BRAINSTORM

THE STUDENT JOURNAL IN BORDEAUX

In this issue

ILLUSTRATION: ARTHUR LEVASSEUR

The values of the journal

- Open Science: our scientific publications must be accessible to anyone, with no exception of any kind. No passwords or money will be required to read our content.

- Relevance of negative results: no new findings is a new finding. Without negative results, science is time and resources consuming. Researchers keep repeating the same experiences again and again because they are not aware that what they did was already done before and did not work out. Plus, publishing only positive results creates an enormous bias: a single positive result out of a thousand negative trials may not be an actual positive result.

- Avoidance of scientific priority: we seek equal representation. We want everybody to have an opportunity to publish. For this reason, we will avoid giving voice only to researchers with solid resumes, with many publications in great journals and with an important reputation in the scientific community.

With the support from:

Graduate Research School / université de BORDEAUX

BRAINSTORM STUDENT JOURNAL

STUDENT BLOG

Astrocytes and juvenile brain injury

Julia Chabbert, Simon Lecomte

September 2022 I Vol.1 No.1

Reactive astrogliosis

Different kinds of cells coexist in the central nervous system (CNS) and participate in its proper functioning. On the one hand, neurons allow the transmission of information through their action potentials. On the other hand, the CNS contains also what we know as glial cells, which for a long time went unnoticed by neuroscientists mainly because they do not trigger action potentials.

The present text focuses on astrocytes, one type of glial cell, and the process known as *reactive astrogliosis*. Astrocytes have multiple roles including the uptake of neurotransmitters from the synaptic cleft, the modulation of neurotransmission by the release of gliotransmitters and the formation of synapses during development. In addition, astrocytes support the activity of neurons by providing them nutrients and capturing their waste products in return. Finally, these cells help to protect the CNS when an aggression occurs (head trauma, ischemia, pathologies or others).

Indeed, when the brain is damaged astrocytes can respond and lead to a phenomenon known as *reactive astrogliosis* (1). This process has been more precisely described (2, 3) through four main aspects:

1) Astrogliosis is the set of potential molecular, cellular, and functional changes in astrocytes in response to all types and degrees of severity of CNS damage and pathology.

2) The changes in reactive astrocytes depend on the severity of the injury along a continuum.

3) These changes are regulated by numerous intracellular and intercellular signaling molecules.

4) These changes can alter astrocyte activity either by gain or loss of function.

Moreover, since astrocytes and neurons are closely related, *reactive astrogliosis* can induce functional changes in neurons as well (5):

- A reduction in GABAergic currents caused by a decrease in the astrocytic expression of glutamine synthetase.
- An increase in glutamatergic neurotransmission caused by an increase in the expression of xCT, an astrocytic cysteine-glutamate transporter allowing the release of glutamate into the extracellular space. This phenomenon, probably in combination with the previous one, can cause seizures and excitotoxicity.
- Changes in the expression of many G protein-coupled receptors (also known as G proteins), and their intracellular calcium signaling pathways.

Therefore, astrocytes constitute a potential therapeutic target against CNS pathologies (8, 9). Strategies aiming to potentiate the beneficial effects of *reactive astrogliosis* and to mitigate its harmful effects can be envisaged. An example of that would be the action on the mechanisms that regulate glutamate homeostasis, the enzymes regulating oxidative stress, and the production of certain cytokines.

It is important to note that *astrogliosis* is not a stereotyped response, but it is rather heterogeneous. In fact, depending on the severity of the damage, the response can be reversible or irreversible. In the context of head trauma, *reactive astrogliosis* follows a spatio-temporal gradient according to the distance between the cell and the site of injury, as well as the time that has elapsed between the trauma and the biopsy (4).

Reactive astrogliosis can be considered an adaptive response that aims to repair the damaged tissue and to protect the adjacent healthy tissue. When this response does not occur, the inflammatory response increases, so does the damage of the tissue. Thus, reactive astrogliosis can be considered a protection of the CNS against inflammatory processes, ionic disorders, excitotoxicity, and oxidative stress.

However, it is possible that the adaptive response turns into a harmful one. Indeed, gliosis can prevent the axonal regeneration that would follow a brain lesion.

This paradox has been the subject of much debate: how is it possible that the astrocytic response can both enable and prevent functional recovery of the CNS? The response may lie in the fact that there are two types of reactive astrocytes (6, 7):

- A1 reactive astrocytes might prevent functional recovery of the CNS. These astrocytes have been shown to promote the transcription of genes leading to neuronal cell death.
- A2 reactive astrocytes might allow functional recovery of the CNS. These astrocytes have been shown to promote the transcription of genes leading to the synthesis of neurotrophic factors, which have a protective effect on synapses.

References

(1) Vibert, J. F., Sébille, A., Lavallard-Rousseau, M. C., Boureau, F., & Mazières, L. (2019). Neurophysiologie : de la physiologie à l'exploration fonctionnelle. Elsevier Health Sciences.

(2) Sofroniew, M. V. (2015). Astrogliosis. Cold Spring Harbor perspectives in biology, 7(2).

(3) Sofroniew, M. V., & Vinters, H. V. (2010). Astrocytes: biology and pathology. Acta neuropathologica, 119(1), 7-35.

(4) Clément, T., Lee, J. B., Ichkova, A., Rodriguez-Grande, B., Fournier, M. L., Aussudre, J., ... & Badaut, J. (2020). Juvenile mild traumatic brain injury elicits distinct spatiotemporal astrocyte responses. Glia, 68(3), 528-542.

(5) Burda, J. E., & Sofroniew, M. V. (2017). Seducing astrocytes to the dark side. Cell research, 27(6), 726.

(6) Burda, J. E., & Sofroniew, M. V. (2014). Reactive gliosis and the multicellular response to CNS damage and disease. Neuron, 81(2), 229-248.

(7) Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., ... & Wilton, D. K. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. Nature, 541(7638), 481-487.

