

# A diversity of cell types, subtypes and phenotypes in the central nervous system:....

[Health & Medicine](#)



**ASSIGN  
BUSTER**

All the cell types in the central nervous system (CNS) cooperate to mediate proper development, function, and plasticity. Similarly, brain repair and neuroprotection, but also demyelination, synaptic loss and neurodegeneration, were increasingly shown to involve non-neuronal cells—both glial cells and peripheral immune cells—among the CNS parenchyma. Adding another degree of complexity, the non-neuronal cell populations are emerging as comprised of different subtypes, endowed with unique properties and functions at steady-state, and which can adopt various phenotypes upon exposure to homeostatic challenges. As a consequence, studying the multidirectional relationships between these different cell types, subtypes and phenotypes in the CNS is now required to provide insights into the mechanisms underlying physiological processes such as neuronogenesis, axon guidance, myelination, vascular formation and remodeling, regulation of neuronal activity, as well as synaptic formation, function and plasticity, and behavioral outputs, among other essential CNS functions.

## **A Diversity of Cell Types, Subtypes, and Phenotypes**

In the CNS, the different types of neurons, which are identified by their neurotransmitters, neurotrophic or neuroprotective factors ( [Que et al., 2019](#) ; [Sugino et al., 2019](#) ; [Cizeron et al., 2020](#) ), are accompanied by non-neuronal cells showing similar, or greater levels of heterogeneity. This cellular diversity pertains to glial cells (microglia, astrocytes, cells of the oligodendrocytic lineage) and the peripheral immune cells that can infiltrate the CNS ( [Oberheim et al., 2012](#) ; [Butt and Verkhratsky, 2018](#) ; [Foerster et al., 2019](#) ; [Stratoulas et al., 2019](#) ; [Dumas and Prinz, 2020](#) ). While the microglial field rejected the M1 and M2 categorization ( [Martinez and Gordon, https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/](#)

[2014](#); [Ransohoff, 2016](#)), the A1 and A1 astrocytic dichotomy is increasingly controversial ( [Oberheim et al., 2012](#); [Verkhratsky and Nedergaard, 2018](#); [Khakh and Deneen, 2019](#); [Westergard and Rothstein, 2020](#) ). Cells of the oligodendrocytic lineage are also emerging as a diverse population with different subsets co-existing among the CNS ( [Foerster et al., 2019](#) ).

Similarly, peripheral immune cells comprised of granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes (T cells and B cells) are highly heterogeneous, and accompanied by additional CNS border-associated populations, yet the nature of the cells infiltrating the CNS, and their distinctive properties once in the CNS environment are less understood ( [Theret et al., 2019](#); [Dumas and Prinz, 2020](#) ). Accumulating findings reveal that glial and peripheral immune cells display distinct subsets that vary in their localization, epigenetic signature, protein and gene expression, but also in their morphological and ultrastructural attributes ( [Bisht et al., 2016](#); [Ayata et al., 2018](#); [Silvin and Ginhoux, 2018](#); [Foerster et al., 2019](#); [Khakh and Deneen, 2019](#); [Stratoulis et al., 2019](#); [Burns et al., 2020](#); [Castellani and Schwartz, 2020](#); [St-Pierre et al., 2020](#); [Tan et al., 2020](#); [Westergard and Rothstein, 2020](#) ). Whether the non-neuronal subsets in the CNS indicate the existence of different subtypes, with unique intrinsic properties and specialized functions, or reflect phenotypes that change their properties and functions upon exposure to challenges, or both, remains in most cases elusive. Understanding how the glial and peripheral immune cell heterogeneity determines varied functions in the CNS, at steady-state and upon various challenges, is importantly required to design cellular interventions that specifically target (modulate, stimulate or inhibit)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

microglia, astrocytes, oligodendrocytic lineage cells or peripheral immune cells performing contextually-desirable or undesirable functions.

