Medicine, Drug discovery

Revealing the neuropathology of ASD based on circuit formation processes in the cerebral neocortex

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Abstract

The cerebral neocortex consists of multiple functional areas with distinct functions, which are connected via direct neuronal connection called association projections. Long association projections, which connect the two areas residing in different cortical lobes, are thought to be involved in higher-order cortical functions such as multi-modal sensory integration and regulation of voluntary movements. However, organization and development of long association projections are not fully understood at cellular level. We established a model system to specifically visualize the long association projection from the primary somatosensory cortex (S1, in the parietal lobe) to the primary motor cortex (M1, in the frontal lobe) in the mouse. Using this system, we examined the developmental processes of axons in long association projection at the single neuron resolution. We found that long association neurons project not only to M1 but also to the corpus callosum that bridges the bilateral hemispheres (Fig.1), and that the projection to M1 is one of the many collateral branches sprouting from the earlier-projecting axons to the corpus callosum (Fig.2).

Background & Results

Cerebral neocortex consists of several dozens of functional areas with different functions. Information processed in a functional area is transferred to another area via neuronal connection called association projection. Long association projections connect two areas on different cortical lobes and are thought to be involved in integration of sensory information in multiple modalities, regulation of voluntary movements, and so on. However, how the long association projections are formed during the developmental processes is yet to be fully elucidated. We examined the developmental processes of the projections from S1 to M1 in mice as a model of long association projections. First, we identified the *Plxnd1* gene as a marker expressed in 80% of long association neurons. Next, using a plasmid vector to express GFP in *Plxnd1*-expressing neurons and in utero electroporation, we established a method to selectively visualize the long association neurons and their axons. After the brains were sampled at different postnatal stages, cortices were flattened and optically cleared, and imaged with confocal microscopy. Our analysis at the single neuron resolution revealed that at postnatal day 7, each long association neuron are dual-projection neurons with projections both to M1 and to the corpus callosum. We also found that the projection to M1 is one and the fastest-extending of the collateral branches sprouted from the earlier-projecting callosal axon.

Significance of the research and Future perspective

Recent fMRI studies showed that the functional connectivity patterns between cortical areas in infants highly accurately predict the symptoms that later emerge in ASD. Thus, classifying the projection patterns and their disorders at early postnatal stages in various mouse models for ASD should pave the way to clarify the neuropathology of and to develop therapeutic approaches to distinct symptoms.

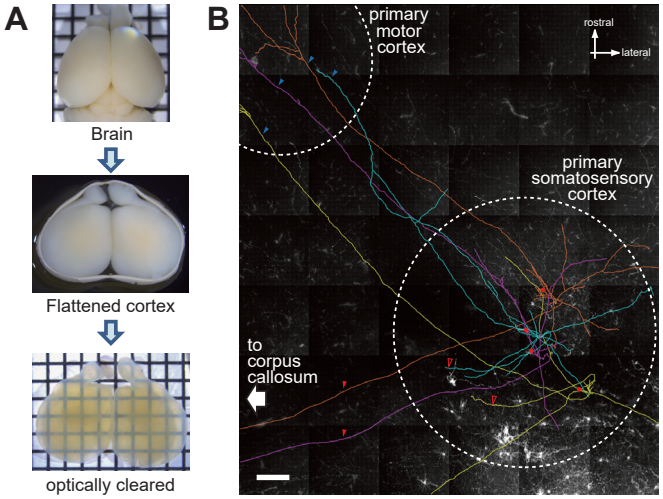

Fig. 1 A. Cerebral cortex was removed from the brain tissue, flattened and optically cleared for confocal imaging. B. Examples of dual-projection neurons visualized with GFP.

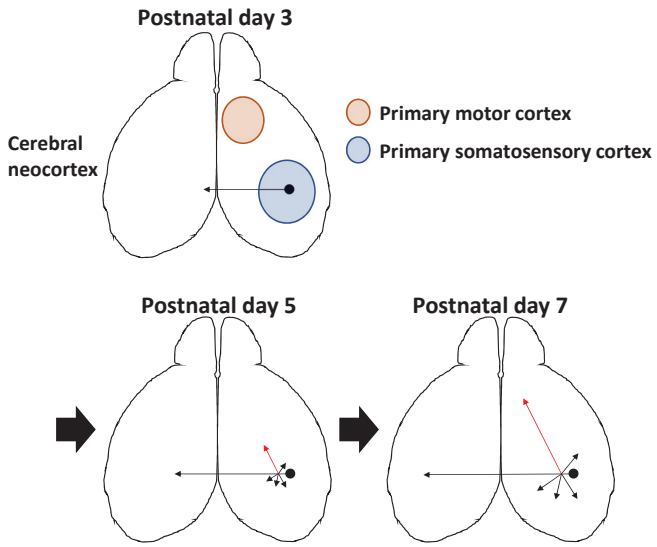

Fig.2 Long association projection between cortical areas is formed as the longest collateral branch (red arrow) sprouted from the earlier-projecting callosal axon.

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