

1 **LRRK2 mutation alters behavioral, synaptic and non-synaptic adaptations to acute social
2 stress**

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15

16 **Abstract**

17 Parkinson's disease (PD) risk is increased by stress and certain gene mutations,
18 including the most prevalent PD-linked mutation *LRRK2*-G2019S. Both PD and stress increase
19 risk for psychiatric symptoms, yet it is unclear how PD-risk genes alter neural circuitry in
20 response to stress that may promote psychopathology. Here we show significant differences
21 between adult G2019S knockin and wildtype (wt) mice in stress-induced behaviors, with an
22 unexpected uncoupling of depression-like and hedonic-like responses in G2019S mice.
23 Moreover, mutant spiny projection neurons in nucleus accumbens (NAc) lack an adaptive,
24 stress-induced change in excitability displayed by wt neurons, and instead show stress-induced
25 changes in synaptic properties that wt neurons lack. Some synaptic alterations in NAc are
26 already evident early in postnatal life. Thus, G2019S alters the magnitude and direction of
27 behavioral responses to stress that may reflect unique modifications of adaptive plasticity in
28 cells and circuits implicated in psychopathology in humans.

29 **Introduction**

30 Genetic and environmental factors collaborate to produce Parkinson's disease (PD) in
31 ways that are not fully understood. The most common genetic cause of late-onset PD is the
32 G2019S mutation in leucine-rich repeat kinase 2 (LRRK2), which increases LRRK2 kinase
33 activity by ~2 fold (Jaleel et al., 2007; West et al., 2005). Both genetic and idiopathic forms of
34 late-onset PD are diagnosed clinically by onset of motor system abnormalities that reflect
35 degeneration of dopamine neurons in substantia nigra. There are prevalent non-motor
36 symptoms associated with PD as well, including cognitive impairment and psychiatric symptoms
37 such as depression (Gaig et al., 2014). These and other non-motor symptoms can first appear
38 years earlier than motor symptoms and are debilitating, but not well understood mechanistically.

39 PD risk is increased by environmental stress and both PD and stress are associated with
40 increased risk for depression. Brain circuits relevant to encoding lasting responses to stress are
41 enriched for LRRK2 expression and in humans carrying G2019S, may develop, function and
42 adapt to stressful experiences differently than those expressing wildtype (wt) LRRK2, but little is

43 known about how environmental stress influences relevant brain circuits in ways that could
44 promote early, PD-associated psychiatric symptoms. Social defeat stress in mice is a validated
45 behavioral assay used to assess vulnerability to social avoidance and anhedonia-like behaviors,
46 core features of human depression (Beery & Kaufer, 2015; Golden, Covington, Berton, &
47 Russo, 2011). Here, we use mice carrying a G2019S knockin mutation in a coordinated set of
48 behavioral, cellular and synaptic experiments to interrogate the effects of environmental stress
49 on brain circuits relevant to human PD.

50

51 **Results**

52 Young adult male wt and G2019S knockin mice underwent acute (1d) social defeat
53 stress (1d-SDS) (**Fig 1A**). Subsequently, defeated mice were tested for social interaction (SI) by
54 tracking their movement as they explored an arena in the absence and subsequent presence of
55 a novel social target within a confined zone (the interaction zone, **Fig 1A**). When in the absence
56 of a social target, 1d-SDS wt and G2019S mice spent comparable time exploring the interaction
57 zone (**Fig 1B-D**) with no significant differences between genotypes in total distance traveled in
58 the arena (**Fig 1E**). However, in the presence of a social target, 1d-SDS G2019S mice spent
59 significantly less time in the interaction zone in comparison with 1d-SDS wt mice (**Fig 1B,C,F**),
60 and traveled less overall in the arena (wt = 761.2 ± 80.13 cm, n= 13, G2019S= 565.1 ± 38.80
61 cm, n=12, p= 0.0428, F=4.621, Student's t-test). Defeat experience was necessary for the
62 increased social avoidance as unstressed G2019S and wt control mice spent equivalent
63 amounts of time in the interaction zone in the presence of a social target (naïve wt mice = 31.23 ± 31.93 sec; naïve G2019 mice = 27.99 ± 19.70 sec, n = 5 per group, p=0.8514, F=2.627,
64 Student's t-test). These data demonstrate that acute (1d) social defeat stress confers
65 significantly greater social avoidance in G2019S mice than wt mice. The pronounced social
66 avoidance of the G2019S mice from 1d-SDS was unexpected because G2019S mice
67 undergoing chronic (10 day) social defeat stress (10d-SDS) are all highly socially interactive,
68 while a significant proportion of wt mice undergoing 10d-SDS display prominent social
69 avoidance (Matikainen-Ankney et al., 2018).