## **The Challenge of Studying Their Complex Relationships**

Distinguishing between glial and immune cell subtypes and phenotypes in the CNS requires fate mapping tools that allow to follow individual cells over time. Such approaches, which are becoming increasingly available, have been used by pioneering investigations to determine the origin of tissue resident macrophages, including microglia ( [Prinz et al., 2014](#) ; [Perdiguero and Geissmann, 2016](#) ), or the turnover and longevity of microglia within the CNS ( [Askew et al., 2017](#) ; [Füger et al., 2017](#) ; [Tay et al., 2017b](#) ), among other important findings. To complement the fate mapping strategies, *in situ* and *in vivo* approaches should be prioritized to study the biological relevance of glial and immune diversity in the CNS, considering that *in vitro* and *ex vivo* preparations modify non-neuronal cell responses ( [Hellwig et al., 2013](#) ; [Gosselin et al., 2014](#) ). Recent technological advances such as single cell transcriptome analysis have revealed an unprecedented heterogeneity in the non-neuronal cells of the CNS's molecular signatures ( [Krasemann et al., 2017](#) ; [Hammond et al., 2019](#) ; [Kierdorf et al., 2019](#) ; [Deczkowska et al., 2020](#) ). Nevertheless, whether the glial and immune cells in the CNS are multitasking or perform specialized functions still remains largely undetermined. Considering that essential CNS functions emerge from the dynamic interactions between all cell types in the CNS, including learning and memory, judgement, emotional transformation, decision making, as well as behavioral outputs, it would be essential to unravel the complex

relationships between cell types, subtypes, and phenotypes of neuronal and non-neuronal cells in the CNS. The neurons, microglia, astrocytes, and oligodendrocytic lineage cells have been shown to interact with another, structurally and functionally, and they communicate with the peripheral leukocytes infiltrating the CNS or transiting via the perivascular space and other CNS borders ( [Neuroimmune Communication, 2017](#) ; [Tay et al., 2017c](#) ; [Carrier et al., 2020](#) ). Microglia can control astrocytic functions, and vice versa, astrocytes can influence microglia, and the same holds for the reciprocal crosstalks taking place between astrocytes, microglia, and oligodendrocytic lineage cells ( [Béchade et al., 2013](#) ; [Kettenmann et al., 2013](#) ; [Domingues et al., 2016](#) ; [Liddel et al., 2017](#) ; [Matejuk and Ransohoff, 2020](#) ). Within this integrative viewpoint, collaborative research endeavors that bridge complementary expertise with the different non-neuronal cell types, subtypes and phenotypes, are now required to provide maximal insights into the functional relevance of these multidimensional relationships within the CNS.

## **The Individual Circumstances Increasing Variability**

Non-neuronal cell types, subtypes and phenotypes vary between CNS regions, stages of life, sex, specie, and context of health or disease ( [Silvin and Ginhoux, 2018](#) ; [Foerster et al., 2019](#) ; [Khakh and Deneen, 2019](#) ; [Stratoulas et al., 2019](#) ; [Castellani and Schwartz, 2020](#) ; [Tan et al., 2020](#) ; [Westergard and Rothstein, 2020](#) ). Their diversity is modulated by the genetic vulnerabilities, environmental challenges (e. g., stress, infection, pollution), lifestyle factors (e. g., diet, sleep, physical activity, alcohol,

