Introduction:
Pediatric high-grade gliomas are highly aggressive brain tumors that often present with seizures. Previous work revealed the importance of GABAergic disinhibition to disease pathophysiology in an adult glioma model where peritumoral neurons exhibited elevated intracellular (Cl−) concentration and consequently depolarizing, excitatory gamma-aminobutyric acid (GABA) responses. In these adult tumors, the plasmalemmal expression of KCC2: a potassium-chloride transporter, which establishes the low Cl− concentration required for GABA receptor-mediated inhibition, was significantly decreased. KCC2 expression is developmentally regulated and causes Cl− to be depolarizing early in development. High grade glioma is less frequent in children and is widely understudied. When gliomas occur in pediatric patients, they often present with seizures. It is unknown whether the expression of KCC2 is altered in pediatric glioma and contributes to peritumoral hyperexcitability. Changes in Cl− homeostasis in the developing brain could affect therapeutic strategies to treat tumor-associated seizures in younger patients.

Methods:
We developed a pediatric glioma model where pediatric patient-derived glioma cells are implanted into the cortex of P2-3 mouse pups. The brains are harvested after 7 days and using fresh brain slices, whole-cell patch clamp recordings of layer 2/3 pyramidal cells were conducted in the area of cortex adjacent to tumor (peritumoral cortex) and results were compared to sham-operated controls. We also used immunohistochemistry and confocal microscopy to evaluate expression levels of KCC2 in the peritumoral cortex compared to areas distant from the peritumoral cortex.

Results:

Pediatric peritumoral hyperexcitability

Peritumoral neurons are depolarized compared to sham neurons. Pediatric peritumoral (PT) neurons are more depolarized compared to sham neurons. Peritumoral neurons fired more APs in response to a 20 pA current (left) injection compared to sham neurons. At current injections above 140 pA (right) peritumoral neurons displayed a depolarization block, causing it not to fire APs, which occurs during seizure activity.

Contribution:
Tumor-induced changes in KCC2 expression and therefore altered GABAergic synaptic transmission may contribute to the peritumoral hyperexcitability observed in our pediatric glioma model. Changes in Cl− homeostasis in the young brain may require targeted therapy to control seizures in pediatric tumor-associated epilepsy, this will be assessed in our future studies.