70 Wildtype mice that display social avoidance following 10d-SDS also display anhedonic-
71 like behaviors (Beery & Kaufer, 2015; Golden et al., 2011). To test the prediction that 1d-SDS-
72 G2019S mice would therefore also display greater levels of anhedonia-like behavior, we
73 subjected wt and G2019S mice to a 3-day sucrose-preference test post-1d-SDS (**Fig 1G**).
74 Surprisingly, G2019S mice showed significantly *increased* average sucrose consumption
75 compared to wt mice (**Fig 1H**), thereby revealing an unexpected uncoupling of "depression-like"
76 and "anhedonic-like" behaviors. In the absence of defeat experience, wt and G2019S mice
77 display similar levels of sucrose consumption (Matikainen-Ankney et al., 2018).

78 Following behavioral characterization, we interrogated underlying modifications to
79 intrinsic excitability and synaptic responses in 1d-SDS-exposed mice by preparing acute slices
80 for whole-cell patch clamp recordings from spiny projection neurons (SPNs) in the nucleus
81 accumbens (NAc), an area rich in LRRK2 expression and known to regulate stress responses
82 and depression-like behaviors in mice and humans (Bosch-Bouju, Larrieu, Linders, Manzoni, &
83 Laye, 2016; Carlezon, Duman, & Nestler, 2005; Han & Nestler, 2017). We first established that
84 in unstressed controls, there were no significant differences between genotypes in intrinsic
85 excitability of SPNs--assessed by comparing the number of action-potentials (APs) generated in

87 response to depolarizing current steps (**Fig. 2A,B**) and by rheobase, the amount of threshold
88 current required to generate the first AP (**Fig. 2C**)—nor were there significant differences in
89 interevent interval (IEI) or amplitude of spontaneous excitatory postsynaptic currents (sEPSCs)
90 (**Fig. 2D-F**). Unexpectedly however, we found that subsequent 1d-SDS-induced cell- and
91 synaptic adaptations differed substantially between genotypes, with wt SPNs showing
92 significant changes in excitability and G2019S neurons showing significant changes in synaptic
93 properties. Following 1d-SDS, wt SPNs displayed significantly increased intrinsic excitability
94 compared to 1d-SDS-G2019S SPNs or to SPNs in unstressed controls (**Fig. 2A-C**), but no
95 significant changes in sEPSC IEI (**Fig. 2D,E**) or amplitude (**Fig. 2D,F**). The elevation in neuronal
96 excitability occurred without changes in resting membrane potential ($p > 0.99$). In contrast, the
97 intrinsic excitability of 1d-SDS-G2019S SPNs was unchanged in comparison with either wt or
98 G2019S unstressed control SPNs (**Fig. 2A-C**). However, following 1d-SDS, G2019S SPNs
99 exhibited a significant decrease in sEPSC IEI (**Fig. 2E**) and a significant increase in sEPSC
100 amplitude (**Fig. 2F**), changes in synaptic properties that 1d-SDS wt SPNs lacked (**Fig. 2D-F**).
101 These data reveal two novel findings. First, acute social stress in wt mice drives significant,
102 presumably adaptive plasticity of intrinsic excitability of SPNs without changing their baseline
103 synaptic properties. Two, acute stress in G2019S mice significantly alters behavioral outcomes
104 in comparison with wt mice, fails to affect membrane excitability but produces changes in
105 sEPSC frequency and amplitude.

106 Because PD risk genes are carried throughout life and could be expected to influence
107 circuit formation in NAc, we probed G2019S or wt NAc SPNs at P21 for differences in baseline
108 synaptic properties that may already be established early postnatally. The data show that
109 G2019S SPNs exhibited significantly greater amplitude of sEPSCs (**Fig. 3A-C**) and larger
110 evoked AMPAR-mediated responses compared to wt (**Fig. 3D,E**), suggesting stronger
111 glutamatergic synapses. There were no significant differences between genotypes in sEPSC IEI
112 (**Fig. 3F**). Because stronger synapses are correlated with larger dendritic spines (Yuste &
113 Bonhoeffer, 2001), we compared spine morphology of biocytin-filled mutant and wt SPNs
114 following whole-cell recording. While there was no significant difference between genotypes in
115 average spine density (**Fig 3G**), cumulative probability distribution of spine-head widths showed
116 G2019S spines were shifted significantly towards larger values compared to wt as predicted by
117 the larger current amplitudes (**Fig 3H,I**). Thus, structural and functional abnormalities in NAc
118 synapses are evident during a period in which striatal circuitry can be readily and permanently
119 modified by activity (Kozorovitskiy, Saunders, Johnson, Lowell, & Sabatini, 2012) and may
120 impact behavioral outcomes that depend on such circuitry later in life.

