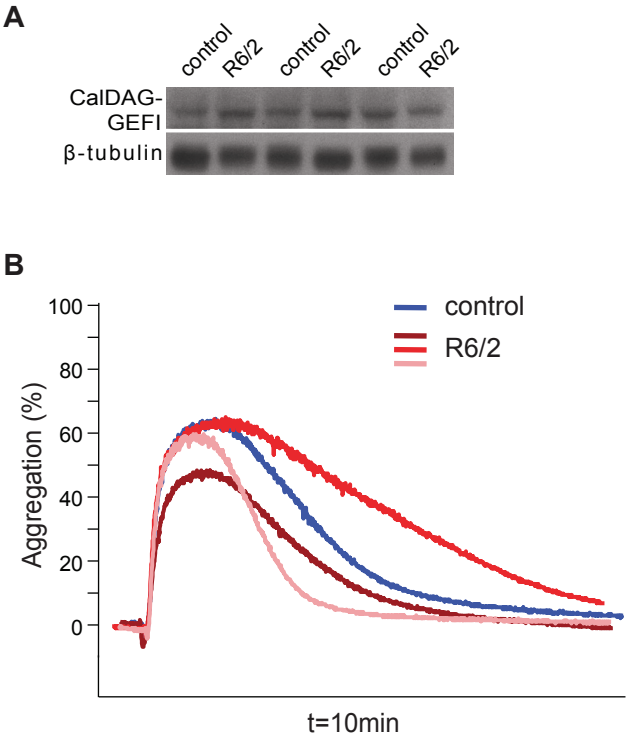
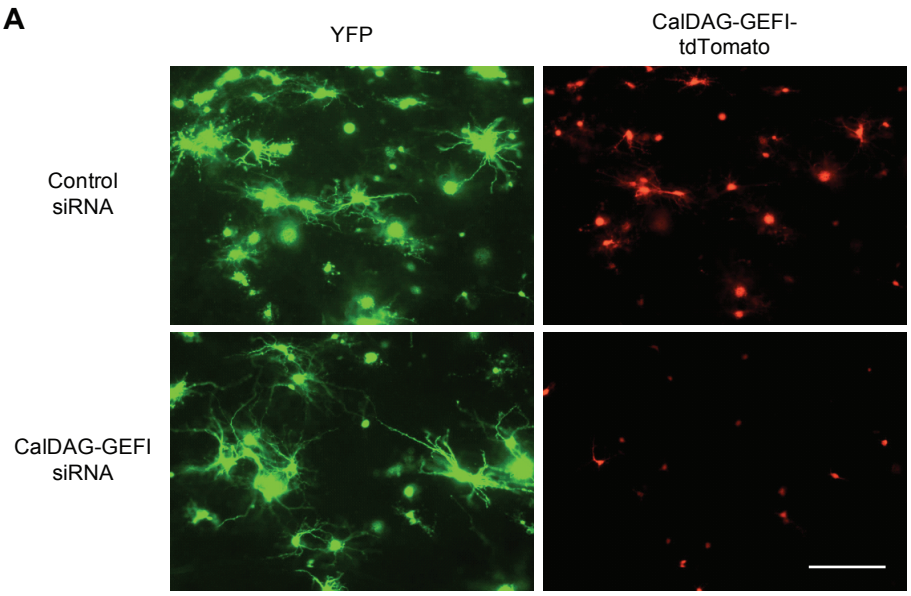
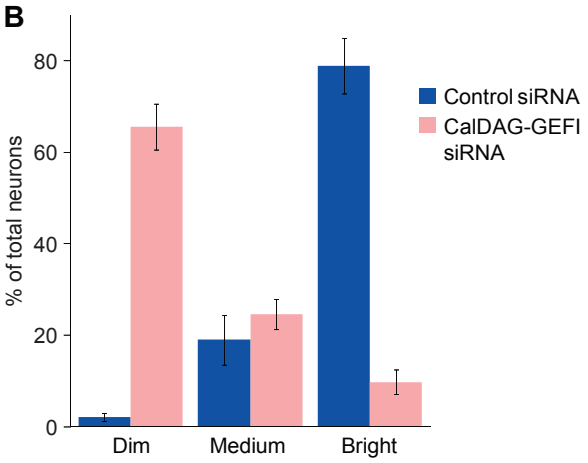
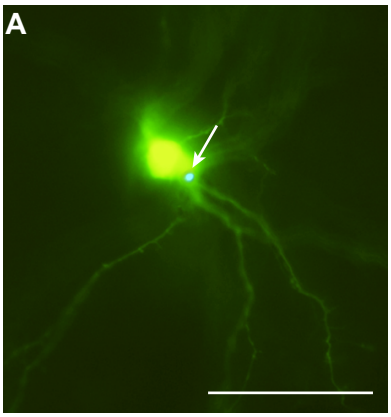


