem investigations note a reduction of Cx in the pre-frontal cortex, hippocampus, and locus coeruleus of suicide completers suffering from depression (Jeanson et al., 2015; Wang et al., 2017). Two types of Cx are expressed by astrocytes: Cx_{43} and Cx_{30}; however, Cx_{43} is the one most discussed in reports (Jeanson et al., 2015).

Connexons can be either homomeric and convey a single message or more commonly, be heteromeric to carry two separate messages (Ayad et al., 2006). Connexons are associated with the release of gliotransmitters such as glutamate and ATP, both sources of cellular energy; however, they are not permanent fixtures lasting only a few hours before being absorbed (Jeanson et al., 2015). Genetic signalling with messaging RNA (mRNA), a genetic communication molecule, is associated with Cxs and can be expected to be influenced by epigenetic changes brought about by environmental factors including the genetic response to antidepressant drugs (Wang et al., 2017). Figure 2 provides a simplified schematic representation of a connexin.

Oligodendrocytes

Oligodendrocytes, or collectively oligodendroglia, are the glial cells that provide myelin to neurons of the CNS. Discovery of these cells has been accredited to Robertson in 1899 (Jakovcevski et al., 2009). An early depiction of oligodendrocytes was published by Del Rio Hortega in 1921 who accurately described them after he had developed a technique to visualise glial cells (Seeker & Williams, 2022). Noting the sparsity of processes compared to other glia, he named them oligodendrocyte, a word derived from the Greek 'oligos meaning few' and 'dendron meaning tree or branches' (Seeker & Williams, 2022).

In 1928, Hortega classified oligodendrocytes according to their location: *interfascicular*, along neuronal tracts, *perineuronal*, beside neurons, or *perivascular*, associated with blood vessels



Source: Mariana Ruiz. From Wikimedia Commons, the free media repository. Retrieved from https://en.wikipedia.org/wiki/Connexin#/media/File:Connexon_and_connexin_structure.svg

FIGURE 2: Schematic representation of an astrocytic connexon protein.

(Seeker & Williams, 2022). He then further differentiated them according to their shape: Type 1, small, rounded bodies with fine processes reaching to thinly myelinated neurons, Type 2, triangular cell bodies with fewer, thicker processes, Type 3, large, rounded bodies with four processes reaching to axons, and Type 4, having elongated bodies and only two processes (Seeker & Williams, 2022). This system of classification has now been largely superseded by biological and molecular markers as descriptors; however, it serves to highlight the heterogeneity or diversity, inherent in oligodendrocytes.

Oligodendrocytes are diverse and vary considerably in morphology and function depending on their anatomical zone of development, stage of developmental differentiation, genetic transcriptome, age, sex as well as being influenced by some biological diseases (Seeker & Williams, 2022).

Oligodendrocytes and oligodendrocyte precursor cells (OPCs), refer Figure 1, are distributed within both white and grey matter throughout the CNS with greater density to be found in the areas of myelinated axons of the white matter tracts (Sherafat et al., 2021). Mature oligodendrocytes form extensions on their endfeet that wrap tightly around neurons creating the myelin insulation that enhances the propagation of action potentials (Crawford et al., 2016). Intuitively, the density of OPCs and oligodendrocytes is greater in the areas of highest myelination such as the axonal tracts of the corpus callosum and the cerebellum; however, as many OPCs remain in the immature state and take on supportive roles in neuronal activity, the number of OPCs exceed the number of oligodendrocytes (Sherafat et al., 2021).

However, since 2013, many new techniques in neurological exploration have greatly expanded our knowledge of the development, properties, and behaviour at a cellular level. Although human foetuses lack effective myelinated white matter at birth, stem cell RNA examination has shown that human foetal oligodendroglia express Epidermal Growth Factor Receptor (EGFR) from about 20 gestational weeks (Seeker & Williams, 2022). The EGFR is thought to play a part in oligodendrogenesis as well as being present in remyelination after injury (Seeker & Williams, 2022).