121

122 Discussion

123 Together, these data highlight three main points. First, G2019S mice respond to acute
124 social stress in ways that are significantly different from wt mice. Moreover, the prominent social
125 avoidance of the mutant mice after 1d-SDS was unanticipated because G2019S mice exposed
126 to 10d-SDS are all significantly *more* socially interactive than 10d-SDS wt mice (Matikainen-
127 Ankeny et al, 2018). Further, G2019S mice—regardless of the amount of social defeat (1d or
128 10d) or the degree of social interaction following defeat—display increased sucrose consumption
129 (**Fig 1H**) (Matikainen-Ankeny et al., 2018) revealing an unexpected disassociation between
130 social interaction behavior and hedonic responses to sucrose following social stress. These

131 differing behavioral responses require defeat experience as no differences between genotypes
132 were evident in its absence. Thus, stress-induced behaviors in G2019S mice defy
133 categorization as “depression-like” or “resilient-like”, and instead suggest G2019S imparts a
134 complex set of temporally evolving behavioral responses to social stress likely reflecting both
135 the nature and duration of the stressor. Whether this is a signature of PD vulnerability or a
136 contributor to disease onset or progression is not known. Future studies will need to test
137 responses to other forms and durations of behavioral stress.

138 Second, we found an unexpected non-synaptic adaptation to acute stress in wt SPNs
139 that was absent in G2019S SPNs. Although no studies we are aware of have examined intrinsic
140 excitability of SPNs following 1d-SDS, previous studies in wt mice undergoing 10d-SDS have
141 shown that D₁R-SPNs, but not D₂R-SPNs, exhibit significantly increased intrinsic excitability but
142 only in those chronic SDS mice showing prominent social avoidance (Francis et al., 2015).
143 While such non-synaptic plasticity may be one of the earliest cellular adaptations to SDS, how
144 such non-synaptic adaptations ultimately influence social interaction or hedonic behaviors is not
145 clear. The complete lack of such stress-induced excitability changes in G2019S mice, coupled
146 with modest but significant synaptic changes in sEPSC amplitude and frequency, which were
147 lacking in wt mice, may have together maladaptively contributed to the prominent social
148 avoidance and/or increased sucrose consumption displayed by the mutants, but this, along with
149 potential differences between SPN subtypes, remains to be tested. While the mechanisms
150 preventing excitability changes or promoting changes in sEPSCs are not yet known, it is
151 plausible that altered function of the Rab family of GTPases, which are principal LRRK2
152 phosphotargets and important for trafficking of membrane channels and receptors (Seol, Nam,
153 & Son, 2019; Steger et al., 2016), could underlie both synaptic and non-synaptic abnormalities
154 observed in the mutants. The Rho family of GTPases has been implicated in excitability
155 changes following chronic SDS (Francis, Gaynor, Chandra, Fox, & Lobo, 2019).

156 Third, we show that glutamatergic synaptic response strength and spine morphology of
157 NAc SPNs were significantly different than wt already by early postnatal ages. This is
158 particularly notable because in striatum and elsewhere, developing synaptic circuits exhibit
159 sensitive periods during the first few postnatal weeks where altered activity persistently changes
160 cell properties and network function (Lieberman et al., 2018; Peixoto, Wang, Croney,
161 Kozorovitskiy, & Sabatini, 2016). This suggests G2019S co-opts synaptic circuits early in life
162 with enduring consequences for altered stress-related responses by young adulthood. Over
163 time this may alter synapse plasticity (Christoffel et al., 2011; Derkx, Krugers, Hoogenraad,
164 Joels, & Sarabdjitsingh, 2016; Stelly, Pomrenze, Cook, & Morikawa, 2016) and inflammatory
165 pathways (Zhu, Klomparens, Guo, & Geng, 2019), ultimately increasing PD vulnerability.

166

167 **Methods**

168 *Mice* Lrrk2-G2019S knockin mice were generated by Eli Lilly and characterized previously
169 (Matikainen-Ankney et al., 2018; Matikainen-Ankney et al., 2016). Mice were congenic on
170 C57Bl/6NTac background, bred as homozygotes, and backcrossed to wt C57Bl/6NTac every
171 fourth generation to prevent genetic drift. Age- and strain-matched wildtype (wt) mice bred and
172 raised under conditions identical to G2019S mice were used as controls. Male and female mice
173 (aged P21) were used for electrophysiology and spine morphology using methods described in
174 detail previously (Matikanen-Ankney et al, 2016). Male mice (10-12 weeks old) were used for

175 behavior. CD1 retired breeders (Charles River, Raleigh, NC) were ≥ 4 months and were
176 screened for aggression. Animal procedures were approved by Mount Sinai's Institutional
177 Animal Care and Use Committee and conformed to National Institutes of Health guidelines.
178 Electrophysiology Whole-cell patch clamp recordings from spiny projection neurons (SPNs) in
179 the NAc shell were conducted on acute coronal slices taken from unstressed wt or G2019S
180 mice or those undergoing 1d-SDS, using methods described in detail previously (Matikainen-
181 Ankney et al., 2018; Matikainen-Ankney et al., 2016). SPNs were identified visually and
182 electrophysiologically (Matikainen-Ankney et al., 2016), sEPSCs were confirmed to be
183 glutamatergic as described (Matikainen-Ankney et al., 2016).

