

**Figure S1. Related to Figure 1. Cocaine Drives Cre-dependent Reporter Expression in Striatal and Cortical Neurons in Arc-TRAP/Ai14 Mice**

(A) Diagram of strategy for gaining genetic access to cocaine-activated neurons. Mice expressing CreER<sup>T2</sup> under the control of the Arc promoter (Arc-TRAP) are crossed with Ai14 Cre-dependent tdTomato reporter mice. When a stimulus is provided simultaneously with 4-hydroxytamoxifen injection, neurons activated by the stimulus will subsequently express tdTomato.

(B) Representative image depicting tdTomato expression in cortex and striatum of a mouse receiving either cocaine (left) or saline (right). Fluorescence intensity for this and subsequent images indicated via lookup table depicted at bottom left.

(C) Fluorescence images of dorsal striatal neurons activated by either cocaine (left) or saline (right).

(D) tdTomato<sup>+</sup> cell density quantified for either the lateral, central, or medial thirds of dorsal striatal coronal slices. Activated neuron density is higher for all dorsal striatal regions in the cocaine (red) condition compared to saline (gray).

(E) Fluorescence images of primary somatosensory cortex (barrel fields).

(F) Barrel cortex tdTomato signal intensity as a function of depth (calculated from pial surface). Signal-to-noise (STN) ratio is determined by dividing the total integrated area under the cocaine curve by that of the saline curve. Error bars on curves indicate  $\pm 1$  SEM.

(G) Fluorescence images of primary motor cortex. Some expected residual fluorescence remains in deeper cortical layers in saline-injected animals (right). However, many more cocaine-activated neurons are detected throughout the cortical column (left).

(H) Motor cortex tdTomato signal intensity as a function of depth. Cocaine-activated neurons greatly outnumber saline-activated neurons regardless of cortical depth.

(I) Fluorescence images of OFC. Cocaine-injected animals show greatly enhanced numbers of tdTomato expressing neurons in all cortical layers.

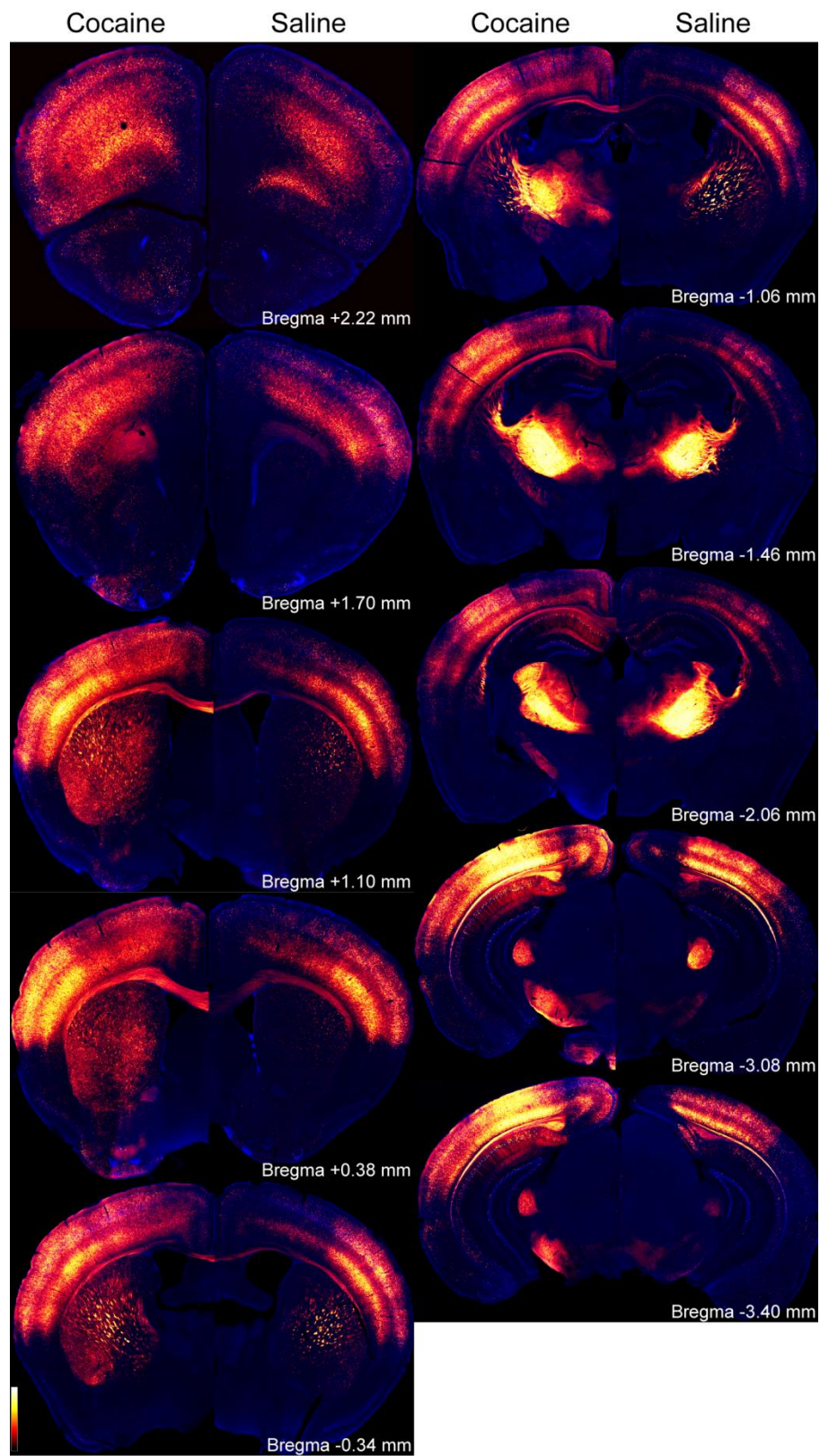
(J) OFC tdTomato signal intensity as a function of depth. tdTomato expression is broadly increased in cocaine-injected animals.