Origins and development

Oligodendrocytes are created initially under the influence of the gene Sonic Hedgehog (Shh) along the ventral region of the neural tube, and then migrate dorsally (Jakovcevski et al., 2009). Studies in mice indicate that OPCs appear as waves, each wave superseding and adding to the previous wave, until eventually populating and myelinating the CNS (Seeker & Williams, 2022).

Cerebellar oligodendrocytes are derived from OPCs that have developed extra-cerebellar and have migrated from the early rhombencephalon into the developing cerebellum (Seeker & Williams, 2022).

When attempting to translate time-points in oligodendrocyte development from mice to humans, Jakovcevski et al. (2009) found that because of the larger size and longer development period of the human brain compared to the mouse brain, the relationship was not linear with substantial variation between specific neural areas. However, from this research,

they could report OPCs emerging in the human forebrain at 10 weeks of gestation and the first premyelinating oligodendrocytes detected expressing myelin basic protein (MBP) at 18 weeks of gestation (Jakovcevski et al., 2009).

Stages of development and differentiation

Stages of development in this context means the transformation of oligodendrocytes along a developmental continuum from newly emerging OPCs to immature cells and then to mature oligodendrocytes. Several immunohistochemistry protein molecular markers are used to identify the oligodendrocyte's stage of development (Seeker & Williams, 2022). Although these techniques are generally confined to the laboratory and *in vitro* studies, they have proved useful in researching neurodevelopmental disorders such as MS.

Genetic heterogeneity

Modern technology has allowed the study of diversity between glia cells at their origin. Examining the transcript sequencing of single cell RNA reveals the existence of a number of oligodendrocyte phenotypes with multiple genetic bases (Seeker & Williams, 2022). The diversity that is reported as being attributable to genetic factors is discussed below.

Heterogeneity related to sex

Recent research, especially with mice, is revealing differences in the myelination/remyelination properties of oligodendrocytes associated with the person's biological sex (Seeker & Williams, 2022). This difference could be mediated by differences in chromosomal contents or maybe responses to male or female steroidal sex hormones (Seeker & Williams, 2022). Although most of this research is *in vitro*, the effects of oestrogen on the promotion of neural stem cells and OPC proliferation has been noted in human suffering from MS, a disorder highly correlated to myelination (Seeker & Williams, 2022). Furthermore, although females are more susceptible to MS than males, females have a greater response to remyelination of MS lesions resulting in poorer outcomes for male sufferers suggestive of genetic based differences (Seeker & Williams, 2022).

Heterogeneity related to age

OPCs emerge at around 10 weeks post-conception with myelination beginning at 30 weeks, but most myelination occurs after birth (Seeker & Williams, 2022). Myelination progresses in a generally rostral to caudal manner with the cerebellum and spinal cord leading myelination followed by the cerebral cortex and finally the pre-frontal cortex reflective of skill learning in response to experiences after puberty (Seeker & Williams, 2022). With ageing, remyelination abilities reduce in a reverse order to development with reducing plasticity associated with age-related cognitive decline and reflective of changing oligodendrocyte properties (Seeker & Williams, 2022).

Changes because of biological diseases

Differences have been found in oligodendrocytes in human samples, often post-mortem, effected by diseases such as MS, Alzheimer's disease, Huntington's disease, and other neuropsychiatric disorders known to be associated with myelination deficits (Seeker & Williams, 2022). The study of these differences is ongoing at present but genes such as Oligodendrocyte Myelin Paranodal and Inner Loop Protein Tmem10 (OPALIN), that express a cross-membrane protein associated with oligodendrocyte states are reported as reliable markers of oligodendrocyte differentiation (Kippert et al., 2008). The finding of genetic markers for oligodendrocyte development has created considerable interest in researching glia's role in human neurological disorders (Seeker & Williams, 2022).

Ependymal cells

Ependymal cells are a type of glia that form an epithelial barrier, the ependyma, that lines the brain's ventricles and the central canal of the spinal cord (MacDonald et al., 2021). These ciliated cells develop from radial glial cells, beginning at conception with the initial differentiation of pioneer cells and are functionally providing an interactional barrier between the newly secreted cerebrospinal fluid (CSF) and the interstitial fluid of the brain after 14 days of embryonic development (MacDonald et al., 2021). The exact mechanism of differentiation from radial glia to ependymal cells is not known, but without transcription factor Foxj1 radial glia does not differentiate into ependymal cells (Shiyu et al., 2023). Ependymal cells perform many functions including sensing and propelling CSF with their cilia, providing molecular homeostasis, and facilitating the two-way movement of immune cells and solutes into and out of the CSF (MacDonald et al., 2021).