184 Behavior For 1d-SDS, age-matched wt or G2019S male mice were subjected to brief periods of
185 physical subordination by a larger aggressor mouse as depicted (**Fig. 1A**). Social interaction
186 (SI) was assessed in the absence and subsequent presence of a novel social target as
187 described (Golden et al., 2011; Matikainen-Ankney et al., 2018). Mouse movement was
188 continuously tracked (Ethovision 5.0; Noldus). For sucrose preference, mice were given a
189 choice of water or 1% sucrose solution as outlined in **Fig 1G**. Amount of sucrose consumed:
190 (vol sucrose consumed/total vol liquid consumed)*100.

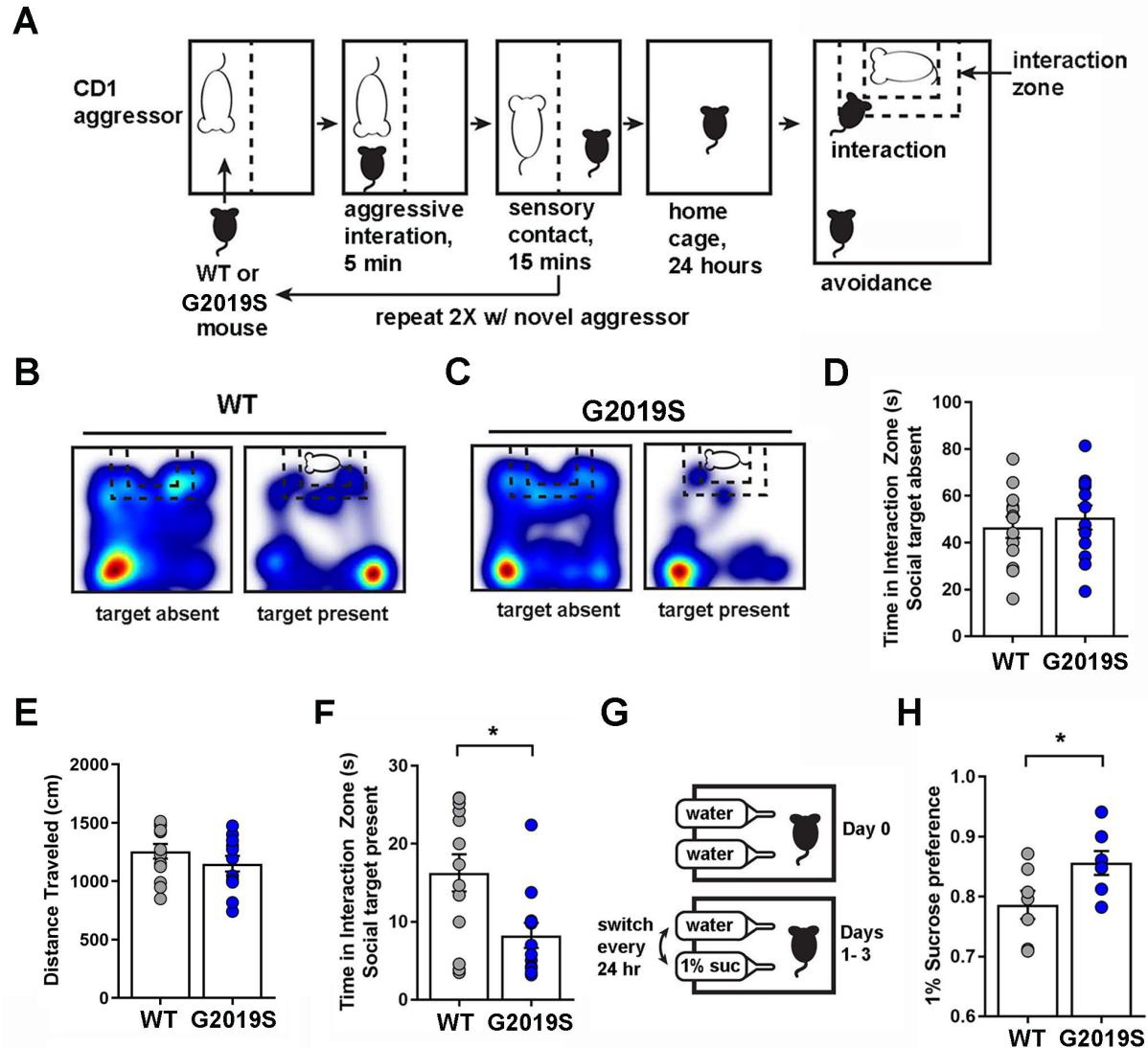
191 Statistical Analyses $P < 0.05$ was considered significant. Analyses were derived from GraphPad
192 Software Prism (v8.2.1). Data are presented as mean values \pm SEM. Numbers (n) listed as: n=
193 number of cells (number of mice) or n= number of mice.