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

cannabis), peripheral comorbidities (e. g., asthma, colitis, arthritis) and other individual circumstances (e. g., exposure to nature, social support), thus tremendously increasing the variability ( [Hanamsagar and Bilbo, 2017](#) ; [Tay et al., 2017a](#) ; [Savage and Tremblay, 2019](#) ; [Madore et al., 2020](#) ). The non-neuronal cells further display differences in their CNS colonization, maturation, gene and protein expression, morphology, ultrastructure, function, and response to challenges between the sexes ( [Schwarz and Bilbo, 2012](#) ; [Hui St.-Pierre et al., 2018](#) ; [Nelson et al., 2019](#) ; [Bordeleau et al., 2020](#) ; [Yasuda et al., 2020](#) ). In the periphery, the concept of “ immunobiography” has been formulated, to reflect the tremendous inter-individual differences in immune function cumulating during life, and propose the idea that the individual immune signature can inform in a very sensitive manner on the state of health or disease, and allow to predict the outcome of various treatment strategies ( [Del Giudice et al., 2017](#) ; [Franceschi et al., 2017](#) ). Similarly, the physiological and immune functions of both microglia and astrocytes are regulated by a multitude of external influences, which can induce cellular memory and epigenetic remodeling ( [Reemst et al., 2016](#) ; [Valero et al., 2016](#) ; [Tay et al., 2017a](#) ; [Ayata et al., 2018](#) ; [Murphy-Royal et al., 2019](#) ; [Wheeler et al., 2019](#) ; [Madore et al., 2020](#) ). As a consequence, elucidating how various individual circumstances guide the multidimensional relationships between neuronal and non-neuronal cell types, subtypes and phenotypes in the CNS, is expected to provide unprecedented opportunities to develop personalized treatment strategies for a wide variety of neurodevelopmental, neuropsychiatric and neurodegenerative diseases in

which the neuronal and non-neuronal cells of the CNS are together critically involved.

## **Author Contributions**

The author confirms being the sole contributor of this work and has approved it for publication.

## **Conflict of Interest**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## **Acknowledgments**

M-ÉT is a Canada Research Chair Tier II in Neurobiology of Aging and Cognition.

## **References**

Askew, K., Li, K., Olmos-Alonso, A., Garcia-Moreno, F., Liang, Y., Richardson, P., et al. (2017). Coupled proliferation and apoptosis maintain the rapid turnover of microglia in the adult brain. *Cell Rep.* 18, 391–405. doi: 10.1016/j.celrep.2016.12.041

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Ayata, P., Badimon, A., Strasburger, H. J., Duff, M. K., Montgomery, S. E., Loh, Y.-H. E., et al. (2018). Epigenetic regulation of brain region-specific microglia clearance activity. *Nature Neurosci.* 21, 1049–1060. doi: 10.1038/s41593-018-0192-3

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Béchade, C., Cantaut-Belarif, Y., and Bessis, A. (2013). Microglial control of neuronal activity. *Front. Cell. Neurosci.* 7: 32. doi: 10.3389/fncel.2013.00032

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Bisht, K., Sharma, K. P., Lecours, C., Sánchez, M. G., El Hajj, H., Milior, G., et al. (2016). Dark microglia: a new phenotype predominantly associated with pathological states. *Glia* 64, 826–839. doi: 10.1002/glia.22966

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Bordeleau, M., Lacabanne, C., Fernández de Cossío, L., Vernoux, N., Savage, J. C., González-Ibáñez, F., et al. (2020). Microglial and peripheral immune priming is partially sexually dimorphic in adolescent mouse offspring exposed to maternal high-fat diet. *J. Neuroinflamm.* 17: 264. doi: 10.1186/s12974-020-01914-1

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Burns, J. C., Cotleur, B., Walther, D. M., Bajrami, B., Rubino, S. J., Wei, R., et al. (2020). Differential accumulation of storage bodies with aging defines discrete subsets of microglia in the healthy brain. *Elife* 9: e57495. doi: 10.7554/eLife.57495.sa2

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>



Butt, A., and Verkhratsky, A. (2018). Neuroglia: realising their true potential. *Brain Neurosci. Adv.* 2, 208–215. doi: 10. 1177/2398212818817495

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Carrier, M., Robert, M.-È., González Ibáñez, F., Desjardins, M., and Tremblay, M.-È. (2020). Imaging the neuroimmune dynamics across space and time. *Front. Neurosci.* 14: 903. doi: 10. 3389/fnins. 2020. 00903