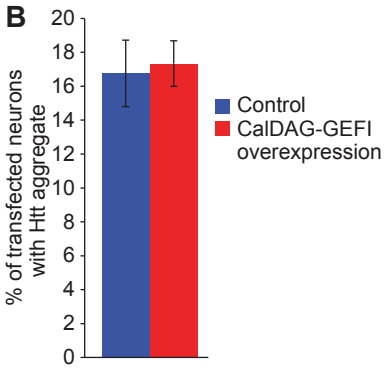
Supplemental Figure 1. CalDAG-GEFI protein levels and function appeared normal in platelets from R6/2 mice. (**A**) Western blot of platelet lysates from three 12 week old R6/2 mice, with polyglutamine repeat lengths between 192 and 194, showed no differences from age-matched controls. Lower band shows beta-tubulin loading control. (**B**) Platelets were isolated from three, 12 week old R6/2 mice and a control sibling and placed into an aggregometer that measures platelet aggregation by increased light transmission. Upon addition of adenosine diphosphate (ADP, 10 μm), which is dependent upon CalDAG-GEFI for platelet activation (Crittenden et. al. 2004), platelets from the three R6/2 mice (pink traces) and the control (blue trace) all showed robust aggregation.

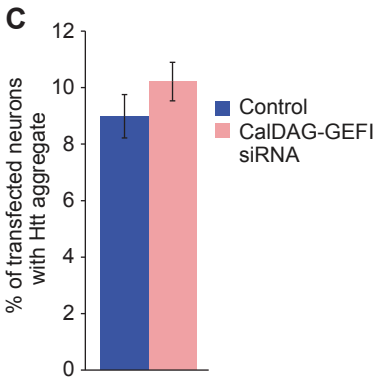




Supplemental Figure 2. Confirmation of knockdown of CalDAG-GEFI protein expression in the brain slice explants. (**A**) A CalDAG-GEFI-tdTomato fusion construct was co-transfected with YFP and either the CalDAG-GEFI siRNA or a negative control siRNA. One day after transfection, brain slices were fixed and mounted, and transfected medium spiny striatal neurons were identified based on their characteristic morphology and positioning within the striatal region of each explant (left images), and then scored for their level of CalDAG-GEFI expression based on the intensity of the tdTomato-fusion reporter (right images). Scale bar, 200 µm. (**B**) All brightly YFP-expressing medium spiny striatal neurons were first blindly identified in the green fluorescence channel for each brain slice explant, and subsequently scored for either dim, medium, or bright expression of the CalDAG-GEFI-tdTomato signal after switching to the red fluorescence channel. Scores were then compiled for the CalDAG-GEFI vs. negative control siRNA transfection conditions, and are expressed as a percentage of total numbers of neurons examined per brain slice + SEM (275 and 311 neurons in a total of 6 brain slice explants each for control vs. CalDAG-GEFI siRNA conditions, respectively). There were significantly more dim cells ($P < 10^{-5}$) and significantly fewer bright cells ($P < 10^{-5}$) in the slices transfected with CalDAG-GEFI siRNA, relative to those transfected with control siRNA. Error bars represent SEM.







Supplemental Figure 3. CalDAG-GEFI overexpression or knockdown did not affect aggregation of polyglutamine-expanded Htt exon 1 in cortico-striatal brain slices. (**A**) Example of a striatal neuron in a corticostriatal brain slice explant co-transfected with polyglutamine-expanded Htt exon 1 fused to CFP, and control siRNA and YFP. Aggregated Htt-CFP is visible in the cell soma (arrow). Scale bar, 50 µm. To test for effects of CalDAG-GEFI overexpression or knockdown on Htt aggregation, cells were co-transfected with polyglutamine-expanded Htt exon 1 fused to CFP and the CalDAG-GEFI cDNA overexpression construct (**B**) or CalDAG-GEFI-targeting siRNA (**C**), relative to empty overexpression or non-targeting siRNA constructs (controls). $P > 0.05$ for both **B** and **C**.