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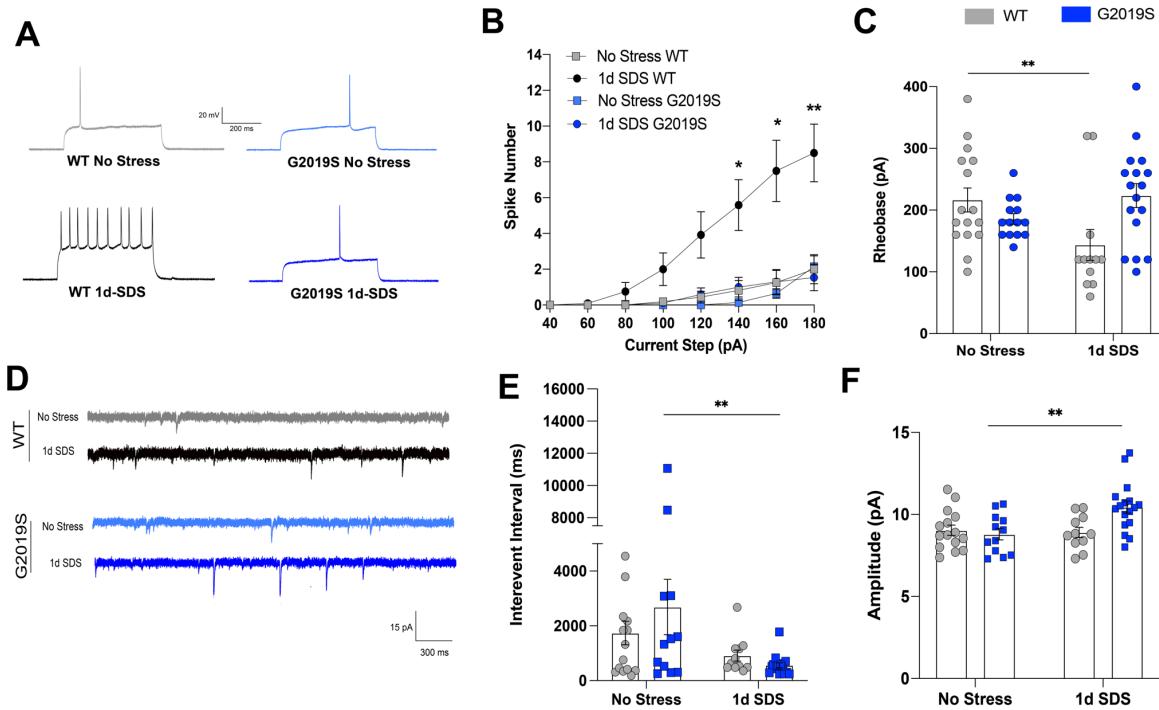
198 **Competing Interests**