The heterogeneity of ependymal cells has been a point of study for many years with crossovers to other cell types such as tanycytes, described later, mixing into the various labelling systems. In one system of labelling, they have been classified into three types of ependymal cells dependent on their cilia density, function, and individual cellular position (Shiyu et al., 2023). E1 is described as being multi-ciliated and the most numerous subtypes in the adult human brain occupying the greatest area of lining in the lateral ventricles, and to a lesser extent the lining of the third and fourth ventricles (Shiyu et al., 2023). Meanwhile, E2 cells also described as ciliated ependymal cells but having less cilia, while found in all ventricles, are mostly associated with the spinal cord CSF lining (MacDonald et al., 2021). Finally, E3 have very few, if any, motile cilia and can be found populating the preoptic and infundibular recesses of the third ventricle (Shiyu et al., 2023).

Tanycytes

This group of glial cells were described by Ramón y Cajal in 1909 and many other scientists, but were not named until Ernst Horstmann in 1954 coined the name tanycyte from the Greek word 'tanus' meaning stretched (Prevot et al., 2018). Type E3 ependymal cells are often referred to as tanycytes because of the elongated cilia found on some that monitor CSF. The use of Golgi staining techniques allowed the cells in

the third ventricle and their extensions to be visualised connecting the infundibular region of the hypothalamus with the ventral surface of the third ventricle indicative of a role in metabolic hypothalamic functions and the release of neuropeptides responsible for CSF secretion (Prevot et al., 2018).

Tanycytes were originally classified into four subtypes, namely α1, α2, β1, and β2, based on their dorsoventral position along the third ventricle and their process extension; but with greater understanding of their functions, this is considered no longer appropriate (Prevot et al., 2018). The reason for this appears to be the crossover in definitions especially between ependymal cells and tanycytes. Shiyu et al. (2023) often refer to E2 and E3 ependymal cells as tanycytes because of their extended cilia and function.

Bergman cells

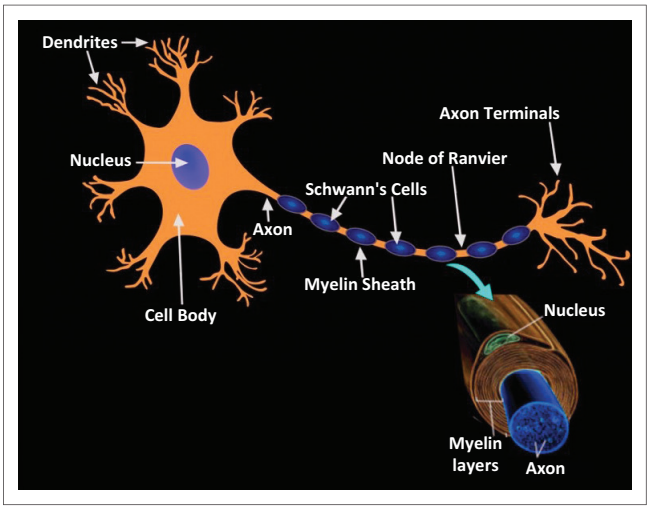
Another functionally and morphologically distinct type of glial cell is the Bergmann glia cell (BC), unique to the cerebellum, each with up to five parasagittally aligned radial processes that control the synapsis of Purkinje cells (De Zeeuw & Hoogland, 2015). Bergman cells are also sometimes known as Golgi epithelial cells and considered a class of astrocyte (Rhyu, 2019). These cells are the most numerous cells in the cerebellum, interconnecting and modulating synaptic contact between Purkinje cells and intercepting neurons such as climbing fibres and granule cell parallel axons (De Zeeuw & Hoogland, 2015). Bergmann glia cells provide early developmental control for migratory granular cells populating the developing cerebellum, extracellular homeostasis of calcium and levels of interstitial ions (De Zeeuw & Hoogland, 2015). Research into the role, function and morphology of BCs is ongoing, especially into their role in information processing, glutamate regulation, and intercellular 'K' levels (De Zeeuw & Hoogland, 2015).