(K) Diagram showing a single whisker (C3) was removed from an 8 week old mouse. 2 days later, Arc-mediated Cre recombination was induced via injection of 4-hydroxytamoxifen.

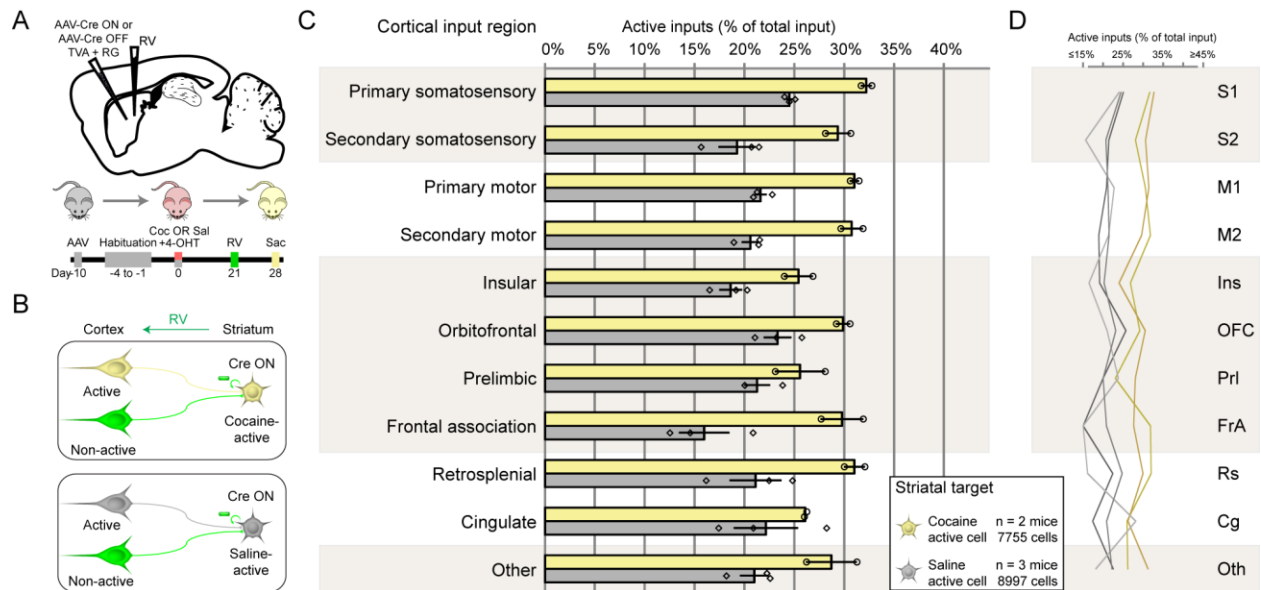
(L) Image of primary somatosensory cortex (barrel fields) in mouse with excised whisker. tdTomato signal is selectively reduced in layer 4 of the barrel corresponding to the excised C3 whisker.

(M) tdTomato expression alone from image in (L) (lookup table in lower left).

(N) DAPI counterstain from image in (L) depicting whisker barrels (lookup table in lower left).



