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*Editorial*

# Astrocyte Syncytium—A Biopower Grid System in the Brain

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Astrocytes populate the entire central nervous system (CNS) and exhibit a remarkable architectural feature: they form a syncytial network through gap junctions. Arguably, astrocytes establish the largest, and potentially the only, organ-wide syncytial network among other syncytial systems in animals, namely, in cardiac muscle and in smooth muscle in the intestines, digestive tracts, and vasculatures. With gap-junctional coupling extending from astrocytes to oligodendrocytes and ependymal cells, this glial syncytium expands further into a more intricate astrocyte-oligodendrocyte-ependyma syncytium, extending to the border region of the CNS and intertwining with every CNS constituent within parenchyma. In this sense, a functional glial reticular system co-exists with the synaptically connected neuronal circuits in the brain [1]. The extensive electrical coupling aggregates astrocytes into an isopotential syncytium. The structural characteristics and operation of the astrocyte syncytium in many ways are analogous to those of an industrial power grid (See Fig. 1). We here discuss the functional implication of this biopower grid, or astro-grid, in the brain and the potential extension of the astro-grid into a broad syncytium that contains not only astrocytes but oligodendrocytes and ependymal cells. Future validation of this notion would conceptually advance our understanding of the glial reticular system in normal brain function and disease pathology.

## 1. Astrocyte-Oligodendrocyte-Ependyma Syncytium in the Brain

Astrocytes, oligodendrocytes, and ependymal cells all have their well-defined roles in the brain [2]. Aggregating these functionally distinct glial subtypes into a uniform syncytium leads to a curious question regarding the functional purpose of this biological design, leaving us to ponder what unique functions this multi-glia network could bestow on the brain that we have yet to appreciate. Broadly speaking, the gap-junction coupling permits adjacent cells to exchange ions, metabolites, and second messengers for the coordination of cellular metabolism and function [3]. Accordingly, a commonly recognized function of astrocyte syncytial coupling is the buffering of disturbed extracellular potassium ($K^+$) ions and the redistribution of metabolites in response to heightened regional neuronal activity. Questions that perhaps deserve more attention in future studies are (a) how the multi-glia syncytium serves as a platform for the convergence of signals from the interstitial environment, myelin sheets, and the ventricular cerebral spinal fluid (CSF), and (b) how the syncytium, in turn, processes those signals and uses them to direct basic and advanced brain functions. Although the existence of a multi-glia syncytial network is recognized [2], much of the structural details still need to be characterized, and more exploratory studies are needed to understand precisely how this system participates in brain homeostasis and information processing.

## 2. Does the Coupling of Astrocyte-Oligodendrocyte-Ependyma Form an Isopotential Syncytium?

One of the breakthroughs in knowledge of the mysterious astrocyte syncytium is the identification of the electrical role of gap-junctional coupling among astrocytes. The intricacies of the structural underpinnings of this glial network are astonishing to say the least. To start, structurally speaking, the terminal astrocytic processes are nanoscopic structures, like high electrical resistance cables, and the astrocyte-astrocyte contacts are exclusively made at their interfaces (see Fig. 1). However, the electrical coupling appears to be counterintuitively strong with an interastrocytic resistance of 4.2 MΩ [3,4], resulting in a phenomenon termed "syncytial isopotentiality" [5], which means that syncytially coupled astrocytes tend to equalize their membrane potentials to comparable levels. This astrocyte-network feature exists among diverse subtypes of astrocytes from protoplasmic astrocytes in the hippocampus, cortex, and spinal cord, to white-matter fibrous astrocytes in the corpus callosum, to specialized velate astrocytes and Bergmann glia in the cerebellum, therefore, emerging as a system-wide feature of astrocytes in the brain [6–8].

Mechanistically, syncytial isopotentiality was posited to be a requisite for the operation of the so-called $K^+$ spatial buffering hypothesis [5]. Indeed, syncytial isopotentiality has been experimentally demonstrated as a required driving force for $K^+$ uptake at brain regions with elevated neuronal activity [5]. By extension, syncytial isopotentiality is also required for the operation of variously expressed sodium ($Na^+$)-dependent transporter systems [2].

