Autism comprises a heterogeneous group of neuro-developmental disorders that affects brain maturation and produces sensory, motor, language and social interaction deficits with early childhood onset. Many studies indicate that the expression of autistic symptoms is a result of the interaction of predisposing genetic factors and environmental signals during embryonic and early-postnatal life. More recently, studies in animal models have demonstrated that embryonic developmental dysfunctions are at the basis of neuronal and synaptic maturation abnormalities leading to impairments in neural circuit and behavior functions similar to those seen in autism. In the VPA animal model of autism, rats prenatally exposed to valproic acid (VPA) also display behavioral, anatomical and physiological abnormalities reminiscent of autism endophenotypes. However, it is still unknown the degree of behavior and neural connectivity inheritability in this exogenously induced model. Here, we evaluated the behavioral performance and the organization of prefrontal cortex inhibitory circuit in young rats born from parents exposed to VPA and compared them to age-matched VPA-treated and untreated controls. Our results show that rats prenatally exposed to VPA (F1 generation) have a delayed latency for eye-opening during early post-natal development, reduced weight gain from P28 to P35, and clear autistic-like behavioral abnormalities during adolescence, such as hyperlocomotion, prolonged stereotyped behaviors and reduced social interaction when compared to untreated controls. Interestingly, their offspring at the same age (F2 generation - not exposed to VPA) resembled more the F1 generation than the untreated controls. F2 animals showed protracted eye-opening latencies, hyperactivity and a significant social interaction deficit as compared to untreated controls. However, these animals had normal weight gain until P35 and no significant differences in stereotypy parameters - thus suggesting an intermediate phenotype. Analysis of cortical GABAergic interneurons revealed a global decrease in the number of parvalbumin+ cells in the medial prefrontal cortex (mPFC) of F1 animals, in contrast to an increase in F2 animals when compared to untreated controls. In F1, the decrease was mostly due to cell loss in the anterior cingulate cortex, whereas in F2 animals the increase was associated to increased number of cells in all mPFC sub-fields (anterior cingulate cortex,
prelimbic area and infralimbic area). The most significant increase in parvalbumin+ cells was seen in the deep cortical layers (V-VI) of F2 animals. Altogether, these findings suggest that an unbalance in prefrontal inhibitory circuits may subserve the locomotor and social behavior deficits observed in rats prenatally exposed to VPA and their offspring. In addition, it shows behavioral and circuit dysfunction inheritance in this animal model of autism.