Schwann cells

Schwann cells, named after German physiologist Theodor Schwann, are to the PNS what oligodendrocytes are to the CNS. However, unlike oligodendrocytes that myelinate multiple axon segments in a nerve bundle, a single SC only myelinates one segment of axon as delineated by the nodes of Ranvier. For a visual representation, refer to Figure 3.

Immature or mature SCs can differentiate in response to intercellular signalling to remove cell damage like microglial, and release growth factors to encourage restorative growth to damaged neurons like astrocytes, as well as providing myelination to axons in the PNS (Bolívar et al., 2020).

Schwann cells differentiate from progenitor cells released from the neural crest of the embryonic neural tube and comigrate with the expanding neuronal network as proliferative Schwann Cell Precursor (SCP) cells throughout the developing PNS (Monk et al., 2015). Although the complete molecular mechanism of differentiation is unknown, a



Source: Image courtesy Dr Chaigasame, from Histology. Schwann Cells, 2024, StatPearls Publishing. Retrieved from https://creativecommons.org/licenses/by-nc-nd/4.0/

FIGURE 3: Schematic representation of a Schwann cell myelinating the nodes of a neuron, and expanded section showing wrappings of the cell and location of the cell nucleus.

transcription factor Sox10 is expressed in neural crest cells and is consistently associated with PNS glia (Monk et al., 2015). Over time, SCPs cease migrating and develop into immature SCs, although the molecular mechanism is not fully understood. Monk et al. (2015) considered it to most likely be a response to Notch Signalling. Schwann Cell Precursors can differentiate into myelinating SCs or into a sub-type of non-myelinating SC, known as a Remak cells during the early post-natal period (Jessen & Mirsky, 2019). While SCs can enwrap and myelinate a single axonal segment, a Remak cell can ensheathe several small axons without myelinating them (Monk et al., 2015). In the adult PNS, Remak cells can also act to repair myelination to optimise axon recovery (Jessen & Mirsky, 2019).

The early development trajectory of SCPs to SCs is highly dynamic with the intermediate immature SCs segregating the neurons to be myelinated from the unmyelinated neurons in a process called radial sorting (Monk et al., 2015). The unmyelinated neurons will remain in Remak bundles that are ensheathed only (Monk et al., 2015). This process begins with SCP migration from the neural crest in early pregnancy and continues into the early post-natal period with neurons to be myelinated forming a 1:1 relationship between the immature SCs and the neuronal segments to be myelinated (Monk et al., 2015).

In the adult PNS, a SC and a Remak cell, although different in structure, molecular expression, and function are potentially interchangeable and the phenotype of the cell will be totally reliant on signals from the axons that they are associated with (Jessen & Mirsky, 2019). Furthermore, both types can alter their form to become repair cells capable of removing damaged myelin, upregulating their expression of trophic factors and surface molecules, promote axonal regeneration and then revert to their original phenotype (Jessen & Mirsky, 2019).

Similarly to the role of astrocytes in the CNS, the SCs store glycogen for reserve metabolic fuel in the PNS. However, their storage capacity is estimated as being up to six times greater because of the larger trunk musculature served by the PNS (Brown et al., 2012).

Satellite cells

Satellite glial cells (SGC) are the support and repair cells of the PNS. They are found on sensory neurons of the sympathetic and dorsal root ganglia surrounding the neuronal soma or cell body, separated by connective tissue, with each soma and SGC assembly forming a unique unit (Mapps et al., 2022). They originate from the same multipotent neural crest cells as Schwann cells and, in similar manner, migrate throughout the PNS (Jessen & Mirsky, 2019).