The rest of the blog posts are available in the following link: https://www.bordeaux-neurocampus.fr/analyses-darticles-scientifiques-par-les-etudiants-en-m1-multipublic

BRAINSTORM STUDENT JOURNAL

REVIEW

Neuroinflammation, from physiology to pathology

Adinda Winderickxord

University of Bordeaux

Received: 19th August 2022| Peer Reviewed: 21st August 2022 | Accepted: 1st September 2022

Adinda was born in Brussels (Belgium). She has Bachelor's degree on Psychobiology from the University of Amsterdam. She is currently part of the second year of Neurasmus master at the University of Bordeaux. She is interested in Molecular and biological neuroscience, autism spectrum disorder and computational neuroscience.

Abstract

Neuroinflammation is regulated by the immune system and is highly important for the protection of the central nervous system (CNS). Uncontrolled neuroinflammation, however, can induce neurotoxicity. The major immune cells in the CNS are microglia and astrocytes. Various signals in their surroundings can cause microglia and astrocytes to acquire a pro-inflammatory, neurotoxic state. Once they are activated, they can in turn secrete specific cytokines which can induce other microglia and astrocytes to become reactive. Several mechanisms underlie the neurotoxic function of reactive microglia and astrocytes. Primarily, increased oxidative stress and the secretion of neurotoxic cytokines and chemokines lead to neuronal damage. Additionally, abnormal release of high amounts of glutamate by reactive astrocytes at the synapse can cause excitotoxicity in neurons. Moreover, pro-inflammatory microglia and astrocytes are also implicated in blood-brain barrier disruption, facilitating the entrance of peripheral neurotoxic factors into the brain.

Thus, chronic and excessive neuroinflammation can cause considerable damage to the brain, eventually resulting in or contributing to neuropathology's. This is evidenced by the role of neuroinflammation in Alzheimer's Disease (AD), where it is neuroprotective in the beginning, but exacerbates the pathology at later stages. This review aims to summarize key findings and deepen the present understanding of pathology-associated uncontrolled neuroinflammation.

Keywords : astrocytes, microglia, neurodegeneration, neuroinflammation, neuroprotection

Introduction

Neuroinflammation is crucial for the defense of the central nervous system (CNS) against pathogens and other foreign materials, infections, injuries, and toxic substances. In addition, neuroinflammation promotes tissue repair and

regrowth. While neuroinflammation is initially neuroprotective, chronic neuroinflammation can become harmful to the CNS by promoting or aggravating pathologies.

The main cellular players in the inflammatory response of the CNS are microglia and astrocytes. Furthermore, elements of the peripheral immune system can be recruited such as neutrophils. For the sake of conciseness, this review will focus on microglia and astrocytes.

Considered the primary defense line of the CNS, microglia are constantly scanning the brain for signs of damage, such as injured cells, or possible threats (1). These cells remain highly dynamic in a wakeful ramified state under basal conditions. This is in opposition to the previous idea that they were either in a resting or activated state. Upon activation, microglia serve as antigen presenting cells for T-lymphocytes, mediating adequate inflammatory responses (2,3). Activators of microglia include inflammatory triggers such as viruses, bacteria, damaged or dead cells, debris, toxins and molecules associated with neuronal damage such as adenosine triphosphate (ATP).

Astrocytes play an important role in brain homeostasis through different functions ranging from blood-brain barrier (BBB) maintenance and synaptic modulation to the removal of dead cells and scar formation (2). Additionally, astrocytes mediate neuroinflammatory effects.

Moderate neuroinflammation is important for protection against pathogens as well as the repair of damaged tissues after injury. Recovery occurs when the neuroprotective function of neuroinflammation outweighs its neurotoxic effects and the duration of the negative consequences is short. However, aberrant and chronic neuroinflammation can significantly damage the central nervous system. When such damage exceeds the regeneration capacity of the brain and repair is insufficient, serious pathologies can arise. However, literature so far remains inconclusive on the exact process behind the switch from moderate and neuroprotective to chronic and neurotoxic neuroinflammation.

Neuroinflammation is a well-documented feature in virtually every neurodegenerative disorder and various other neuropathologies. Therefore, its role during the progression of various neuropathologies should not be overlooked.

This review first discusses the importance of the balance between proinflammatory and anti-inflammatory states in neuroinflammation. Next, the mechanisms through which excessive microglia and astrocyte activation can exert neuronal damage are explored. Finally, the role of neuroinflammation in Alzheimer's disease (AD) pathology is used as an example of the harmful effects of uncontrolled neuroinflammation in neurodegenerative disorders.

Methods

For the present review, a distinction was made between information on the role of microglia and astrocytes in neuroinflammation and the role of neuroinflammation in neurodegenerative diseases.

For discussing the role of microglia and astrocytes in neuroinflammation, this review focused on eighteen studies that used cell cultures and/or animal models. Indeed, regarding fundamental research, more progress has been made with non-human models and much more literature is available.

Eight studies were selected on the role of neuroinflammation in neurodegenerative diseases. Three studies in human subjects are also included within this article selection because it is more pertinent for the aim of this section.

The included papers were found using the Google Scholar database with different combinations of the following keywords: astrocytes, blood brain barrier, M1/M2, microglia, network homeostasis,

neuroinflammation, neuropathology, synaptic loss.

Results

Balancing proinflammatory and anti-inflammatory states of microglia and astrocytes

Traditionally, two different neuroinflammation-induced activation states of microglia and astrocytes are described in literature: the pro-inflammatory and the anti-inflammatory phenotype. These states are characterized by transformation of microglia to M1 and M2, and astrocytes to A1 and A2. M1 microglia are proinflammatory and cytotoxic, whereas M2 microglia are anti-inflammatory and neuroprotective.

