In the new ‘peering’ based study of Schuppli and van Schaik [8], and the challenge of its conclusions, we may be seeing a significant leap in our efforts to capture the true scope of ape culture. The underlying approach may significantly extend the methods applied to study social learning research in the future, in a variety of species other than apes.

REFERENCES


Glia: A Gate Controlling Animal Behavior?

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Although glia are known to have the potential to alter neuronal activity, their behavioral relevance is not well understood. A recent study has discovered that, when zebrafish give up on performing a visuo-motor task, glia integrate information from neuromodulatory neurons to stop motor output.

The word ‘glia’ is derived from the ancient Greek word γλία for glue, as glial cells were initially discovered in the search for connective tissue in the brain [1]. Glia are non-neuronal cells of the nervous system and the term covers astrocytes, oligodendrocytes, oligodendrocyte progenitor cells, ependymal cells, radial glial cells and microglial cells (the macrophages of the CNS which enter from the periphery). There are at least as many, if not more, glial cells than neurons in the brain, yet their importance has long been underappreciated, glia being overshadowed by their glamorous, more electrically-excitable neighbours. Modern neuroscience has, however, revealed a diversity of crucial functions for glia, which intimately communicate with neurons to ensure the development, maintenance, and function of the brain. For example, oligodendrocytes build the myelin sheaths that surround axons of specific neurons to modulate conduction properties, and can do so in an activity-dependent manner [2]. Oligodendrocyte progenitor cells are excitable cells [3]. Microglia shape the migration of inhibitory neurons in the brain during development [4], thereby influencing the critical excitation–inhibition balance in the cortex, and have also been implicated in synaptic pruning during the refinement period of neural circuit formation. Astrocytes contribute to many
aspects of brain metabolism and homeostasis, regulating extracellular composition, bridging neuronal to vascular structures and generating various regulatory signals that can impact neuronal activity.

There is particular excitement over the idea that glia may participate directly in information processing via calcium-dependent release of neurotransmitters onto neurons [5,6]. This phenomenon, known as gliotransmission, was initially observed in vitro [7]; subsequent studies have vastly complicated the picture and the existence of gliotransmission under physiological conditions is hotly debated [8,9]. Vesicular gliotransmission is not the only means by which glia might influence the activity of neurons, and there could be other mechanisms of glia–neuron communication, for example via rapid regulation of extracellular ion composition [10,11]. Despite numerous evidence that astrocytes can modulate the activity of neurons and synaptic plasticity in vivo, their actual contribution to behavior has remained elusive. A recent study by Mu et al. [12] has now provided a novel model system for exploring the role of astrocytes in the regulation of behavior.

Mu et al. [12] took advantage of the reliable optomotor response of zebrafish larvae, an important reflex that enables the fish to maintain position when drifting in a current. When subjected to a moving grating, head-embedded larvae will repeat swim bouts to follow and match the optical flow [13]. When performing consecutive futile behavioral responses without achieving its goal of compensating for the virtual drift, a zebrafish larva will eventually become passive and stop responding to the moving grating (Figure 1A). Using whole-brain calcium imaging in pan-neuronal and pan-glial transgenic zebrafish lines, the authors investigated how radial astrocytes and neurons operate together in the zebrafish brain to implement passivity after behavioural failures.

Mu et al. [12] discovered that this transition of a zebrafish larva from activity to passivity involves a previously unknown mismatch signal which encodes swim failures in noradrenergic neurons of the medulla oblongata. The simultaneous imaging of neurons and radial astrocytes during this transition led to a surprising discovery of a large, gradually-increasing calcium surge in glial cells with processes in the lateral medulla oblongata, which become strongly activated after futile swim attempts (Figure 1B). The authors then performed an exhaustive series of activation, ablation, and inhibition experiments targeting radial astrocytes to show that the activity of radial astrocytes is necessary and sufficient to precipitate epochs of passivity.

It has been previously shown in mammals that astrocytes receive inputs...
from noradrenergic neurons [14]. The study of Mu et al. [12] is remarkable in providing a neural basis for the detection of failed behaviors and the implementation of subsequent passivity. The authors were able to show that the recruitment of noradrenergic neurons in the medulla oblongata precedes that of the radial astrocytes. Critically, the activity of noradrenergic neurons is greatest when there is a mismatch between swim intensity and perceived visual feedback — the authors therefore suggest these neurons essentially act as failure detectors. A similar set of activation and ablation experiments directed against these neurons established that these neurons modulate radial astrocytes. But how do these radial astrocytes modulate the motor output? The authors identified a population of GABAergic neurons in the lateral medulla oblongata that are activated when the fish switches from active to passive states, or following optogenetic stimulation of radial astrocytes, and in turn, when activated, these inhibitory neurons reduce locomotion.

Prior to the work of Mu et al. [12], there had been few in vivo studies linking glia to the activity of neuromodulatory circuits underlying behavioral states [15]. The new study [12] is thorough and should inspire the field of communication between neurons and glia, by showing how a complex neuro-glial network can stop motor output in case of repeated failures in vivo. This original work also raises numerous questions. For example, what is the nature of the glial cells that mediate the process of giving up? Radial astrocytes or astroglial cells in the fish brain have features of both mammalian astrocytes with bushy processes and radial glia as they bear a radial process emanating from the soma [16,17]. The term astroglia has been used to encompass both radial glia and astrocytes [18]. In fish, these cells appear not to have specialized into two cell types. The fish astroglia may be similar in nature to Bergmann glia, with astrocytic function but a more radial morphology; although more efforts including RNA sequencing analysis will be required to comprehensively characterize this cell type in fish, it is clear that they share many features with mammalian astrocytes, including responsiveness to noradrenaline [14].

What are the mechanisms associated with the calcium surge in radial astrocytes? And what are the mechanisms induced by the optogenetic activation or silencing of radial astrocytes? The activation of the opsins that mediate optogenetic control of glia will most likely fill the cell with cations, depolarizing astrocytes and reversal of neurotransmitter transporters and changes in homeostasis. Activation of a sparsely-expressed TRPV1 channel in ~1% of radial astrocytes also triggers a calcium wave, suggesting that glial network can intrinsically support the spread of calcium through currently unknown mechanisms, possibly via gap junctions or other glia-to-glia communication pathways.

What are the underlying mechanisms to modulate the activity of GABAergic interneurons? Mu et al. [12] have not investigated the mechanisms underlying the modulation by glia of inhibitory neurons, but they propose two possibilities based on previous studies in the field: release of neurotransmitters (ATP, GABA, glutamate, D-serine); or modulation of ion concentrations in the extracellular matrix. Further work will need to focus on these possibilities by genetically disrupting intracellular calcium release or vesicular fusion in glia [19] and recording from the GABAergic neurons in the lateral medulla oblongata that are modulated by radial astrocytes. By showing the behavioral relevance of the recruitment of glia in a small vertebrate brain and its complex interplay with neuronal activity from neuromodulator centers, the study of Mu et al. [12] is an elegant and original dissection of a glio-neural circuit affecting the crucial decision to give up when facing an overwhelming task. Inspired by this result, future studies should investigate whether similar communication between astrocytes, neuromodulatory and inhibitory neurons may occur during fatigue and failures in the mammalian brain [20].

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