**Figure S2. Related to Figure 1. Sample Images of Arc-mediated tdTomato Expression in Animals Administered Cocaine (left) or Saline (right)**



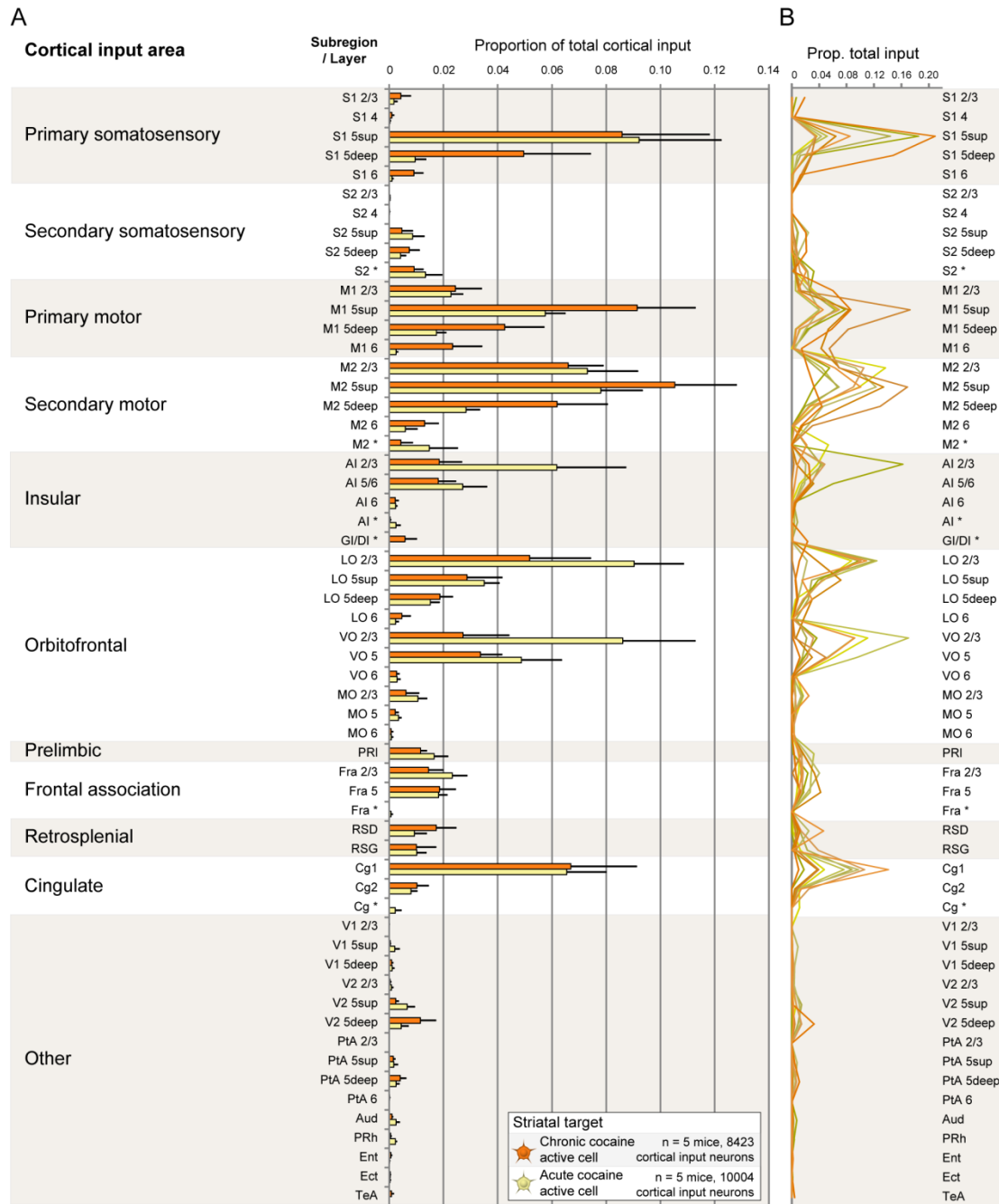
**Figure S3. Related to Figure 3. Connectivity Between Cocaine-activated Cortical and Striatal Neurons is Higher Than That for Saline-activated Neurons**

(A) Diagram of targeting strategy to label monosynaptic inputs to either cocaine-activated neurons (Coc day 0) or saline-activated neurons (Sal day 0).

(B) Schematic legend depicting either active or non-active inputs to either cocaine-activated or saline-activated neurons.

(C) Proportion of activated cortical input neurons to targeted striatal neurons that are activated by either cocaine (n=2 animals, 7755 neurons, yellow) or saline (n=3 animals, 8997 neurons, gray). (Means significantly different via two-way ANOVA:  $F(1,33)=116.2$ ,  $p<0.001$ ).