199 The authors declare no financial or non-financial competing interests.



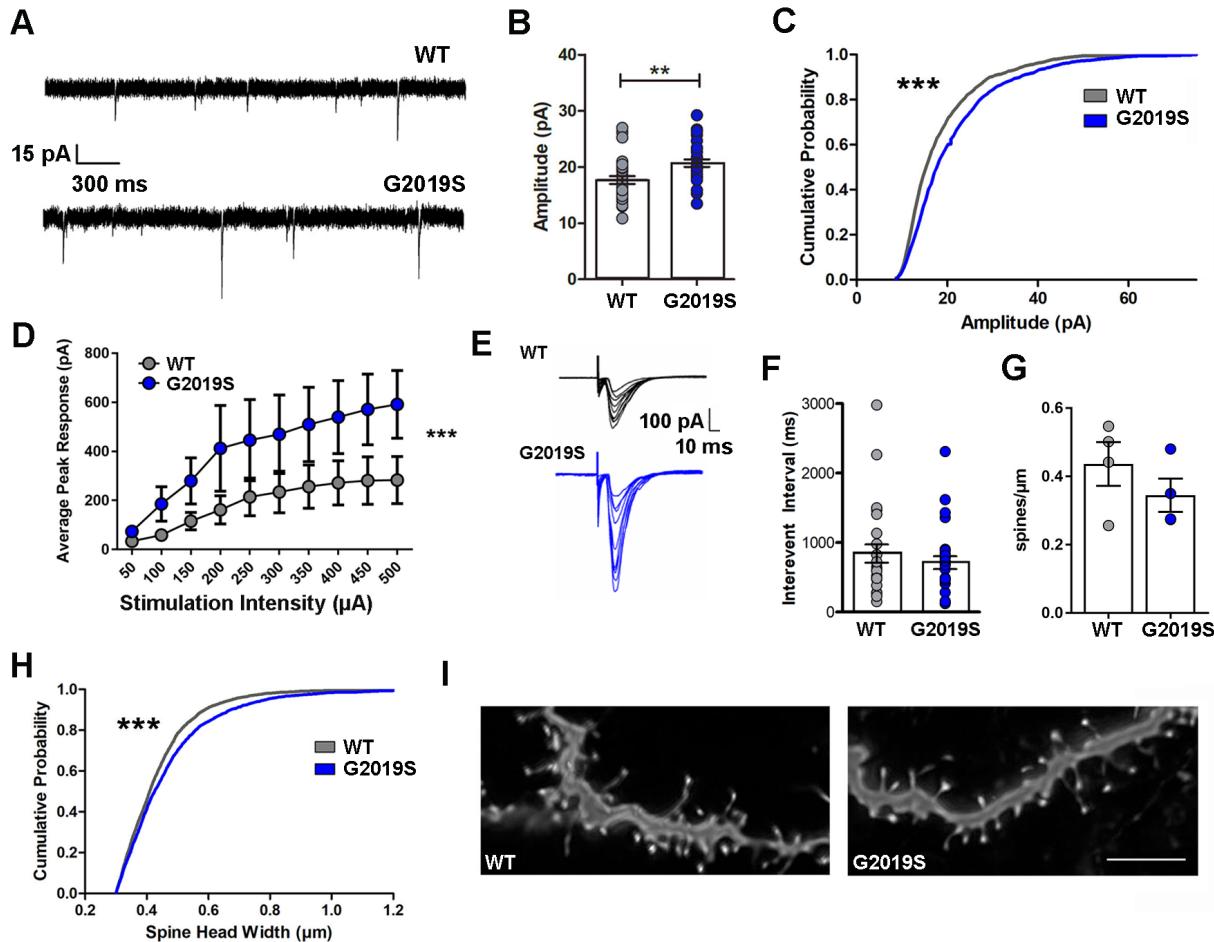
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201 **Figure 1.** Behavioral differences between G2019S and wt mice following 1d-SDS. (A) 1d-SDS
202 paradigm. (B,C) Representative heat maps showing movement of wt (B) and G2019S (C) mice
203 during SI test with a novel target absent or present. Blue indicates path travelled; warmer colors
204 indicate increased time. (D) Graph of time in interaction zone with no social target present
205 ($p=0.5478$, $F=1.186$). (E) Total distance travelled in the arena ($p=0.2593$, $F=1.023$) (F) Graph of
206 time in interaction zone with a novel social target present ($p= 0.0117$, $F=2.404$; wt (n=13 mice),
207 G2019S (n=12 mice)). (G) Schematic showing 3-day sucrose preference test paradigm. (H)
208 Following 1d-SDS, G2019S mice show greater sucrose consumption compared to wt ($p =$
209 0.0432, $F=1.399$; wt (n= 7 mice), G2019S (n =8 mice)). D, E, F, and H, Student's t-tests.
210



211
212 **Figure 2. Differential adaptations in excitability and synaptic properties in G2019S and wt SPNs**
213 following 1d-SDS. **(A)** Representative traces of action potentials generated by current injection
214 (-180 pA) into NAc SPNs, taken from mice from each behavioral condition shown. **(B)** Plot
215 showing number of spikes elicited as a function of increasing current injected into SPNs from wt
216 or G2019S mice from the behavioral conditions shown. Increased excitability was observed in
217 1d-SDS wt SPNs compared with no stress wt SPNs (at 140 pA: $p=0.0189$; at 160 pA: $p=0.0115$;
218 at 180 pA: $p=0.0064$). **(C)** Graph showing average rheobase recorded from SPNs in wt or
219 G2019S mice following no-stress or 1d-SDS conditions. wt SPNs following 1d-SDS show
220 significantly decreased rheobase in comparison with no stress wt SPNs ($p = 0.0098$). **(D)**
221 Sample traces of sEPSCs recorded from wt or G2019S SPNs for each condition. **(E)** Graph
222 showing average interevent interval (IEI) of sEPSCs recorded from wt or G2019S SPNs.
223 Following 1d-SDS, sEPSC IEI is significantly lower in G2019S SPNs compared to no stress
224 G2019S SPNs ($p = 0.0099$). **(F)** Graph showing average amplitude of sEPSCs recorded from wt
225 or G2019S SPNs. Following 1d-SDS, G2019S SPNs show significantly increased amplitude in
226 comparison with G2019S no stress SPNs ($p=0.0025$). For all experiments, $n = 4-5$ mice/12-17
227 cells per group. Repeated measures two-way ANOVA was applied to data shown in **B**. Mixed
228 effects models with Sidak post hoc tests for multiple comparisons were applied to data shown in
229 **C, E, F.** * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Error bars represent S.E.M.