While a great amount of research has focussed on the repair function of Schwann cells after neural injury, much less has been expended on the restorative role of SGCs (Avraham et al., 2020). Newer research using animals has found that the number of SGC surrounding the soma of sensory neurons increases as the size of the soma increases reaching the final number in adulthood (Avraham et al., 2020). In similarity to astrocytes, SGCs convert glutamate to ATP, have calcium controlled cross-membrane channels, express GFAP, and communicate inter-cytoplasmically through connexons (Avraham et al., 2020). Of particular interest to researchers is their role in the modulation of pain thresholds as manifested by their morphological changes in response to inflammation, neuropathic pain, and neural injury (Avraham et al., 2020). In their research, Avraham et al. (2020), using mice, found that following neural lesion injury, the SGCs upregulated metabolism of ATP, interconnectivity by connexons, and expression of regenerative genetic materials, all of which are thought to enhance neural regeneration.

Enteric glial cells

Enteric glial cells (EGC) have been known about since the end of the 19th century but, until recently, were considered to play a secondary support role only (Yu & Li, 2014). The importance of EGCs is evidenced by the significant disruptions of the enteric neuro-network that have been evident in patients with Crohn's disease, a very serious gut disorder that can have life-threatening consequences (Yu & Li, 2014). Enteric glial cells are part of the PNS and arise from multipotent neural crest cells similar to Schwann cells with which they were once confused (Boesmans et al., 2022). Recent research is changing this perception pointing out that EGCs are not only more numerous by a considerable factor than enteric neurons but constitute the major component of the ENS (Yu & Li, 2014). They are similar to other glial cells previously described having filaments rich in GFAP, express calcium binding membrane proteins, and communicate with other EGCs and epithelial cells by gap junctions or Cx (Yu & Li, 2014). Enteric glial cells can ensheathe enteric neurons cell bodies in similar fashion to satellite cells, with their processes forming a communication network between the gut lining, blood vessels, and other adjoining enteric neurons (Yu & Li, 2014).

There are many types of EGCs. Boesmans et al. (2022) advise that the current classification devised in 1994 links four EGCs morphologies to gut-wall locations. These classifications are based on the guinea pig and have been applied successfully to murine research; however, although some of the glia classifications have been identified in humans, the classification system of EGCs is the subject of ongoing research (Boesmans et al., 2022).

Researchers have devised classification systems for the various morphologies seen in EGCs; however Boesmans et al. have suggested caution as most of the study are of murine species and may not prove accurate when applied to humans. Enteric glial cells are located at many levels and regions of the gut; therefore, they will be subjected to many differing environments and can be expected to be morphologically heterogeneous to meet the tasks applicable to each location (Boesmans et al., 2022).

Microglia

Microglia colonise the brain and spinal cord from the earliest stages of development and are capable of cell division and transformation (Pinel & Edwards, 2008). There are two theories regarding the origin of microglia: the mesodermal hypotheses and the theory of monocytic origin (Cho & Choi, 2017). The mesodermal theory suggests that microglia form in the embryonic yolk-sac and migrate with the expanding mesoderm, while the theory of monocytic origin believes that amoeboid microglia originated from the transformation of monocytes in the surrounding bloodstream (Cho & Choi, 2017).

Microglia are heterogeneous in nature and the state of the cell at any time is depicted by their shape. Microglia, when constantly at rest (acquiescent), are said to be in a ramified state and constantly monitoring their environment by the interaction of glial-transmitter compounds from their extended processes or ramifications, and their adjacent neuron cells through synaptic connectors (Cho & Choi, 2017). In the event of neural injury, microglia morph from the *at rest* ramification phenotype into an amoeboid configuration where the ramifications become less pronounced, and the cell takes on a more rounded shape, similar to an amoeba in shape and function, allowing for efficient phagocytosis (Cho & Choi, 2017).

In a *healthy* situation, they function as macrophages with the ability to carry out routine phagocytosis to provide protection to neurons of the CNS (Pinel & Edwards, 2008). They do this by clearing the debris from synaptic activity and decaying neural connections (Lee et al., 2015). In an *unhealthy* situation, such as after injury, resident microglia stimulated by neural cell death contribute to inflammation of the injury site by producing proinflammatory cytokines, reactive oxygen species (ROS), nitric oxide to facilitate blood vessel dilation, and proteases or peptides, all part of the intrinsic healing processes (Lee et al., 2015). This inflammation of tissue also

results in oligodendrocyte death (de-myelination) as well as neural death (Lee et al., 2015).