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Castellani, G., and Schwartz, M. (2020). Immunological features of non-neuronal brain cells: implications for Alzheimer's Disease immunotherapy. *Trends Immunol.* 41, 794–804. doi: 10. 1016/j. it. 2020. 07. 005

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cizeron, M., Qiu, Z., Koniaris, B., Gokhale, R., Komiyama, N. H., Fransén, E., et al. (2020). A brain-wide atlas of synapses across the mouse lifespan. *Science* 369, 270–275. doi: 10. 1126/science. aba3163

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Deczkowska, A., Weiner, A., and Amit, I. (2020). The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway. *Cell* 181, 1207–1217. doi: 10. 1016/j. cell. 2020. 05. 003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Del Giudice, G., Goronzy, J. J., Grubeck-Loebenstien, B., Lambert, P.-H., Mrkvan, T., Stoddard, J. J., et al. (2017). Fighting against a protean enemy: immunosenescence, vaccines, and healthy aging. *npj Aging Mech. Dis.* 4, 1–8. doi: 10.1038/s41514-017-0020-0

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Domingues, H. S., Portugal, C. C., Socodato, R., and Relvas, J. B. (2016). Oligodendrocyte, astrocyte, and microglia crosstalk in myelin development, damage, and repair. *Front. Cell Dev. Biol.* 4: 79. doi: 10.3389/fcell.2016.00079

[CrossRef Full Text](#) | [Google Scholar](#)

Dumas, A. A., and Prinz, M. (2020). The myeloid side of the CNS. *Brain Pathol.* e12907. doi: 10.1111/bpa.12907. [Epub ahead of print].

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Foerster, S., Hill, M. F. E., and Franklin, R. J. M. (2019). Diversity in the oligodendrocyte lineage: plasticity or heterogeneity? *Glia* 67, 1797–1805. doi: 10.1002/glia.23607

[CrossRef Full Text](#) | [Google Scholar](#)

Franceschi, C., Salvioli, S., Garagnani, P., de Eguileor, M., Monti, D., and Capri, M. (2017). Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. *Front. Immunol.* 8: 982. doi: 10.3389/fimmu.2017.00982

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Füger, P., Hefendehl, J. K., Veeraraghavalu, K., Wendeln, A.-C., Schlosser, C., Obermüller, U., et al. (2017). Microglia turnover with aging and in an Alzheimer's model via long-term *in vivo* single-cell imaging. *Nat. Neurosci.* 20, 1371–1376. doi: 10. 1038/nn. 4631

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Gosselin, D., Link, V. M., Romanoski, C. E., Fonseca, G. J., Eichenfield, D. Z., Spann, N. J., et al. (2014). Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. *Cell* 159, 1327–1340. doi: 10. 1016/j. cell. 2014. 11. 023

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hammond, T. R., Dufort, C., Dissing-Olesen, L., Giera, S., Young, A., Wysoker, A., et al. (2019). Single-cell RNA sequencing of microglia throughout the mouse lifespan and in the injured brain reveals complex cell-state changes. *Immunity* 50, 253–271. e6. doi: 10. 1016/j. immuni. 2018. 11. 004

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hanamsagar, R., and Bilbo, S. D. (2017). Environment matters: microglia function and dysfunction in a changing world. *Curr. Opin. Neurobiol.* 47, 146–155. doi: 10. 1016/j. conb. 2017. 10. 007

[CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Hellwig, S., Heinrich, A., and Biber, K. (2013). The brain's best friend: microglial neurotoxicity revisited. *Front. Cell. Neurosci.* 7: 71. doi: 10.3389/fncel. 2013. 00071

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hui St.-Pierre, A., El Hajj, H., Remy, Y., Hébert, S. S., Luheshi, G. N., et al. (2018). Prenatal immune challenge in mice leads to partly sex-dependent behavioral, microglial, and molecular abnormalities associated with schizophrenia. *Front. Mol. Neurosci.* 11: 13. doi: 10.3389/fnmol. 2018. 00013