230



231

232 **Figure 3. G2019S increases sEPSC amplitude and spine head-width in NAc SPNs at P21. (A)**
233 Sample traces of sEPSCs recorded from wt or G2019S NAc SPNs. **(B)** Graphs showing
234 average amplitudes of sEPSCs ($p = 0.0028$, $F = 1.043$. WT $n=30(4)$, G2019S, $n=30(4)$). **(C)**
235 Cumulative probability distributions of sEPSC amplitudes of the first 50 events per cell from wt
236 or G2019S SPNs. Rightward shift is significant, $p=0.0001$, WT $n=30(4)$, G2019S $n=30(4)$. **(D)**
237 AMPAR-current input-output curve: evoked current magnitude vs. increasing input current for wt
238 or G2019S ($n= 12(4)$ each group), $p<0.0001$ for genotype effect. **(E)** Example traces from wt or
239 G2019S evoked AMPAR currents. **(F)** Average interevent intervals (IEI) of sEPSCs from wt or
240 G2019S SPNs. wt, $n=30(4)$, G2019S, $n=30(4)$, $p= 0.1047$, $F=2.809$ and $p=0.4064$, $F=1.893$,
241 respectively. **(G)** Graph of average spine densities per animal, wt vs. G2019S; $p=0.2963$, $n=3-4$
242 animals/genotype. **(H)** Cumulative probability distributions of wt or G2019S SPN spine head
243 widths. Spine-head widths in G2019S SPNs show a significant rightward shift, $p = 0.0001$;
244 $n=20(4)$ for each group. **(I)** Examples of deconvolved (Autoquant) confocal image z-stacks
245 (100X objective, Zeiss LSM780; Nyquist sampling) of biocytin filled, Alexa594-labeled G2019S
246 or wt SPN dendrite segments; scale bar = 4 μ m. All graphs, gray = WT; blue = G2019S; **B, F**,
247 and **G**, Student's t-test. **C** and **H**, Kolmogorov-Smirnov test. **D**, 2-way ANOVA.
248 .

249 **References**

250 Beery, A. K., & Kaufer, D. (2015). Stress, social behavior, and resilience: insights from rodents. *Neurobiol
251 Stress*, 1, 116-127. doi:10.1016/j.yunstr.2014.10.004

252 Bosch-Bouju, C., Larrieu, T., Linders, L., Manzoni, O. J., & Laye, S. (2016). Endocannabinoid-Mediated
253 Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress. *Cell
254 Rep*, 16(5), 1237-1242. doi:10.1016/j.celrep.2016.06.082

255 Carlezon, W. A., Jr., Duman, R. S., & Nestler, E. J. (2005). The many faces of CREB. *Trends Neurosci*, 28(8),
256 436-445. doi:10.1016/j.tins.2005.06.005

257 Christoffel, D. J., Golden, S. A., Dumitriu, D., Robison, A. J., Janssen, W. G., Ahn, H. F., . . . Russo, S. J.
258 (2011). IkappaB kinase regulates social defeat stress-induced synaptic and behavioral plasticity. *J
259 Neurosci*, 31(1), 314-321. doi:10.1523/jneurosci.4763-10.2011

260 Derkx, N. A., Krugers, H. J., Hoogenraad, C. C., Joels, M., & Sarabdjitsingh, R. A. (2016). Effects of Early
261 Life Stress on Synaptic Plasticity in the Developing Hippocampus of Male and Female Rats. *PLoS
262 One*, 11(10), e0164551. doi:10.1371/journal.pone.0164551

263 Francis, T. C., Chandra, R., Friend, D. M., Finkel, E., Dayrit, G., Miranda, J., . . . Lobo, M. K. (2015). Nucleus
264 accumbens medium spiny neuron subtypes mediate depression-related outcomes to social
265 defeat stress. *Biol Psychiatry*, 77(3), 212-222. doi:10.1016/j.biopsych.2014.07.021

266 Francis, T. C., Gaynor, A., Chandra, R., Fox, M. E., & Lobo, M. K. (2019). The Selective RhoA Inhibitor
267 Rhosin Promotes Stress Resiliency Through Enhancing D1-Medium Spiny Neuron Plasticity and
268 Reducing Hyperexcitability. *Biol Psychiatry*, 85(12), 1001-1010.
269 doi:10.1016/j.biopsych.2019.02.007

