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Parkinson's disease gene mutation perturbs behavioral and synaptic adaptions to social defeat stress

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Parkinson's disease (PD) is associated with cognitive and psychiatric (depression) non-motor symptoms that appear early, are independent of dopamine neuron loss and are poorly understood. While most PD is idiopathic, familial forms can be modeled in mice, which we used here to generate a PD context, in which to evaluate the impact of social defeat stress (SDS) and mechanisms driving depression-like behaviors. We used mice carrying a G2019S knockin mutation in leucine-rich repeat kinase 2 (LRRK2), the most prevalent genetic cause of PD. Lrrk2 is enriched in striatal projection neurons (SPNs) in the Nucleus Accumbens (NAc) and in cortical and hippocampal pyramidal neurons furnishing NAc projections. We subjected young adult male G2019S and wildtype (wt) mice to either acute (1d) or chronic (10d) SDS, then probed for behaviorally-driven adaptations in cellular and/or synaptic plasticity. Following 1d-SDS, G2019S mice were significantly socially avoidant compared to 1d-SDS wt mice. Subsequent whole-cell recordings in NAc revealed that mutant SPNs failed to exhibit changes in intrinsic excitability that 1d-SDS wt SPNs exhibited, and instead exhibited synaptic changes that wt SPNs lacked. In contrast, following 10d-SDS, while wt mice exhibited the expected frequencies of socially avoidant and interactive subpopulations, G2019S mice were all highly socially interactive. Comparing AMPAR current-voltage relationships in SPNs of 10d-SDS mice suggested that the mutation may interfere with trafficking of calcium-permeable AMPARs. Together, these data indicate that G2019S drives a temporally-evolving set of cellular and synaptic adaptations to behavioral stress that may impact onset of psychiatric symptoms in human PD patients.