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Kettenmann, H., Kirchhoff, F., and Verkhratsky, A. (2013). Microglia: new roles for the synaptic stripper. *Neuron* 77, 10–18. doi: 10.1016/j.neuron. 2012. 12. 023

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Khakh, B. S., and Deneen, B. (2019). The emerging nature of astrocyte diversity. *Ann. Rev. Neurosci.* 42, 187–207. doi: 10.1146/annurev-neuro-070918-050443

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Kierdorf, K., Masuda, T., Jordão, M. J. C., and Prinz, M. (2019). Macrophages at CNS interfaces: ontogeny and function in health and disease. *Nat. Rev. Neurosci.* 20, 547–562. doi: 10.1038/s41583-019-0201-x

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., et al. (2017). The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. *Immunity* 47, 566–581. e9. doi: 10. 1016/j. immuni. 2017. 08. 008

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Liddel, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541, 481–487. doi: 10. 1038/nature21029

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Madore, C., Yin, Z., Leibowitz, J., and Butovsky, O. (2020). Microglia, lifestyle stress, and neurodegeneration. *Immunity* 52, 222–240. doi: 10. 1016/j. immuni. 2019. 12. 003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Martinez, F. O., and Gordon, S. (2014). The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep* 6: 13. doi: 10. 12703/P6-13

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Matejuk, A., and Ransohoff, R. M. (2020). Crosstalk between astrocytes and microglia: an overview. *Front. Immunol.* 11: 1416. doi: 10.3389/fimmu.2020.01416

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Murphy-Royal, C., Gordon, G. R., and Bains, J. S. (2019). Stress-induced structural and functional modifications of astrocytes-Further implicating glia in the central response to stress. *Glia* 67, 1806–1820. doi: 10.1002/glia.23610

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Nelson, L. H., Saulsbery, A. I., and Lenz, K. M. (2019). Small cells with big implications: microglia and sex differences in brain development, plasticity and behavioral health. *Prog. Neurobiol.* 176, 103–119. doi: 10.1016/j.pneurobio.2018.09.002

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Neuroimmune Communication (2017). *Nat. Immunol.* 18: 115. doi: 10.1038/ni.3676

[CrossRef Full Text](#)

Oberheim, N. A., Goldman, S. A., and Nedergaard, M. (2012). Heterogeneity of astrocytic form and function. *Methods Mol. Biol.* 814, 23–45. doi: 10.1007/978-1-61779-452-0\_3

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Perdiguero, E. G., and Geissmann, F. (2016). The development and maintenance of resident macrophages. *Nat. Immunol.* 17, 2–8. doi: 10.1038/ni.3341

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Prinz, M., Tay, T. L., Wolf, Y., and Jung, S. (2014). Microglia: unique and common features with other tissue macrophages. *Acta Neuropathol.* 128, 319–331. doi: 10.1007/s00401-014-1267-1

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Que, L., Winterer, J., and Földy, C. (2019). Deep survey of GABAergic interneurons: emerging insights from gene-isoform transcriptomics. *Front. Mol. Neurosci.* 12: 115. doi: 10.3389/fnmol.2019.00115

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Ransohoff, R. M. (2016). A polarizing question: do M1 and M2 microglia exist? *Nat. Neurosci.* 19, 987–991. doi: 10.1038/nn.4338

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Reemst, K., Noctor, S. C., Lucassen, P. J., and Hol, E. M. (2016). The indispensable roles of microglia and astrocytes during brain development. *Front. Hum. Neurosci.* 10: 566. doi: 10.3389/fnhum.2016.00566

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Savage, J. C., and Tremblay, M.-È. (2019). Studying laboratory mice - into the wild. *Trends Neurosci.* 42, 566–568. doi: 10.1016/j.tins.2019.05.004

