Layer 3 Excitatory and Inhibitory Circuitry in the Prefrontal Cortex: Developmental Trajectories and Alterations in Schizophrenia

Supplemental Information

Chandelier Neurons

Chandelier Neurons in Schizophrenia

In contrast to PVBCs, parvalbumin-containing chandelier cells (PVChCs) and their axonal targets, the axon initial segments (AIS) of pyramidal cells, show a different pattern of alterations in schizophrenia. The density of chandelier cell (ChC) axon cartridges detected by GABA membrane transporter (GAT1) immunoreactivity is lower, whereas the density of pyramidal cell AIS detected by $GABA_A$ α2 receptor subunit immunoreactivity is higher, in the DLPFC of subjects with schizophrenia (**Figure 2D-F**); these pre- and postsynaptic alterations are significantly inversely correlated (1;2). Blockade of GABA reuptake through GAT1 inhibition can prolong unitary inhibitory postsynaptic currents (IPSCs) by relying on GABA release from multiple sites following repetitive activation (3). The combination of lower presynaptic GAT1 in ChC cartridges (which would prolong the availability of extracellular GABA) and the upregulation of postsynaptic $GABA_A$ α2 subunits in AIS (which would increase the strength of inhibition) were initially interpreted as compensatory responses to a deficit in GABA synthesis in PVChCs (4). However, a recent study documents that protein levels for the GABA synthesizing enzyme, GAD67, are unaltered in PVChC cartridges in schizophrenia (5), indicating that these cells are among the PV neurons that do *not* have marked decrements in GAD67 mRNA (6). These findings suggest the need for an alternative explanation to account for the pattern of changes at PVChC inputs to pyramidal neurons in schizophrenia. Because PVChC inputs can be depolarizing when cortical neural networks are quiescent (7), perhaps GABA neurotransmission is upregulated at ChC inputs to pyramidal neuron AIS in order to boost the activity of intrinsically hypoactive pyramidal neurons.

Chandelier Neurons in Development

Compared to PVBCs, the timing and pattern of developmental changes in the expression of biochemical markers in PVChCs are clearly different. During postnatal development, the density of PVChC axonal cartridges immunoreactive for either PV or GAT1 changes markedly in monkey DLPFC. Although the precise time course differs for these two markers, the density of labeled cartridges is low in the newborn, increases to reach a peak prior to the onset of puberty and then declines markedly during the peripubertal period to adult levels (8;9). In addition, PVChC bouton development directly contrasted with the developmental changes in PVBC boutons described above. The mean number of PVChC boutons per pyramidal neuron AIS was markedly lower in postpubertal than prepubertal monkeys, whereas the levels of PV protein levels per PVChC bouton did not change with age (10) (**Figure 4D,E**). Thus, PVChCs and PVBCs appear to use opposite developmental strategies to achieve postpubertal levels of innervation of their pyramidal cell targets.

In the adult DLPFC, the majority of $GABA_A$ α2 subunit-containing receptors are found in pyramidal neuron AIS (11), the postsynaptic target of PVChC axon cartridges and the principal site of action potential generation in pyramidal neurons. The density of pyramidal cell AIS immunoreactive for the $GABA_A$ α2 subunit is highest at birth and then steadily declines across postnatal development into postpuberty (12) (**Figure 4F**). Functionally, GABA α2 subunits have a higher affinity for GABA and slower deactivation times than $GABA_A$ α1 subunits. Therefore, a decrease in the density of α2-labeled AIS may reflect developmental changes in both a decrease in strength and a reduction in speed of GABAergic transmission at AIS, in addition to a reduction in the number of GABAergic synapses onto AIS (10).

Supplemental References

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