Characteristics of Primary Cilia in Neuronal Circuit in Human Cerebral Cortex

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Introduction

Primary cilia are microtubule-based sensory organelles present in the majority of mammalian cells, including cerebral cortical neurons (Liu et al., 2021). These antennae-like structures play an essential role in the development, connectivity, and function of the human central nervous system. It is found that dysfunction of primary cilia contributes to the pathophysiology of several neuronal circuit discorders, including intellectual disabilities, epilepsy, and psychiatric disorders. (Liu et al., 2021).

To evaluate potential influence of neuronal primary cilia in patterned neural circuits, we focused on a new class of fusiform projection neurons identified in layer 5 and 6 of human cerebral cortex. These neurons have a large apical dendrite, characteristic of pyramidal neurons, but they also have a large basal dendrite that projected horizontally within the layer. Depending on the individual fusiform neuron, these basal dendrites project in opposing directions (forward-going or reverse-going) orthogonal to the pia to white matter orientation of the cortical volume. Axonal input to these neurons is biased towards neurons with similar basal dendrite orientation (i.e., axons tend to choose pairs of neurons with similar basal dendrite orientation). Further, these two groups of neurons are distributed in radial clumps of ~250µm width. We examined if any of the specific circuit organization inherent to these deep layer fusiform neurons scale with the characteristic of primary cilia in these neurons, in particular we want to examine if primary cilium position and orientation correlates with dendrite orientation, if connected fusiform neurons with opposing basal dendrite orientation preferentially share a common set of ciliary connections, or if radial patches of similarly oriented fusiform neurons share common ciliary connection patterns.

Result

We detected: (1) Radial organization of distinct groups of fusiform neurons (Fig. 1), (2) cilia in connected pairs of fusiform neurons (Fig. 2), and (3) cilia of connected fusiform neurons have common cellular links (Fig. 3).

Fig. 1 Cortical circuit fusiform neurons in opposite direction in alternative pattern

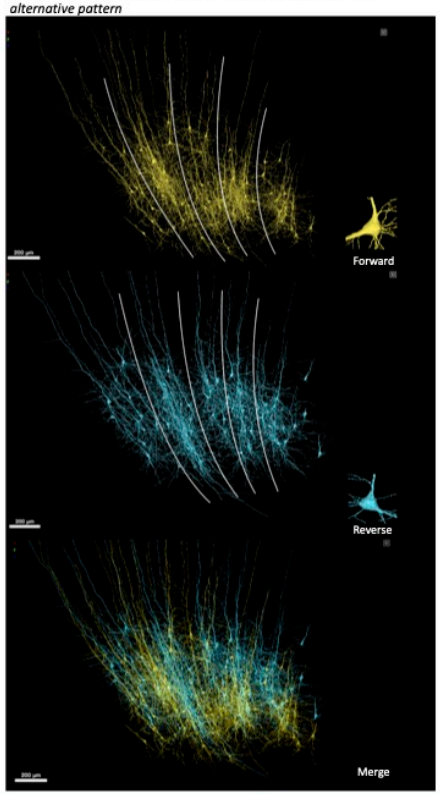


Fig. 2 Cilia on the connected pairs of fusiform neuron

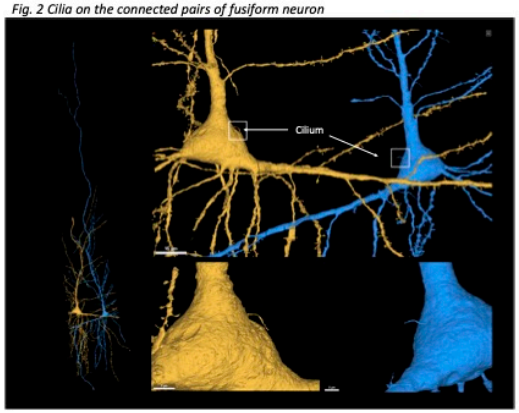
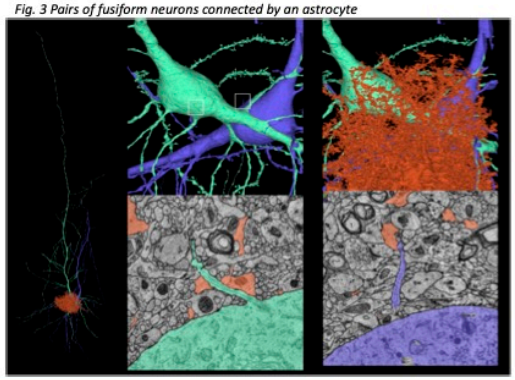


Fig. 3 Pairs of fusiform neurons connected by an astrocyte



Discussion

Primary cilium, although only one-thousandth of the volume of the soma, works to hyper-concentrate the neuronal signals within its unique structure. Furthermore, primary cilia could function as a non-synaptic signaling tool to help shape and refine the neuronal network. Primary cilia may play a significant role in the circuit-level neuronal regulation in response to environmental signals. Primary cilia in essence may help create small, local modulatory signaling ensembles within a larger neuronal circuit subserving specific cortical functions (Liu et al., 2021). Further characterization of the specific fusiform neuronal circuits we describe here may help define how primary cilia signaling sculpts neuronal circuit dynamics.

Acknowledgements

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References

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Methods

1. Measurement of Cilia Length and Orientation

Cilia length is recorded in µm with one estimated decimal place. The orientation is described by forward/reverse, towards pia matter/white matter, with numerical record of angle related to main apical, basal dendrites and axon. Position of cilium in the neuron is also quantified.

2. Circuits of cells contacted by the cilia of paired neurons

On the EM side, we select all the cells that are in membranal contact with the cilium. We will examine (1) if cell pairs that are connected make contacts with a common set of cells, (2) if they have similar patterns of connectivity in terms of composition of cells/cell parts they are contacting (3) the number of synaptic connection between pairs

3. Synaptic contact

The number of synaptic contacts and types (mainly excitatory?) between the two cells in a pair will be recorded.

4. Cilia and circuit organization radial clumps of fusiform neurons

The cells in the same set tend to locate close to each other and form radial clumps of ~250mm width. It is hypothesized that clusters of cells of same orientation tend to receive preferential signals, which will also be measured by looking at the above three measurements in cells belonging to the same clump. We will define (1) if neuronal cilia in these radial clumps tend to connect to common set of cells, (2) if neuronal cilia in a specific clump are oriented in a comparable directions, (3) if neuronal cilia in a specific clump have similar lengths and complexity (smooth/beaded), and (4) if the neurons in a specific clump are connected by common neurons such as chandelier cells.