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Sex differences in α4βδ GABAA receptor mediated motor behavior flexibility correlated with pruning of mushroom spines in motor cortex, but not thalamus, of adolescent mice.

Adolescent synaptic pruning is critical for neurodevelopment, and we have demonstrated selective pruning of mushroom spines in the motor cortex of female, but not male, mice. This event is mediated by α4βδ GABAA receptors (GABAAR). These receptors have high expression in the ventrolateral (VL) thalamic relay nuclei which projects to motor cortex, but synaptic pruning has not been assessed in this area. Thus, for this study we assessed adolescent VL synaptic pruning. To this end, spine density/types were assessed in Golgi-stained brain slices from z-stack projection (0.2 μm) photomicrographs taken with a Nikon DS-U3 camera mounted on a Nikon Eclipse Ci-L microscope using a 100x oil objective. Both wildtype and α4 -/- mice were assessed at puberty (~P35, vaginal opening), and post puberty (P56). There were no significant changes in spine density or spine type across adolescence for either genotype. We additionally examined potential sex differences in motor learning flexibility, since spine pruning is needed for learning flexibility. To this end, we performed a rotarod test with both male and female post-pubertal mice of both genotypes. For this test the mice were first trained at 4 RPM for 4 trials. Then to test learning flexibility, I trained them the next day at an accelerated speed of 4 to 40 RPM over 5 minutes for 4 trials. The latency to fall off the rotarod was assessed as a measure of motor learning across trials. Only female wildtype mice showed improvement on the learning flexibility task (T1 = 87±12 seconds, T4=138±9 seconds, P<0.05) but not the α4 -/- mice or the males. These results suggest that sex differences in the pruning of mushroom spines in motor cortex are associated with improved behavioral flexibility on a motor task post-pubertally in females, an effect prevented by knock-out of α4βδ GABAARs. They further suggest that the pruning of mushroom spines in motor cortex is not indirectly caused by pruning of their thalamic projection neurons.