270 Gaig, C., Vilas, D., Infante, J., Sierra, M., Garcia-Gorostiaga, I., Buongiorno, M., . . . Tolosa, E. (2014).
271 Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. *PLoS One*, 9(10),
272 e108982. doi:10.1371/journal.pone.0108982

273 Golden, S. A., Covington, H. E., 3rd, Berton, O., & Russo, S. J. (2011). A standardized protocol for
274 repeated social defeat stress in mice. *Nat Protoc*, 6(8), 1183-1191. doi:10.1038/nprot.2011.361

275 Han, M. H., & Nestler, E. J. (2017). Neural Substrates of Depression and Resilience. *Neurotherapeutics*.
276 doi:10.1007/s13311-017-0527-x

277 Jaleel, M., Nichols, R. J., Deak, M., Campbell, D. G., Gillardon, F., Knebel, A., & Alessi, D. R. (2007). LRRK2
278 phosphorylates moesin at threonine-558: characterization of how Parkinson's disease mutants
279 affect kinase activity. *Biochem J*, 405(2), 307-317. doi:10.1042/bj20070209

280 Kozorovitskiy, Y., Saunders, A., Johnson, C. A., Lowell, B. B., & Sabatini, B. L. (2012). Recurrent network
281 activity drives striatal synaptogenesis. *Nature*, 485(7400), 646-650. doi:10.1038/nature11052

282 Lieberman, O. J., McGuirt, A. F., Mosharov, E. V., Pigulevskiy, I., Hobson, B. D., Choi, S., . . . Sulzer, D.
283 (2018). Dopamine Triggers the Maturation of Striatal Spiny Projection Neuron Excitability during
284 a Critical Period. *Neuron*, 99(3), 540-554.e544. doi:10.1016/j.neuron.2018.06.044

285 Matikainen-Ankney, B. A., Kezunovic, N., Menard, C., Flanigan, M. E., Zhong, Y., Russo, S. J., . . . Huntley,
286 G. W. (2018). Parkinson's Disease-Linked LRRK2-G2019S Mutation Alters Synaptic Plasticity and
287 Promotes Resilience to Chronic Social Stress in Young Adulthood. *J Neurosci*, 38(45), 9700-9711.
288 doi:10.1523/jneurosci.1457-18.2018

289 Matikainen-Ankney, B. A., Kezunovic, N., Mesias, R. E., Tian, Y., Williams, F. M., Huntley, G. W., &
290 Benson, D. L. (2016). Altered Development of Synapse Structure and Function in Striatum
291 Caused by Parkinson's Disease-Linked LRRK2-G2019S Mutation. *J Neurosci*, 36(27), 7128-7141.
292 doi:10.1523/JNEUROSCI.3314-15.2016

293 Peixoto, R. T., Wang, W., Croney, D. M., Kozorovitskiy, Y., & Sabatini, B. L. (2016). Early hyperactivity and
294 precocious maturation of corticostriatal circuits in Shank3B(-/-) mice. *Nat Neurosci*, 19(5), 716-
295 724. doi:10.1038/nn.4260

296 Seol, W., Nam, D., & Son, I. (2019). Rab GTPases as Physiological Substrates of LRRK2 Kinase. *Exp*
297 *Neurobiol*, 28(2), 134-145. doi:10.5607/en.2019.28.2.134

298 Steger, M., Tonelli, F., Ito, G., Davies, P., Trost, M., Vetter, M., . . . Mann, M. (2016). Phosphoproteomics
299 reveals that Parkinson's disease kinase LRRK2 regulates a subset of Rab GTPases. *Elife*, 5.
300 doi:10.7554/eLife.12813

301 Stelly, C. E., Pomrenze, M. B., Cook, J. B., & Morikawa, H. (2016). Repeated social defeat stress enhances
302 glutamatergic synaptic plasticity in the VTA and cocaine place conditioning. *Elife*, 5.
303 doi:10.7554/eLife.15448

304 West, A. B., Moore, D. J., Biskup, S., Bugayenko, A., Smith, W. W., Ross, C. A., . . . Dawson, T. M. (2005).
305 Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase
306 activity. *Proc Natl Acad Sci U S A*, 102(46), 16842-16847. doi:10.1073/pnas.0507360102

307 Yuste, R., & Bonhoeffer, T. (2001). Morphological changes in dendritic spines associated with long-term
308 synaptic plasticity. *Annu Rev Neurosci*, 24, 1071-1089. doi:10.1146/annurev.neuro.24.1.1071

309 Zhu, Y., Klomparens, E. A., Guo, S., & Geng, X. (2019). Neuroinflammation caused by mental stress: the
310 effect of chronic restraint stress and acute repeated social defeat stress in mice. *Neurol Res*,
311 41(8), 762-769. doi:10.1080/01616412.2019.1615670

312