Analogous to microglia, activated astrocytes can be categorized into pro-inflammatory A1, and anti-inflammatory A2 phenotypes. In contrast, with neuroprotective A2 astrocytes, A1 astrocytes exert highly cytotoxic effects (4). It is important to note that especially the M1/M2 dichotomy has been brought to question, as the complexity of microglial phenotypes calls for a broader classification spectrum (5).

A crosstalk between microglia and astrocytes is crucial in mediating their activation state. Through the secretion of cytokines, microglia can induce pro-inflammatory reactive astrocyte state A1 (4), or anti-inflammatory astrocyte state A2 (6). Conversely, astrocytes can attenuate microglia activation through TGF-beta secretion (7).

Although inflammation is an important mechanism to fight infection and reduce injury, a chronic and/or excessive inflammatory state can cause serious harm to the brain. Therefore, optimal neuroprotection requires a tight balance between pro-inflammatory and anti-inflammatory phenotypes. In healthy cases, M1/A1 mediated inflammation is initially needed to fight potential threats, and M2/A2 glial cells provide subsequent anti-inflammatory signals and tissue repair. Importantly, neuronal damage caused by excessive neuroinflammation can further enhance neuroinflammatory mechanisms, resulting in a self-propelling system.

In conclusion, neuroinflammation involves different types of activation states of microglia and astrocytes, some of which are neuroprotective and some of which can become neurotoxic. An imbalance between pro-inflammatory and anti-inflammatory states can result in uncontrolled neuroinflammation.

The role of microglia in neuroinflammation-induced CNS damage

In the mature brain, microglia are essential for maintaining synapse activity and network homeostasis. Evidence from an induced neuroinflammation mouse model shows that this function is disrupted in neuroinflammation (8).

Moreover, microglia activation can induce detrimental alterations to the BBB. In an induced neuroinflammation rat model, activated microglia can disrupt the BBB (9). Consequent alterations in BBB permeability can allow the entrance of potentially harmful factors and circulating immune cells from the periphery, further enhancing neuroinflammatory responses. Interestingly, a study by Gao and colleagues (10) found that reducing microglia and neutrophil recruitment to the damaged tissue attenuated BBB disruptions.

In conclusion, aberrant and chronic neuroinflammation induces excessive proinflammatory microglial activation. This can harm the CNS through multiple mechanisms including the secretion of neurotoxic substances, increased oxidative stress, altered synaptic maintenance and BBB disruption.

The role of astrocytes in neuroinflammation-induced CNS damage

Cytokines and chemokines secreted by reactive microglia can activate reactive astrocytes (4,11). This activation can in turn induce reactive astrocytes to release neurotoxic factors, significantly increasing the cytokine-chemokine concentration (9,12,13). Similar to microglia, it was found that activated astrocytes lead to disruptions of the BBB (14).

Homeostatic functions of astrocytes are impaired during neuroinflammation. Synapse maintenance is altered, affecting synaptic transmission and network homeostasis. Decreased phagocytic capacity of reactive A1 astrocytes can lead to the

accumulation of neurotoxic debris in the brain (4). It was also shown that neuroinflammation-associated chemokine SDF1-alpha alters glutamate homeostasis at the synapse, increasing glutamate release from astrocytes at the synapse and thus facilitating excitotoxicity (15). Moreover, A1 reactive astrocytes form weaker and fewer synapses than resting astrocytes (4).

Summarized, though astrocyte activation is initially neuroprotective, excessive neuroinflammation leads to uncontrolled astrocyte activation. This can elicit adverse effects such as secretion of neurotoxic substances and disruption of the BBB. Additionally, alterations in astrocytic function can lead to decreased support of neurons leading to neuronal loss and alterations in network functioning.

Neuroinflammation in Alzheimer's disease

One of the most common neurodegenerative diseases, AD, is characterized by the formation of β-amyloid plaques and phosphorylated tau aggregates. A significant relationship between tau pathology and neuroinflammation was found in patients with early AD (16). Interestingly, markers of neuroinflammation can be detected in the cerebrospinal fluid of patients at preclinical stages of AD (17).

At the beginning of AD pathology, neuroinflammation is neuroprotective. For example, the initial activation of microglia helps clear β-amyloid plaques in a mouse model of AD (18). However, neuroinflammation can also be harmful, worsening the detrimental features of the disease. β-amyloid plaques and tau pathology can activate the NLP3 inflammasome (19,20,21), triggering pro-inflammatory responses. Inhibition or loss of the NLP3 inflammasome has protective effects against tau pathology, whereas NLP3 inflammasome activation exacerbates tau pathology (19,21).

In post-mortem brain samples of AD patients, nearly 60% of astrocytes were classified as neurotoxic A1 reactive type (4). Evidence points towards detrimental effects of this increase in reactive astrocyte activity. Using two transgenic mouse models of AD, Park and colleagues (22) found that blocking microglial activation of astrocytes improved neuronal survival as well as memory and spatial learning.

Combining these results, a considerable role emerges for neuroinflammation in Alzheimer's progression. In the early stages of AD pathology neuroinflammation can be neuroprotective. However, as the disease progresses, excessive inflammation exacerbates the pathology instead of attenuating it. Thus, AD offers an interesting model to understand the importance of balance between proinflammatory and anti-inflammatory mechanisms.

Conclusion

Neuroinflammation is an important tool for the protection of the CNS. However chronic and excessive neuroinflammation can lose its protective function and lead to adverse results. The main effector cells in neuroinflammation are microglia and astrocytes. Microglia and astrocytes can polarize into different activation types with different neuroprotective or neurotoxic effects. Reactive microglia and astrocytes can lead to the secretion of chemokines which in turn results in the activation of other microglia and astrocytes. Whilst traditionally a distinction is made between the pro-inflammatory M1/A1 and the anti-inflammatory M2/A2 activation type, evidence points towards a more complex system of different activation types.

The neurotoxic effects of reactive astrocytes and microglia in neuroinflammation are caused by a number of alterations. Neuroinflammation is characterized by the secretion of cytokines and chemokines by both astrocytes and microglia, which can be neurotoxic. Additionally, increased oxidative stress further drives neuronal damage, and can eventually lead to neuronal loss.

