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Peer Review

Review of: "Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry"

Jan Pieter Konsman[1]

1. CNRS UMR 5164 ImmunoConcept, University of Bordeaux, Bordeaux, France

The review by Talero-Lopez “Infectious vs. Sterile Neuroinflammation: Differential Consequences on Neuronal Circuitry” develops an interesting and useful distinction between forms of neuroinflammation. While I quite appreciate that effort, I think the manuscript can be improved further by 1) including definitions of neuroinflammation from authors who are somewhat critical of the notion, 2) considering the CNS site as an important factor in how neuroinflammation affects neuronal circuits, and 3) linking the context-dependency of neuroinflammation to the immune privileged status of the CNS (which refers to the particular ways in which immune responses occur in the CNS, not to their absence). In addition, I think it would be helpful for future readers 1) to provide concrete clinical or veterinary examples of infections affecting the CNS and 2) to focus on one distinction in neuroinflammation and to develop this (either infectious vs. sterile neuroinflammation or acute vs. chronic neuroinflammation. In the present version, there seems to be a shift from the former to the latter, which may reflect the author’s evolution but may be confusing for the reader). In my mind, these and other points, detailed below, need to be addressed to improve the manuscript.

Detailed points of criticism

1. Introduction, page 2: “Neuroinflammation refers to the context-dependent immune response that arises within the central nervous system (CNS) in response to disturbances of homeostasis, including infection, trauma, ischemia, or neurodegeneration. This response is primarily mediated by resident immunocompetent cells, such as microglia and astrocytes, and, under specific conditions, by infiltrating peripheral immune cells, and is characterized by the production of inflammatory mediators that can modulate neuronal and synaptic function.[1][2][3][4].” Besides citing only work that has embraced the notion of neuroinflammation, I think it could help make the

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author's case to include more critical voices and previous distinctions like those of Estes and McAllister (Brain Pathol., 2014), Schwartz and Deczkowska (Trends Immunol., 2016) and of Masgrau and colleagues (Trends Mol. Med., 2017). Please include.

2. Introduction, page 2: "The classical conception of the CNS as a strictly immune-privileged compartment has been substantially revised. Although access of peripheral immune cells remains highly regulated, the discovery of meningeal lymphatic vessels and resident immune cell populations at the CNS borders has redefined immune privilege as a state of active regulation rather than an absence of immune activity. [5][6][7]." I think this is a conceptually inaccurate way of framing things. First of all, immune privilege refers metaphorically to the special status of diplomates. Second, the translation of immune privilege to 'deprived of immune responses' was only true for adaptive immune responses when Medawar first coined the term (see Konsman, Neuroimmunomodulation, 2026). Third, the rediscovery of meningeal lymphatics is simply not relevant because the immune-privileged status concerns the brain parenchyma and not the meninges, where full-blown immune responses have long been known to occur. Please, modify accordingly.
3. Throughout the manuscript, I think it would be important to include CNS site as an important factor in determining contextual neuroinflammatory responses. This remark is, in part, inspired by the point just made. There are now many papers indicating that one cannot reach general conclusions regarding immune responses for the whole CNS and that, instead, different compartments need to be distinguished (see Andersson et al., Neuroscience, 1992; Galea et al., Trends Immunol., 2007; Konsman, Neuroimmunomodulation, 2026). In addition, astrocytes and microglia are known to respond differently as a function of their anatomical site in the CNS. Finally, neuronal responses are known to differ by CNS site, already because the excitatory/inhibitory difference balance differs widely between circuits. Please, add and modify the manuscript taking into account CNS site.
4. Introduction, page 3: "Infectious neuroinflammation, driven by the recognition of PAMPs, is typically associated with rapid and transient immune responses, whereas sterile neuroinflammation, triggered by DAMPs released following stress or tissue injury, tends to involve sustained glial activation in the absence of pathogens." Please, provide references backing up these general statements.
5. Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits, page 3: "Circuit dysfunction is therefore defined as alterations in the activity, connectivity, and information processing of neuronal networks in the absence of overt structural damage, such as neuronal loss or

macroscopic lesions.[15][16]" This, to me, seems like a definition that is too broad and encompassing, as I have the feeling that it will include changes associated with learning, which are typically considered functional. Please, add a more elaborate discussion of function and dysfunction regarding the CNS and provide a better-argued definition of circuit dysfunction based on that.

6. Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits, page 4: "Within this framework, neuroinflammation emerges as a central modulator of circuit-level functional dysfunction. Immune signals derived from microglia, astrocytes, and, in certain contexts, peripheral immune cells alter neuronal excitability, synaptic transmission, and plasticity without necessarily inducing cell death.[10][12][15][17][19] Proinflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNFα) modulate synaptic receptors, glutamatergic and GABAergic neurotransmission, and mechanisms of long-term potentiation (LTP), thereby disrupting E/I balance at the circuit level. [15][17][19][20][21]" Here, I think it is important that the author acknowledges that cytokines in the brain do not always play a role in inflammation and that inflammation can be physiologically relevant and is not necessarily associated with dysfunction. Indeed, in the hippocampus, cytokines like IL-1 beta seem to be produced by and act on neurons and can modulate LTP. This neuromodulatory role of IL-1 beta does not seem to have much to do with the role of this cytokine in (neuro)inflammation. Please, acknowledge this possibility and modify the manuscript accordingly.
7. Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits, page 4: "The existence of neuronal circuits sensitive to immune signals is supported by the identification of neuronal populations that express specific receptors, such as IL-1R1, enabling them to respond to cytokines through non–cell-autonomous transcriptional programs. [12][15][20] These circuits constitute the neural substrate of sensory, affective, and cognitive symptoms induced by immune activation, even in the absence of central structural damage, and are integrated into specific functional neuroimmune axes —such as brain–skin circuits in atopic dermatitis and psoriasis—that can perpetuate pathological states through circuit–immunity feedback loops. [22][23]". First of all, I think readers would need some introduction on "non–cell-autonomous transcriptional programs". Second, I think this would be a good place to introduce and discuss sickness behavior (which now only appears much later), also because these behavioral changes have been proposed to be adaptive. Please, add these elements to the manuscript.
8. Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits, page 6: "IL-1β regulates synaptic plasticity in a concentration-dependent manner, suppressing long-term

potentiation (LTP) at elevated levels and impairing learning and memory processes. These effects are mediated through activation of p38 MAPK, interference with brain-derived neurotrophic factor (BDNF) signaling, and epigenetic mechanisms that repress gene programs associated with plasticity. [49][43][44][48][50] Neuronal expression of IL-1R1 delineates circuits that are specifically sensitive to immune signals, providing a direct link between inflammation and cognitive, affective, and sensory alterations. [20]". Please, specify that this frequently concerns the role of neuronally produced IL-1 beta and may therefore not have much to do with neuroinflammation. Please, also indicate that there may be important species differences in neuronal expression of IL-1R1.

9. Throughout the manuscript and Functional Framework: Neuroinflammation, Glia, and Modulation of Neuronal Circuits, page 6: "Whereas acute inflammation typically induces reversible functional changes, chronic inflammation stabilizes maladaptive plasticity states through transcriptional and epigenetic modifications, perpetuating circuit dysfunction even after resolution of the initial stimulus. [21][30][44][48][50]" Please, specify how acute and chronic inflammation can be distinguished in this manuscript beyond reversible and maladaptive changes.
10. Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence, page 7: "Among TLRs, TLR2, TLR3, TLR4, and TLR9 recognize specific bacterial or viral motifs, whereas some of these receptors—particularly TLR4—also respond to endogenous signals and noninfectious stress stimuli, acting as contextual sensors rather than exclusively pathogen-specific detectors. [29][52][53][54]" Please provide some examples of those endogenous signals.
11. Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence, page 11: "These alterations include slowing of gamma oscillations, emergence of beta-band activity, and episodes of neuronal hyperexcitability, even in the absence of neuronal death. [52][53]" Please, include a discussion of the role of cytokines in the regulation of sleep.
12. Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence, page 12: "Episodes of acute, self-limited neuroinflammation—whether infectious or sterile—induce transient alterations in synaptic plasticity, reversible E/I imbalance, and short-term cognitive deficits that tend to resolve following the restoration of glial and neuronal homeostatic programs. [1][43][83][84][85][86][87]" Please, explain to the reader what "self-limited neuroinflammation" refers to.
13. Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence, page 12: "In contrast, sustained or unresolved neuroinflammation, whether driven by persistent infection, ongoing sterile injury, or chronic pathology, is associated with long-lasting synaptic

dysfunction, maladaptive plasticity, and persistent E/I imbalance that progresses toward circuit disconnection and neurodegeneration. [1][43][83][87] This qualitative shift is linked to prolonged exposure to proinflammatory cytokines such as IL-1β, TNFα, and IL-6, sustained activation of microglia and astrocytes, and persistent engagement of inflammatory pathways such as the NLRP3 inflammasome. [83]" Here I have the feeling that one is witnessing a shift from infectious vs. sterile neuroinflammation to acute vs. chronic neuroinflammation. As I feel this may be confusing for the reader, I would recommend using the latter distinction as the potential explanatory principle throughout the manuscript. Please modify the manuscript accordingly.

14. Infectious vs. Sterile Neuroinflammation: Functional Convergence and Contextual Divergence, page 15: "Autonomic circuits, particularly vagal and cholinergic pathways of the brainstem, exert a context dependent descending modulation of the immune response during neuroinflammation. Through the inflammatory reflex, afferent signals derived from infection or tissue damage are integrated at the brainstem level and translated into a cholinergic efferent output that suppresses peripheral cytokine release via activation of α7 nicotinic receptors on immune cells. [104][105][106]". To use of the term "inflammatory reflex" is misleading because there is no simple neuronal circuit in the spinal cord or brainstem mediating this. Please, modify phrasing.

Throughout the manuscript, please provide more concrete (not LPS or viral fragments) examples of infectious neuroinflammation. In addition, it is important to specify better what happens after LPS administration as a model. In fact, LPS, when administered systemically as a model of bacterial sepsis, may reflect a case of sterile neuroinflammation secondary to systemic inflammation, as the CNS parenchyma is frequently not affected in terms of LPS detection. Please add and specify.

Declarations

Potential competing interests: No potential competing interests to declare.