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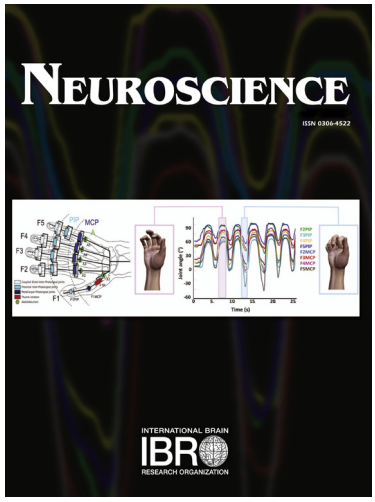

Repeated prenatal exposure to valproic acid results in cerebellar hypoplasia and ataxia

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ABSTRACT

Autism spectrum disorder (ASD) is a developmental brain disorder characterized by restricted and repetitive patterns of behavior, social and communication defects, and is commonly associated with difficulties with motor coordination. The etiology of ASD, while mostly idiopathic, has been linked to hereditary factors and teratogens, such as valproic acid (VPA). VPA is used clinically to treat epilepsy, mood disorders, and in the prevention of migraines. The use of VPA during pregnancy significantly increases the risk of ASD in the offspring. Neuropathological studies show decreased cerebellar function in patients with ASD, resulting in gait, balance and coordination impairments. Herein, we have exposed pregnant rats to a repeated oral dose of VPA on embryonic days 10 and 12 and performed a detailed investigation of the structure and function of the cerebellar vermis. We found that throughout all ten lobules of the cerebellar vermis, Purkinje cells were significantly smaller and expression of the calcium binding protein calbindin was significantly reduced. We also found that dendritic arbors of Purkinje cells were shorter and less complex. Additionally, animals exposed to a repeated dose of VPA performed significantly worse in a number of motor tasks, including beam walking and the rotarod. These results