Moreover, during neuroinflammation synapse maintenance and network homeostasis can be negatively impacted by a plethora of factors: alterations in phagocytic capacity of astrocytes can impact the clearance of neurotoxic debris at the synapse, which can result in their accumulation with a consequential synaptic loss. Whereas astrocytes normally mediate glutamate homeostasis, reactive astrocytes can release large amounts of glutamate at the synapse. This can

induce excitotoxicity and lead to neuronal loss. Neuroinflammation-mediated activation of microglia and astrocytes can also induce BBB disruptions. As a result, the BBB becomes more permeable, potentially allowing the entrance of peripheral neurotoxic factors into the brain.

Taking into account these detrimental outcomes of excessive chronic neuroinflammation, one can understand why neuroinflammation plays an important role in numerous neuropathologies. In AD, neuroinflammatory mechanisms can already be detected at an early, preclinical stage. Activation of the NLP3 inflammasome by tau and β-amyloid pathology can induce further neuronal damage. Moreover, studies show that throughout disease progression, this neuroinflammatory response can exacerbate β-amyloid and tau pathology. Nevertheless, it is thought that in the early stages of AD, neuroinflammation fulfils a neuroprotective role, evidenced by increased clearance of β-amyloid. Thus, AD progression provides a clear example of how chronic neuroinflammation can become harmful, worsening the pathology instead of attenuating it.

References

(1) Nimmerjahn, A., Kirchhoff, F., & Helmchen, F. (2005). Resting Microglial Cells Are Highly Dynamic Surveillants of Brain Parenchyma in Vivo. Science, 308(5726), 1314–1318.

(2) H. S., & Koh, S.-H. (2020). Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. Translational Neurodegeneration, 9(1), 42.

(3) N., Pan, R., Qin, X.-J., Yang, W.-L., Qi, Z., Liu, W., & Liu, K. J. (2014). Ischemic neurons activate astrocytes to disrupt endothelial barrier via increasing VEGF expression. Journal of Neurochemistry, 129(1), 120–129.

(4) Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W.-S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. Nature, 541(7638), 481–487.

(5) Deng, W., Mandeville, E., Terasaki, Y., Li, W., Holder, J., Chuang, A. T., Ning, M., Arai, K., Lo, E. H., & Xing, C. (2020). Transcriptomic characterization of microglia activation in a rat model of ischemic stroke. Journal of Cerebral Blood Flow & Metabolism, 40, 34–48.

(6) Shinozaki, Y., Shibata, K., Yoshida, K., Shigetomi, E., Gachet, C., Ikenaka, K., Tanaka, K. F., & Koizumi, S. (2017). Transformation of Astrocytes to a Neuroprotective Phenotype by Microglia via P2Y1 Receptor Downregulation. Cell Reports, 19(6), 1151–1164.

(7) Norden, D. M., Fenn, A. M., Dugan, A., & Godbout, J. P. (2014). TGFβ produced by IL-10 redirected astrocytes attenuates microglial activation: IL-10 Redirects Immune Activated Astrocytes. Glia, 62(6), 881–895.

(8) Akiyoshi, R., Wake, H., Kato, D., Horiuchi, H., Ono, R., Ikegami, A., Haruwaka, K., Omori, T., Tachibana, Y., Moorhouse, A. J., & Nabekura, J. (2018). Microglia Enhance Synapse Activity to Promote Local Network Synchronization. Eneuro, 5(5), ENEURO.0088-18.2018.

(9) Shigemoto-Mogami, Y., Hoshikawa, K., & Sato, K. (2018). Activated Microglia Disrupt the Blood-Brain Barrier and Induce Chemokines and Cytokines in a Rat in vitro Model. Frontiers in Cellular Neuroscience, 12, 494.

(10) Gao, W., Zhao, Z., Yu, G., Zhou, Z., Zhou, Y., Hu, T., Jiang, R., & Zhang, J. (2015). VEGI attenuates the inflammatory injury and disruption of blood–brain barrier partly by suppressing the TLR4/NF-κB signaling pathway in experimental traumatic brain injury. Brain Research, 1622, 230–239.

(11) Kirkley, K. S., Popichak, K. A., Afzali, M. F., Legare, M. E., & Tjalkens, R. B. (2017). Microglia amplify inflammatory activation of astrocytes in manganese neurotoxicity. Journal of Neuroinflammation, 14(1), 99.

(12) Ambrosini, E., Remoli, M. E., Giacomini, E., Rosicarelli, B., Serafini, B., Lande, R., Aloisi, F., & Coccia, E. M. (2005). Astrocytes Produce Dendritic Cell-Attracting Chemokines In Vitro and in Multiple Sclerosis Lesions: Journal of Neuropathology and Experimental Neurology, 64(8), 706–715.

(13) Uddin, J., Garcia, H. H., Gilman, R. H., Gonzalez, A. E., & Friedland, J. S. (2005). Monocyte-Astrocyte Networks and the Regulation of Chemokine Secretion in Neurocysticercosis. The Journal of Immunology, 175(5), 3273–3281.

(14) Li Y. B., Nagai, A., & Kim, S. U. (2002). Cytokines, chemokines, and cytokine receptors in human microglia. Journal of Neuroscience Research, 69(1), 94–103.

(15) Bezzi, P., Domercq, M., Brambilla, L., Galli, R., Schols, D., De Clercq, E., Vescovi, A., Bagetta, G., Kollias, G., Meldolesi, J., & Volterra, A. (2001). CXCR4-activated astrocyte glutamate release via TNFα: Amplification by microglia triggers neurotoxicity. Nature Neuroscience, 4(7), 702–710.