In the amoeboid state, microglia are implicated in both pro- and anti-inflammation of an injured site by their influence on immune cells depending on the cytokines (signalling compounds) they are induced to release (Cho & Choi, 2017). Increased microglial activity also results in greater neuronal phagocytosis; however, in the event of ischaemic (blood flow) related injury, morphology is restricted, and phagocytosis is reduced (Cho & Choi, 2017). This has an influence on many neurodegenerative pathological conditions.

Microglia in a steady-state, represented by the ramification phenotype, secrete several neurotrophic factors that include insulin-like growth factor 1 (IGF1), brain-derived neurotrophic growth factor (BDNF), and nerve growth factor (NGF) (Cho & Choi, 2017). This process is relevant to any discussion regarding the effects of prescription drugs on glial cells. Cho and Choi (2017) reported that, in animal studies, amoeboid macrophages are highly active in the early post-natal time, and then, as the novelty of the new environment reduces, convert back to the ramification state when the degree of phagocytosis diminishes, and the CNS activity enters a stage of relative quiescence. Microglia play an instrumental role in most pathological disorders and are, therefore, influenced by most anti-psychotic drugs in some way (Nicolai et al., 2017). Ramified microglia activate by two separate processes. Firstly, microglia have pattern recognition receptors (PRR) that allow them to interpret pathogen-related molecular patterns (PAMPs) as distinct from damage-associated molecular patterns (DAMPs). Secondly, they act in similar fashion to an immune system by recognising and reacting to neurodegenerative, disease-specific, protein aggregates such as α-synuclein and amyloid β (Cho & Choi, 2017). Degenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) are associated with microglial deficiency (Cho & Choi, 2017).

Microglia tend to work in concert with other microglia. For instance, sensing microglia can influence other microglia to release cytokines and chemokines that act upon other associated microglia causing the release of cascades of compounds such as microglial-derived tumour necrosis factor (TNF-α), a substance that mediates neuronal death, and interleukin 1 beta (IL-1β), a cytokine that mediates inflammation (Cho & Choi, 2017). Conversely, microglia may also release transforming growth factor beta 1 (TGF-β), which is an anti-inflammatory cytokine that has an important influence on the human immune system, specifically in respect to T and B cells (Cho & Choi, 2017). Additionally, Wang et al. (2017) went on to explain that microglia play an active role in neuropathology in certain conditions by influencing both inappropriate morphological activity and by underscoring the neural senescence often implicated in mood disorders.

Findings

Modern research technologies and techniques have promoted glia cells. Once just the glue that held neurons in place, it is now the essential 'other half' that together with neurons make up the brain in a relationship of co-dependency. Neurons could not function effectively in the hostile environment that would surround them without the moderating activities and properties of glia. Glial cells provide much more than structural support and neural boundaries within the architecture of the brain as once believed. Neurons relied on glia cells to maintain the extracellular environment necessary for efficient neural activity as well as providing paths of intercellular-communication. Neurons relied on the speed of transmission afforded by myelin to respond appropriately, and this is evident in myelin related neural disorders such as multiple sclerosis. Furthermore, glial cells are implicated in an ever-increasing number of medical and mental disorders as well as providing targets for future treatments especially in pharmacology. Finally, it is only with gratitude and wonder that we can read of the achievements of the early scientists who not only pioneered our knowledge of glial cells, but also invented the means of studying them, some of which are still in use today.

Implications and recommendations

Although research and investigation has provided an in-depth knowledge of glia, neurons are often the only player considered when contemplating the human nervous system. The ever-increasing importance of glial cells suggests that learning institutes' programmes of teaching should contain an increasing emphasis on the understanding of glia. Further research should be directed to understanding the effects of pharmaceutical and other drugs on glia, not only neurons and neurotransmitters. While this review cannot cover every aspect of these versatile neural cells, it is hoped it may spark the curiosity of readers to become better informed about this important player in the system that makes us who we are.

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Data availability

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