ABSTRACT

Neuronal primary cilia are sensory organelles that respond to extracellular signals critical for neurodevelopment and cortical organization. Disruption in the function of primary cilia in the human brain can lead to disrupted circuit formation and connectivity, manifesting in neurological deficits, intellectual disabilities, psychiatric disorders, and epilepsy. These effects suggest that primary cilia have a fundamental role in shaping neural connections in the cerebral cortex. To understand how this may occur, we comprehensively mapped the interactions of neuronal primary cilia in the human cortical connectome using a serial EM and 3D reconstruction of a whole human cerebral cortex. The primary cilia of interneurons and pyramidal neurons in all 6 cortical layers were analyzed. Structurally, we found neuronal and layer-type differences in the length, orientation, and location of primary cilia. Each neuronal cilium also made local and unique patterns of contacts depending on its layer location and neuron type; the primary cilia of interneurons contact an average of 36 other cortical cells, while the primary cilia of pyramidal neurons contact an average of 42 cells. Interneuronal cilia contacted both interneurons and pyramidal neurons almost equally, whereas pyramidal neuronal cilia preferred to form contacts with other pyramidal neurons. Primary cilia also made more membrane contacts with axons than dendrites and contacted neurons more than glial cells. Importantly, neuronal primary cilia make gap junction-like contacts with other cells and are components of excitatory and inhibitory synapses. This diversity in the neuronal primary cilia connectome may underlie their ability to appropriately modulate neuronal circuit function in health and disease.