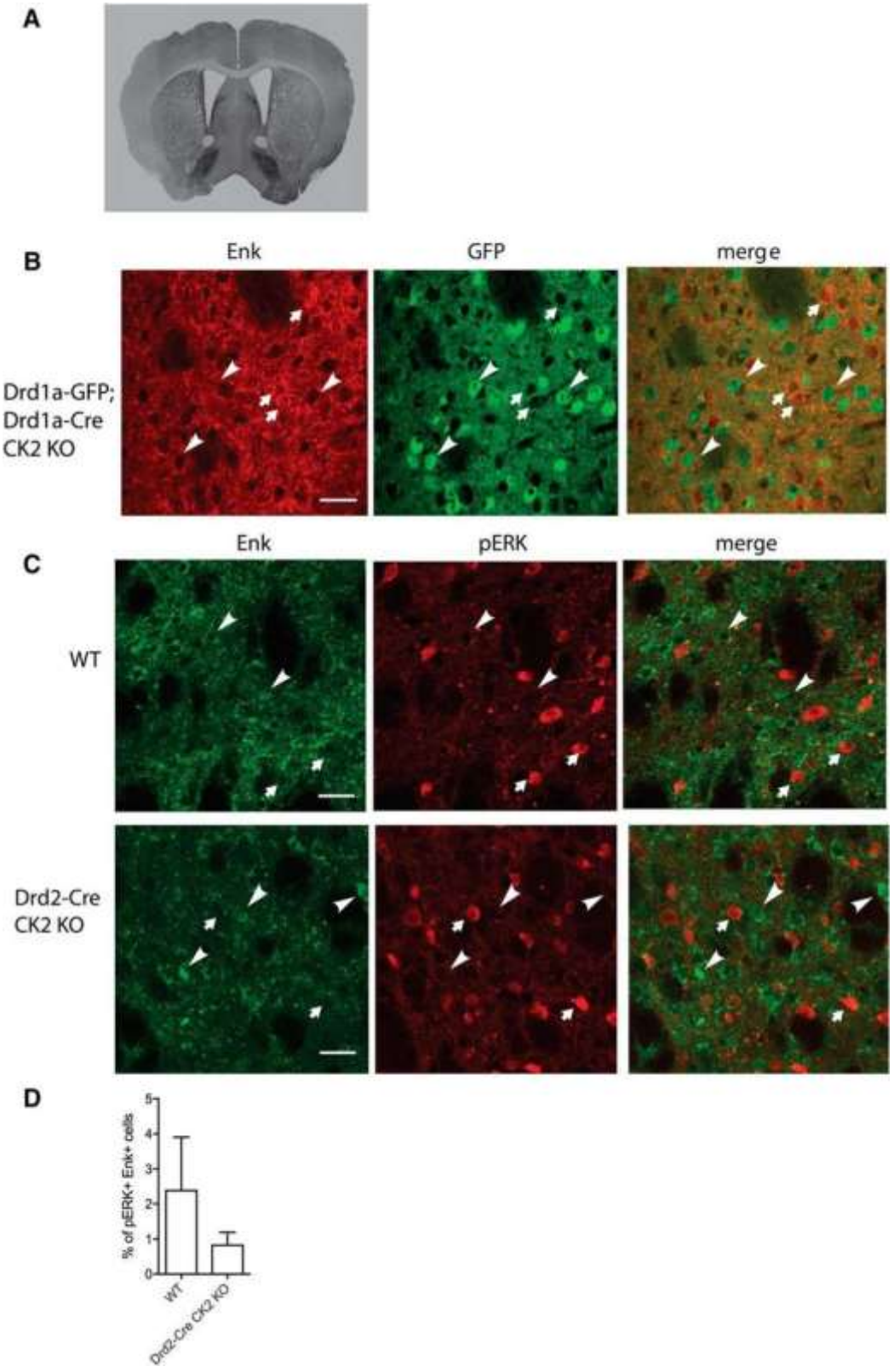
Cortes et al. 2017. J Neurosci

Cortés M, Malave L, Castello J, Flajolet M, Cenci MA, Friedman E, Rebholz H. CK2 Oppositely Modulates l-DOPA-Induced Dyskinesia via Striatal Projection Neurons Expressing D1 or D2 Receptors. J Neurosci. 2017 Dec 6;37(49):11930-11946. doi: 10.1523/JNEUROSCI.0443-17.2017. Epub 2017 Nov 2. PubMed PMID: 29097596; PubMed Central PMCID: PMC6596830.



We have previously shown that casein kinase 2 (CK2) negatively regulates dopamine D1 and adenosine A2A receptor signaling in the striatum. Ablation of CK2 in D1

receptor-positive striatal neurons caused enhanced locomotion and exploration at baseline, whereas CK2 ablation in D2 receptor-positive neurons caused increased locomotion after treatment with A2A antagonist, caffeine. Because both, D1 and A2A receptors, play major roles in the cellular responses to l-DOPA in the striatum, these findings prompted us to examine the impact of CK2 ablation on the effects of l-DOPA treatment in the unilateral 6-OHDA lesioned mouse model of Parkinson's disease. We report here that knock-out of CK2 in striatonigral neurons reduces the severity of l-DOPA-induced dyskinesia (LID), a finding that correlates with lowered pERK but unchanged pPKA substrate levels in D1 medium spiny neurons as well as in cholinergic interneurons. In contrast, lack of CK2 in striatopallidal neurons enhances LID and ERK phosphorylation. Coadministration of caffeine with a low dose of l-DOPA reduces dyskinesia in animals with striatopallidal knock-out to wild-type levels, suggesting a dependence on adenosine receptor activity. We also detect reduced Golf levels in the striatonigral but not in the striatopallidal knock-out in response to l-DOPA treatment.Our work shows, in a rodent model of PD, that treatment-induced dyskinesia and striatal ERK activation are bidirectionally modulated by ablating CK2 in D1- or D2-positive projection neurons, in male and female mice. The results reveal that CK2 regulates signaling events critical to LID in each of the two main populations of striatal neurons.SIGNIFICANCE STATEMENT To date, l-DOPA is the most effective treatment for PD. Over time, however, its efficacy decreases, and side effects including l-DOPA-induced dyskinesia (LID) increase, affecting up to 78% of patients within 10 years of therapy (Hauser et al., 2007). It is understood that supersensitivity of the striatonigral pathway underlies LID, however, D2 agonists were also shown to induce LID (Bezard et al., 2001; Delfino et al., 2004). Our work implicates a novel player in the expression of LID, the kinase CK2: knock-out of CK2 in striatonigral and striatopallidal neurons has opposing effects on LID. The bidirectional modulation of dyskinesia reveals a central role for CK2 in striatal physiology and indicates that both pathways contribute to LID.