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Schwarz, J. M., and Bilbo, S. D. (2012). Sex, glia, and development: interactions in health and disease. *Horm. Behav.* 62, 243–253. doi: 10.1016/j.yhbeh.2012.02.018

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Silvin, A., and Ginhoux, F. (2018). Microglia heterogeneity along a spatio-temporal axis: More questions than answers. *Glia* 66, 2045–2057. doi: 10.1002/glia.23458

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

St-Pierre, M.-K., Šimončíčová, E., Bögi, E., and Tremblay, M.-È. (2020). Shedding light on the dark side of the microglia. *ASN Neuro* 12: 1759091420925335. doi: 10.1177/1759091420925335

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Stratoulas, V., Venero, J. L., Tremblay, M.-È., and Joseph, B. (2019). Microglial subtypes: diversity within the microglial community. *EMBO J.* 38: e101997. doi: 10.15252/embj.2019101997

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>



Sugino, K., Clark, E., Schulmann, A., Shima, Y., Wang, L., Hunt, D. L., et al. (2019). Mapping the transcriptional diversity of genetically and anatomically defined cell populations in the mouse brain. *eLife* 8: e38619. doi: 10.7554/eLife. 38619. 048

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Tan, Y.-L., Yuan, Y., and Tian, L. (2020). Microglial regional heterogeneity and its role in the brain. *Mol. Psychiatry* 25, 351–367. doi: 10.1038/s41380-019-0609-8

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Tay, T. L., Béchade, C., D'Andrea, I., St-Pierre, M.-K., Henry, M. S., Roumier, A., et al. (2017a). Microglia gone rogue: impacts on psychiatric disorders across the lifespan. *Front. Mol. Neurosci.* 10: 421. doi: 10.3389/fnmol. 2017.00421

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Tay, T. L., Mai, D., Dautzenberg, J., Fernández-Klett, F., Lin, G., Sagar, null, et al. (2017b). A new fate mapping system reveals context-dependent random or clonal expansion of microglia. *Nat. Neurosci.* 20, 793–803. doi: 10.1038/nn. 4547

[CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Tay, T. L., Savage, J. C., Hui, C. W., Bisht, K., and Tremblay, M.-È. (2017c). Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. *J. Physiol.* 595, 1929–1945. doi: 10. 1113/JJP272134

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Theret, M., Mounier, R., and Rossi, F. (2019). The origins and non-canonical functions of macrophages in development and regeneration. *Development* 146: dev156000. doi: 10. 1242/dev. 156000

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Valero, J., Paris, I., and Sierra, A. (2016). Lifestyle shapes the dialogue between environment, microglia, and adult neurogenesis. *ACS Chem. Neurosci.* 7, 442–453. doi: 10. 1021/acschemneuro. 6b00009

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Verkhratsky, A., and Nedergaard, M. (2018). Physiology of Astroglia. *Physiol. Rev.* 98, 239–389. doi: 10. 1152/physrev. 00042. 2016

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Westergard, T., and Rothstein, J. D. (2020). Astrocyte diversity: current insights and future directions. *Neurochem. Res.* 45, 1298–1305. doi: 10. 1007/s11064-020-02959-7

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/a-diversity-of-cell-types-subtypes-and-phenotypes-in-the-central-nervous-system-the-importance-of-studying-their-complex-relationships/>

Wheeler, M. A., Jaronen, M., Covacu, R., Zandee, S. E. J., Scalisi, G., Rothhammer, V., et al. (2019). Environmental control of astrocyte pathogenic activities in CNS inflammation. *Cell* 176, 581-596. e18. doi: 10.1016/j.cell.2018.12.012

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Yasuda, K., Maki, T., Kinoshita, H., Kaji, S., Toyokawa, M., Nishigori, R., et al. (2020). Sex-specific differences in transcriptomic profiles and cellular characteristics of oligodendrocyte precursor cells. *Stem Cell Res.* 46: 101866. doi: 10.1016/j.scr.2020.101866

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)