Additionally, the strength of syncytial isopotentiality differs substantially in different brain regions. For example, compared to the hippocampus, the strength of syncy-

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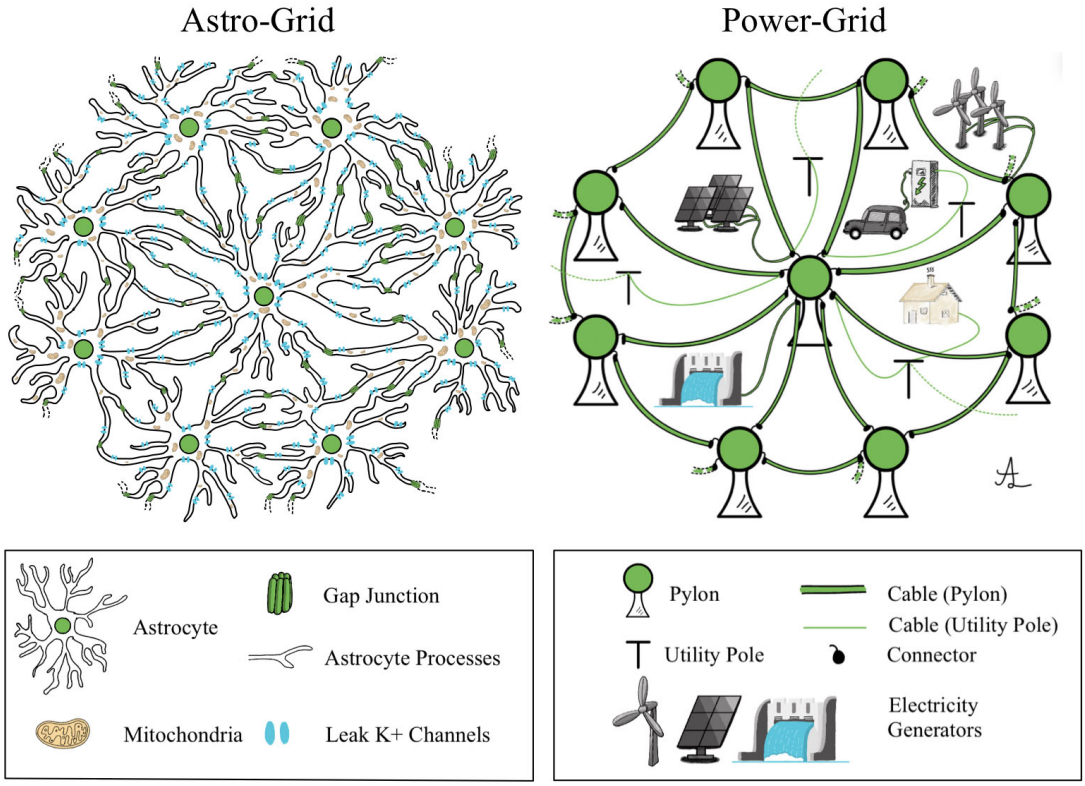


**Fig. 1. Astro-grid in the brain is analogous to an industrial power grid.** Left: astrocytes in an isopotential syncytium, or astro-grid. Right: an industrial power grid system. The similarity of running and maintaining an isopotentiality in both systems make the astro-grid analogous to the industrial power grid. The structural similarities between the cables, connectors, and electricity generators in a power grid and astrocyte processes, gap junctions, mitochondria/$K^+$ channels in an astro-grid, respectively, are illustrated. $K^+$, potassium ions.

tial isopotentiality in the visual, sensory, and motor cortical regions is about 3.5- to 7.6-fold stronger. The neuronal circuits likewise vary across different brain regions [6]. However, little is known about how the activity of local neuronal circuits define and regulate the strength of syncytial coupling. Nevertheless, with our current knowledge it is at least conceivable that the dynamic regulation of astrocyte electrical coupling can occur at the molecular, cellular, and spatial-organization levels. For example, at the molecular level, syncytial coupling can be regulated by varying the number of gap junctions deployed at astrocyte-astrocyte interfaces [3], and the capacity of syncytial isopotentiality can be regulated by varying expression of leak $K^+$ channels on individual astrocytes [9] (See Fig. 1). The astrocyte density and interastrocytic distance are also determinants of the strength of syncytial coupling [10]. Overall, astrocytes make use of these variables, either individually or together, to regulate the strength of syncytial isopotentiality, in order to accommodate the structural and functional needs of the local neuronal circuit.