(16) Terada, T., Yokokura, M., Obi, T., Bunai, T., Yoshikawa, E., Ando, I., Shimada, H., Suhara, T., Higuchi, M., & Ouchi, Y. (2019). In vivo direct relation of tau pathology with neuroinflammation in early Alzheimer's disease. Journal of Neurology, 266(9), 2186–2196.

(17) Jalidze, S., Mattsson, N., Stomrud, E., Lindberg, O., Palmqvist, S., Zetterberg, H., Blennow, K., & Hansson, O. (2018). CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease. Neurology, 91(9), 867–877.

(18) DiCarlo, G. (2001). Intrahippocampal LPS injections reduce AÎ2 load in APP+PS1 transgenic mice. Neurobiology of Aging, 22(6), 1007–1012.

(19) Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S. V., Vieira-Saecker, A., Schwartz, S., Albasset, S., McManus, R. M., Tejera, D., Griep, A., Santarelli, F., Brosseron, F., Opitz, S., Stunden, J., Merten, M., Kayed, R., Golenbock, D. T., Blum, D., … Heneka, M. T. (2019). NLRP3 inflammasome activation drives tau pathology. Nature, 575(7784), 669–673.

(20) Nakanishi, A., Kaneko, N., Takeda, H., Sawasaki, T., Morikawa, S., Zhou, W., Kurata, M., Yamamoto, T., Akbar, S. M. F., Zako, T., & Masumoto, J. (2018). Amyloid β directly interacts with NLRP3 to initiate inflammasome activation: Identification of an intrinsic NLRP3 ligand in a cell-free system. Inflammation and Regeneration, 38(1), 27.

(21) Stancu, I.-C., Cremers, N., Vanrusselt, H., Couturier, J., Vanoosthuyse, A., Kessels, S., Lodder, C., Brône, B., Huaux, F., Octave, J.-N., Terwel, D., & Dewachter, I. (2019). Aggregated Tau activates NLRP3–ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. Acta Neuropathologica, 137(4), 599–617.

(22) Park, J.-S., Kam, T.-I., Lee, S., Park, H., Oh, Y., Kwon, S.-H., Song, J.-J., Kim, D., Kim, H., Jhaldiyal, A., Na, D. H., Lee, K. C., Park, E. J., Pomper, M. G., Pletnikova, O., Troncoso, J. C., Ko, H. S., Dawson, V. L., Dawson, T. M., & Lee, S. (2021). Blocking microglial activation of reactive astrocytes is neuroprotective in models of Alzheimer's disease. Acta Neuropathologica Communications, 9(1), 78.

BRAINSTORM STUDENT JOURNAL

LETTER

Open Science from the perspective of two Ph.D. students

Eduarda Centeno ∗ ‡ and Fjola Hyseni ∗ †
∗ Univ. Bordeaux, CNRS, IMN, UMR 5293, F-33000 Bordeaux, France
† Univ. Bordeaux, CNRS, Bordeaux INP, LaBRI, UMR 5800, F-33400 Talence, France
‡ Amsterdam UMC location Vrije Univ. Amsterdam, Anatomy and Neurosciences, De Boelelaan 1117, Amsterdam, the Netherlands
Email: egervinizamp@u-bordeaux.fr and fjola.hyseni@u-bordeaux.fr

Fjola Hyseni was born in Vlorë (Albania). She has a MSc in General Medicine and Surgery. She is currently PhD student in computational neurosciences at the IMN and is interested in temporal processing, sensorimotor learning, open science, and artificial intelligence.

Eduarda Gervini was born in Pelotas (Brasil). She has a Bachelor's degree on Biotechonology and a MSc in Neuroscience. She is currently a PhD student in computational neurosciences at the IMN. She is interested in Open Science and programming in Python. Outside the PhD she is working as a Research Assistant in the MULTINET Lab (VUMc – Amsterdam).

Abstract

Open Science is a new framework for knowledge building in research and education. In this letter, we would like to share our personal perspectives on this movement and how it has impacted our work and careers.

I. What is open science and how we got acquainted with it?

"Open Science is the practice of science in such a way that others can collaborate and contribute, where research data, lab notes and other research processes are freely available, under terms that enable reuse, redistribution and reproduction of the research and its underlying data and methods

(FOSTER Open Science Definition). In a nutshell, Open Science is transparent and accessible knowledge that is shared and developed through collaborative networks (Vicente-Sáez & Martínez-Fuentes 2018)" (1).

There is an increasing number of information sources on Open Science (OS) and its initiatives, including step-by-step guides detailing how anyone can contribute to this movement. In this letter, however, we would like to focus more on our personal experience and the impact this framework has had on our formation and, ultimately, on our research routine.

We are two Neuroscience Ph.D. students at the Bordeaux Neurocampus, and this is our journey with open and reproducible research practices.

Eduarda: My first contact with OS was during my M1 internship with Dr. Arthur Leblois (currently my Ph.D. supervisor) and Dr. André Garenne in Bordeaux. Part of my project was to build a data analysis pipeline for the team in Python (an open-source programming language) and post it on GitHub (an open-access repository for code). I truly enjoyed the experience and became much more motivated with the perspective of helping someone's project with my tools. From then on, I knew I wanted to continue working in line with OS and Python.

I then moved to Amsterdam, where I did my M2 thesis with Dr. Linda Douw and Dr. Fernando Santos in the MULTINET Lab (Vrije Universiteit Medical Center - VUmc). My internship's goal was to develop an open-source hands-on tutorial on network and topological data analysis in neuroimaging research (2). This project resulted in various excellent outcomes. I was invited to publish in a scientific journal (3) and present it at a conference at Sorbonne University (4) and in different meetings in France, the Netherlands, and the USA. More importantly, I often receive heartwarming emails and feedback from students from different parts of the world saying that my tutorial helped them in their projects. It's the best!

Fjola: I was fresh out of my third year of medical school, when I had my first research experience. As a medical student, not exposed much to research and academia, I was quite naive to the intricacies it entailed, and it so happened that my first experience with science was also my first experience with OS. There was no difference that I was aware of between the two.

