

### **Oxidative and Nitrate Injury to Cajal-Retzius and Subplate Neurons in PVL**

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Previously we detected statistically significant free radical injury in premyelinating oligodendrocytes in periventricular leukomalacia (PVL), and, to a milder but still significant extent, in pyramidal neurons in the overlying cerebral cortex, using immunohistochemistry and grading of cell densities. In this study using the same dataset, we hypothesized that the subplate and Cajal-Retzius (CR) neuron populations also are susceptible to free radical injury, which could have important consequences for normal cortical development and function. Using human autopsy brain slides immunostained for nitrotyrosine (NT), malondialdehyde (MDA), and hydroxynonenal (HNE) adducts, we scored neuronal staining as present (1 or 2 immunostained cells per high-power microscopic field) or absent (0), after survey of all fields in 11 PVL and 23 control cases between 20 and 183 postconceptional weeks. We found that the subplate was stained by at least one free radical adduct marker in 10/11 PVL cases, with 5 cases immunostained for all three markers. CR neurons were also immunopositive for at least one such marker in 9/11 PVL cases, and in 3 cases for all three markers. We found significantly increased presence of neuronal staining in subplate neurons for HNE and NT and in CR cells for HNE and MDA. We conclude that oxidative/nitrate damage to these "pioneer" neurons may contribute to gray matter volume losses and cognitive/behavioral impairments in survivors of perinatal brain injury.