In regard to an extended multi-glia syncytium, astrocytes use connexin43 (Cx43), and to a lesser extent Cx30 and Cx26, to form a syncytium. Ependymal cells also use Cx43 to aggregate into a syncytium. The ependymal Cx43 mostly forms homotopical Cx43:Cx43 gap-junction coupling with astrocytes [11]. Additionally, ependymal cells express $K_{ir}4.1$, which creates a hyperpolarized membrane potential comparable to that of astrocytes [12]. As such, ependymal cells are functionally analogous to astrocytes, making them favorable candidates in an isopotential network with astrocytes. As for oligodendrocytes, they use Cx47 and Cx32 to establish heterotypic gap-junctional coupling with astrocytes, termed “panglial networks” [13], but we still do not know whether the gap-junctional coupling functionally includes oligodendrocytes in a shared isopotential network with astrocytes and ependymal cells. We are curious to know whether the electrical coupling of heterotypic gap junctions, e.g., Cx43 (astro):Cx47 (oligo), or Cx43 (astro):Cx32 (oligo), are strong enough to generate an isopotential panglial syncytium. If the multi-glia syncytium is indeed an isopotential reticular system, our conceptual understanding of the brain homeostatic system should expand into a syncytium including not only astrocytes but oligodendrocytes and ependymal cells. Physiologically, such a glial reticular system would cover and regulate brain homeostasis with an even broader scope.

## 3. Astrocyte Syncytium—A Biopower Grid in the Brain

The operation of an astrocyte syncytium, as mentioned, in many ways resembles the industrial power grid system. A key shared characteristic leading to this comparison is the isopotential running on both systems (see Fig. 1). The power grid is vital for our daily life and the economy of our society. Likewise, the astrocyte syncytium, an "astro-grid" in the brain, is vital for maintaining an optimal biochemical and electrical environment in the brain. Astrocyte processes are cable-like elements in a power grid, and gap junctions are connectors that wire these "cables" into an astro-grid (see Fig. 1). In the astro-grid, the leak $K^+$ channels, such as $K_{ir}4.1$, are electricity generators. Placing astrocyte $K^+$ channels into this perspective explains the need for such an abundant expression of leak $K^+$ channels by astrocytes, i.e., not only do the $K^+$ channels make the astrocyte membrane highly permeable to $K^+$ ions, but they also generate a high capacity of hyperpolarized membrane (or battery) potential in individual astrocytes in order to establish and steadily control the isopotentiality in the astrocyte network [9]. There is increasing evidence for a dense mitochondria network in astrocytes [4] (see Fig. 1), which implies a substantial energy demand to maintain $K^+$ and $Na^+$ gradients, which, in turn, maintain the isopotentiality in the astro-grid. A major difference between the industrial power grid and astro-grid is the output of electricity. For the industrial power grid, the design purpose is for the generation and transportation of electricity to the customers, whereas in the astro-grid, the electricity is consumed by astrocytes for the homeostatic regulation of the interstitial environment.

An important question to be examined in the future is how pathological conditions affect the astro-grid in the brain, and how alterations in the astro-grid, in turn, contribute either as causes or contributing factors in neurological disorders. For example, chronic stress in an animal model of depression impairs the structure of "cables", i.e., causes atrophy in astrocytic processes, and functionally disrupts the network isopotentiality in mouse prefrontal cortex and hippocampus [14]. In an experiment in which microglia were ablated by inhibition of microglia colony stimulating factor 1 receptor (CSF1R) receptors, astrocyte syncytial isopotentiality was disrupted due to the loss of Cx43 and Cx30, and this was associated with weakened synaptic transmission [15]. Despite the astrocyte syncytium emerging as a new perspective for examining the role of astrocytes in neurological diseases, this remains a new research area requiring further investigation. Likewise, there is an urgent need to validate the existence of a multi-glia astrocyte-oligodendrocyte-ependyma isopotential syncytium and to consider this reticular system holistically in future neuropathology studies.

## Author Contributions

ZAL conducted literature review, conceptualized, and wrote the manuscript and created illustration. MZ conceptualized and designed the study, designed the figure and performed literature search. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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