This experience was an internship in 2016 at Erasmus University Medical Center with Prof. Tonya White, where I used OS tools like R (open-source programming language), and I became the first author in an open-access article (5). I got into research expecting similar experiences, but soon after, I started noticing differences. For instance, many articles I needed were not open access, I could find openly available code for some projects, whereas others, while available, were almost impossible to reproduce. With that, I realized that OS was not always the norm. It became clear that my expectations were different from reality, and that I would prefer working in an environment that encompassed transparency and collaboration, *i.e.*, an OS environment.

In my second research experience, in Tübingen, I was using Python to build an Electrocardiogram (ECG) toolbox (6). During this work, I learned the importance of documentation not only for myself but also to make the code reusable by colleagues at the lab at first and later by other peers. The script was later made available on GitHub.

II. The convergence: BordeauxTea

Eduarda: In Amsterdam, a friend and I started a journal club on Open Science - the ReprodubiliTea VU Amsterdam. The ReproducibiliTea initiative (7), per definition, encompasses discussions about diverse issues, papers, and ideas on science, reproducibility, and the OS movement. My experience in Amsterdam showed me that the journal club was a great way to start a discussion on OS and, in 2021, when I returned to Bordeaux for my Ph.D., I decided to bring this initiative with me.

After receiving tremendous support from the Bordeaux Neurocampus Graduate Program and, especially, from Cristina Lemos (the graduate program's project manager), I launched the BordeauxTea in February 2021 (8) . My idea was to have it as monthly sessions where students and researchers could join in educating themselves on OS.

During the first year, Dana Conlisk and I hosted the journal club and held eight sessions on a wide range of topics (open-access publishing, open methodology, open-source tools, *etc*) (9). In the beginning of our second year, we received the accreditation of the Graduate Program to become a Ph.D. course, and that is when Fjola decided to join as a co-host.

Fjola: As an OS enthusiast, even before becoming a co-host, I was very excited at the prospect of BordeauxTea. The presentations and discussions provided a warm and cozy setting to learn more about OS standard practices, share ideas, inform, discuss uncertainties, and more. Therefore, I was more than happy to become part of this initiative and actively contribute to the organisation of the sessions by inviting students to join and present, making suggestions, mediating the discussions, editing and publishing our videos, and interacting with influential names in the community. In that sense, BordeauxTea has amazingly granted me the opportunity to speak about OS and try my best to promote it.

Our perspective as co-hosts: As a Ph.D. course, the BordeauxTea consists of monthly sessions on various subjects inside the OS framework. The students are responsible for the presentations, followed by a discussion among the participants. Our sessions are intended to be a safe space to brainstorm new ways of doing science and meet new people. We believe that our journal club allows everyone involved to learn more and better prepare for this framework change, practice essential communication skills, and share everyday academic/research struggles, making the BordeauxTea an important space for community building.

We also recognize that our journey as BordeauxTea organizers has taught us much more than just OS. It has trained us to create, run, and manage bottom-up initiatives in a university context, communicate better with students and other parties, and network with other OS leaders and initiatives.

As highlights of 2022, alongside our student-led sessions, we held special sessions hosted by some prominent names in the OS community. Flavio Azevedo, founder of the Framework for Open and Reproducible Research Training – FORRT (10) gave us a great overview of his initiative and how it has impacted the academic community. Ai Sugiura, UNESCO's Science Programme Specialist for Science Policy and Capacity Building brought us the perspective of a worldwide organization and how OS has become a central priority in its recommendations to member states (11). Christopher Chambers, currently chair of the Registered Reports (RR) committee supported by the Center for Open Science, was virtually present (on Twitter) during the discussion part of our session on RRs, kindly answering any questions from our attendees (12). These fantastic sessions are available online on a YouTube channel kindly offered by the CNSeminars (13,14). Moreover, at the Neurocampus, we have been invited twice to lead a round-table on OS as part of the Bordeaux Summer School - Introduction to Experimental

Neuroscience and to give a presentation to fellow researchers in our team in the Institute of Neurodegenerative Diseases on the benefits of implementing OS in their research.

We are happy to contribute to this momentum in OS and grateful for having such a fantastic experience during our Ph.D. journey.

III. How is OS applied in our work routine?

As strong OS advocates, we try our best to practice it in our work.

Eduarda: OS is a core part of my work as a Ph.D. student in Bordeaux and as a research assistant in Amsterdam.

In my Ph.D., OS is present in several ways: the main goal of my thesis is to standardize data collection, analysis, and sharing while building an open-source Python pipeline to answer different neuroscientific questions; I am part of the International Neuroinformatics Coordinating Facility (INCF) working group on standardized data to learn the best practices when sharing my own data; I am co-supervised by an experienced open-source tool developer in neuroelectrophysiology, Samuel Garcia, thus having the fantastic opportunity to learn from his work and improve my open coding skills; and I recently published my first preregistration (15) for one of my Ph.D. projects. The aim of preregistering is to have a time-stamped registry of your data collection and analysis plan before the execution of the project. It delineates what was planned in advance and how the analysis deviated from the original plan. Writing my first preregistration has been enriching and allowed me to get an overview of the literature and set clear goals before executing investigations on my data. It has been a very formative experience.

In Amsterdam, as the MULTINET Lab OS leader, my job is to implement OS-related tools, coordinate a coding peer-review system, and lead an OS working group that aims to change the department's culture toward open practices. This position has allowed me to meet various OS influential figures in the Netherlands and learn how to implement this framework on lab and department-wide scales.

Finally, as a general OS enthusiast, I try to attend different OS conferences and courses and stay as close as possible to new initiatives and resources. Getting closer to OS has definitely changed my career for the better - I am very grateful I crossed paths with it.