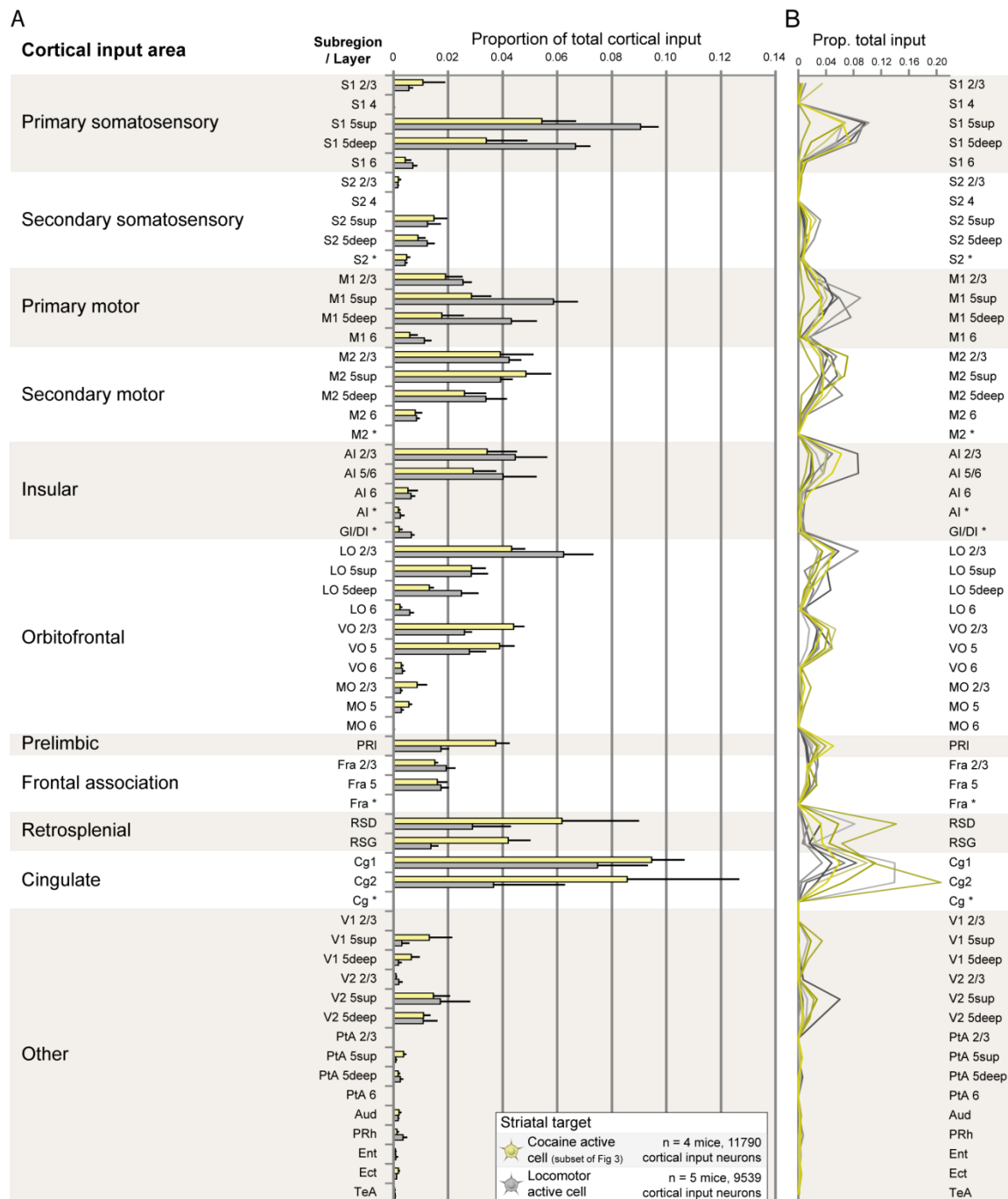
(D) Visualization of data displayed in (C), but with all applicable data points for an individual animal charted as a single line.



**Figure S4. Related to Figure 5. Cocaine-activated Neurons in Mice Previously Exposed to Chronic Cocaine Receive Similar Cortical Inputs to Those in Mice Exposed to Acute Cocaine**

(A) Origins of ALL cortical projections to cocaine-activated striatal neurons, in mice either previously exposed to chronic cocaine (orange), or only receiving the acute cocaine challenge (yellow). Error bar indicates 1 SEM. Abbreviations described in Figure 2.

(B) Each line indicates proportions of total cortical input for an individual animal across all input regions.



**Figure S5. Related to Figure 7. Origins of Cortical Inputs to Locomotor Activated Striatal Neurons**

(A) Location of ALL corticostriatal inputs to either cocaine-activated neurons (cohort-matched subset of animals displayed in Figure 3, yellow) or hyperlocomotion-activated neurons (gray). Error bars indicate 1 SEM. Abbreviations described in Figure 2.

(B) Each line indicates proportions of total cortical input for an individual animal across all input regions.