Fjola: Open and reproducible science is a very important professional aspect for me, and I try my best to implement its principles in my everyday work. As my work mainly involves mathematical modeling, this attempt consists in producing reproducible code with detailed information (documentation) on its properties and sharing it in an open-access manner through repositories like GitHub. Practically, the script would be online, easy-to-find and free, accompanied by the respective documentation to make it understandable and easy to adapt to specific needs. Moreover, GitHub allows to create issues addressed to the code developers, contribute, track changes across time and collaborate to build a better, more efficient script.

I am fortunate that one of my Ph.D. supervisors is Nicolas P. Rougier, a leader in several OS initiatives. He has helped me progressively perfect my skills of producing open and reproducible scripts. A great article by him summarizing the main principles to keep in mind while producing scientific code is: Transforming Code into Scientific Contribution (16). A part of my work involves the replication of existing models, the code of which is not fully available or is not in an open-source programming

language. I have adapted one of these models to serve as teaching material for modeling courses and have already used it successfully for several classes. It can be found on GitHub (17).

In addition, I also try to keep in touch with the latest developments in OS by attending OS conferences and classes. Discussions with colleagues, researchers, and friends about it are always a source of joy, as I notice an ever-increasing welcoming approach.

IV. Future perspectives

We hope to see OS being discussed and implemented more in research and education. We believe that this discussion should become more mainstream and part of the training in all education/career stages. In our professional lives, we plan to continue learning more about OS and applying it as much as possible to our work. We hope you join us in this movement! Feel free to reach out and subscribe to our newsletter here: https://t.co/VuakUBwMsU.

References

1) The Open Science Training Handbook,URL https:// book.fosteropenscience.eu/. Section: Open Concepts and Principles.
2) Eduarda Centeno, Fernando Nobrega Santos, and Multi- netLab. Notebook for network and topological analysis in neuroscience, 2021. URL https://doi.org/10.5281/zenodo. 4483651.
3) Eduarda Gervini Zampieri Centeno, Giulia Moreni, Chris Vriend, Linda Douw, and Fernando Antonio No- brega Santos Santos. A hands-on tutorial on network and topological neuroscience. Brain Structure and Function, 227(3):741–762, 2022.
4) Eduarda Gervini Zampieri Centeno, Giulia Moreni, Chris Vriend, Linda Douw, and Fernando Antonio No- brega Santos Santos. A python hands-on tutorial on network and topological neuroscience. In International Conference on Geometric Science of Information, pages 665–673. Springer, 2021.
5) Fjola Hyseni, LME Blanken, R Muetzel, FC Verhulst, H Tiemeier, and T. White. Autistic traits and neuropsy- chological performance in 6- to-10-year-old children: a population-based study. Child Neuropsychol., (25(3)):352–369, 2019 Apr. doi: 10.3389/fninf.2017.00069.
6) ECG Toolbox; Github. URL https://github.com/fjolah/ECGtoolbox.
7) ReproducibiliTea. URL https://reproducibilitea.org/about/.
8) ReproducibiliTea: Open Science Journal Club. URL https://www.bordeaux-neurocampus.fr/en/reproducibilitea-open-science-journal-club/.
9) BordeauxTea. URL https://osf.io/jqxw6/wiki/Schedule-21/.
0) Framework for Open and Reproducible Research Train-ing (FORRT). URL https://forrt.org/about/us/.
1) UNESCO at the BordeauxTea. URLhttps://www.bordeaux-neurocampus.fr/event/unesco-talk-about-open-science-dr-ai-sugiura/.
2) C.D. Chambers and L. Tzavella. The past, present and future of registered reports. Nat Hum Behav 6, 29–42, 2022. doi: https://doi.org/10.1038/s41562-021-01193-7.
3) Clinical Neuroanatomy Seminars, . URL https://www.clinicalneuroanatomyseminars.com/.
4) BordeauxTea - Reproducibility and Open Science; YouTube Playlist. URL https://www. youtube.com/playlist?list=PLg2e4R8SdhpeuGmNC YpqA75rRFg81Pg-.
5) Brian A. Nosek, Charles R. Ebersole, Alexander C. DeHaven, and David T. Mellor. The preregistration revolution. Proceedings of the National Academy of Sciences, 115(11):2600–2606,

2018. doi: 10.1073/ pnas.1708274114. URL https://www.pnas.org/doi/abs/ 10.1073/pnas.1708274114.

6) Fabien C. Y. Benureau and Nicolas P. Rougier. Re-run, repeat, reproduce, reuse, replicate: Transforming code into scientific contributions. Frontiers in Neuroinformat- ics, 2018. doi: 10.1080/09297049.2018.1465543.

7) Modeling Course; Github. URL https://github.com/ bordeaux-neurocampus/WIEN2021.

Neurojoke

What does an astrocyte tell a neuron when breaking up?

Hey bro I'm sorry but from now on you have to take care of ***yourcell***

Carmen Guerrero, 2nd year of neuroscience master

Neurogame: word search

Find the 12 neurotransmitters. Words can be hidden in all directions (vertical, horizontal, and diagonal; from right to left, and from left to right).

B	C	P	L	R	N	R	Z	E	Y	A	T	P	S	A	Q	Z	N	O	B
E	A	E	G	N	I	C	O	T	Y	X	O	Q	E	N	W	X	E	Z	O
N	T	H	C	Q	R	S	Y	G	D	M	B	N	R	Y	M	C	N	A	N
I	Y	Z	P	M	H	D	L	U	T	T	I	Q	O	P	M	L	V	X	O
L	A	D	P	W	P	S	F	D	S	U	B	S	T	A	N	C	E	P	C
O	E	X	T	S	E	H	P	O	R	B	I	E	O	Q	T	W	L	Z	L
H	Q	U	P	K	N	L	T	P	T	J	D	B	N	K	A	M	Y	S	X
C	J	D	E	A	I	S	L	A	T	P	R	W	I	G	S	I	K	D	Z
L	T	O	A	W	P	U	C	M	I	S	F	O	N	H	A	G	Y	Y	C
Y	W	F	R	O	E	D	M	I	V	F	N	B	E	C	A	S	F	E	Y
T	Z	H	K	Q	R	M	R	N	W	O	D	J	U	B	E	X	D	F	R
E	V	C	U	S	O	K	C	E	K	V	U	G	A	H	V	I	M	H	E
C	U	I	Y	W	N	U	T	V	I	A	T	J	L	P	X	T	N	N	H
A	S	P	A	R	T	A	T	E	P	Q	N	I	X	O	K	Y	I	R	M
S	A	H	J	P	M	R	L	Q	G	S	J	O	C	U	Q	M	C	F	G
H	T	G	B	A	C	X	H	W	V	R	B	I	G	Y	A	D	Y	C	V
Q	W	P	T	C	N	J	A	B	D	B	R	C	E	T	E	F	L	G	W
X	G	U	H	P	N	I	Q	R	Z	T	K	O	S	F	U	W	G	X	P
J	L	I	N	M	O	M	H	Q	I	J	P	I	G	L	W	Q	Z	O	I
G	R	L	G	K	E	P	I	N	E	P	H	R	I	N	E	U	O	L	J

Solution to the neurogame

B	C	P	L	R	N	R	Z	E	Y	A	T	P	S	A	Q	Z	N	O	B
E	A	E	G	N	I	C	O	T	Y	X	O	Q	E	N	W	X	E	Z	O
N	T	H	C	Q	R	S	Y	G	D	M	B	N	R	Y	M	C	N	A	N
I	Y	Z	P	M	H	D	L	U	T	T	I	Q	O	P	M	L	V	X	O
L	A	D	P	W	P	S	F	D	S	U	B	S	T	A	N	C	E	P	C
O	E	X	T	S	E	H	P	O	R	B	I	E	O	Q	T	W	L	Z	L
H	Q	U	P	K	N	L	T	P	T	J	D	B	N	K	A	M	Y	S	X
C	J	D	E	A	I	S	L	A	T	P	R	W	I	G	S	I	K	D	Z
L	T	O	A	W	P	U	C	M	I	S	F	O	N	H	A	G	Y	Y	C
Y	W	F	R	O	E	D	M	I	V	F	N	B	E	C	A	S	F	E	Y
T	Z	H	K	Q	R	M	R	N	W	O	D	J	U	B	E	X	D	F	R
E	V	C	U	S	O	K	C	E	K	V	U	G	A	H	V	I	M	H	E
C	U	I	Y	W	N	U	T	V	I	A	T	J	L	P	X	T	N	N	H
A	S	P	A	R	T	A	T	E	P	Q	N	I	X	O	K	Y	I	R	M
S	A	H	J	P	M	R	L	Q	G	S	J	O	C	U	Q	M	C	F	G
H	T	G	B	A	C	X	H	W	V	R	B	I	G	Y	A	D	Y	C	V
Q	W	P	T	C	N	J	A	B	D	B	R	C	E	T	E	F	L	G	W
X	G	U	H	P	N	I	Q	R	Z	T	K	O	S	F	U	W	G	X	P
J	L	I	N	M	O	M	H	Q	I	J	P	I	G	L	W	Q	Z	O	I
G	R	L	G	K	E	P	I	N	E	P	H	R	I	N	E	U	O	L	J

Editorial board

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree in Neurosciences, Juan is now pursuing a PhD at the University of Bordeaux, France. His PhD focuses on the role of lactate in basal synaptic transmission, which allows him to combine his research interests in biochemistry, electrophysiology and neurometabolics. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Sara Carracedo

Sara is not only a PhD student at the Neurodegénératives Diseases Institute (IMN), but also works as a marketing manager in a 4BioDx startup. She comes from Pontevedra, Spain and holds a Veterinary Bachelor's degree from the University of Santiago de Compostela, Spain and she did the International Master of Neuroscience in Bordeaux. Her PhD is focused on understanding the role of P2X4 receptor in ALS pathogenesis and biomarker where she is interested in neuroinflammation and receptor trafficking.

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the International Master of Neuroscience from Bordeaux. He is a PhD student studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses from which one can guess that his interests lie in memory, synaptic communication and the hippocampus. He also runs a blog "Astrocytes et traumatismes crâniens juvéniles".

Khadija Inam

Khadija is a Pakistani student currently pursuing a training as a Clinical Research Associate at the University of Bordeaux. She graduated with a Bachelor's degree in Applied Biosciences from the National University of Sciences and Technology, and later the NeuroBIM Master's degree in Neurosciences from the University of Bordeaux. Her research interests are in the scope of pharmacology and neurological disorders.

Louise Eygret

Born in Gien, France, Louise did her Bachelor's in Life Sciences followed by the NeuroBIM Master's in Neurosciences. Currently, she is pursuing a PhD focused on the neural substrates underlying odor modulation of food intake regulating neuronal circuits. Her research interests are primarily in nutrition, olfaction and hypothalamus.

How can you participate?

Brainstorm, a journal by students and for students

Are you a MSc or a PhD student in neuroscience? Then you are more than welcome to participate in our journal.

You can write either a short-review on a topic of your choice, or a one-page letter (a reflection, a project or an insight you would like to share with the scientific community), a dissemination article about clinical neuroscience (neurodegeneration, neurodevelopmental disorders, psychiatric disorders…) with the aim to reach a more general public, or a neurojoke.

Don't start to worry, you won't be alone! You will work hand-by-hand with our editors and we will send you guidelines and a template to make your life easier. Perhaps you would like to know that the best review will get a special prize by June 2023.

If writing is not your thing and you prefer to express yourself through art, we have a place for you too! For each issue we recruit an artist to design the cover page illustration. And remember that microscopic images are also a form of art!

Wanna be part of the next issue?

Reach us at brainstorm.sci.journal@gmail.com

Wanna be part of the next issue?

Reach us at

brainstorm.sci.journal@gmail.com