The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex

Supplemental Information

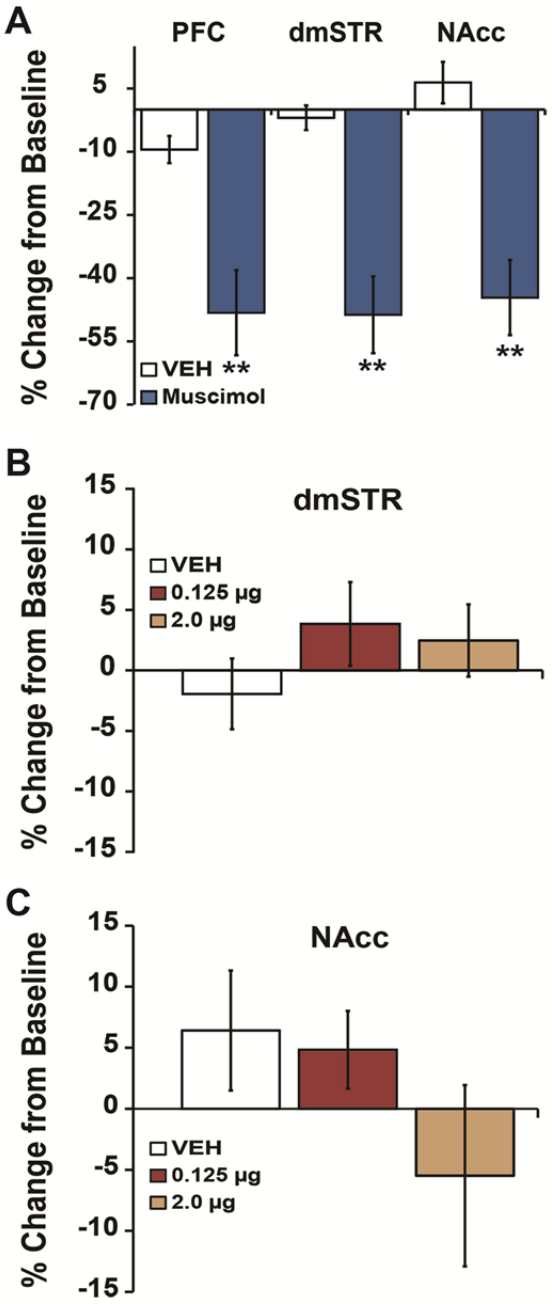

Figure S1. Methylphenidate (MPH) action within the striatum is not sufficient for cognition-enhancement. (**A**) Inactivation of the prefrontal cortex (PFC), dorsomedial striatum (dmSTR), or ventromedial striatum (vmSTR, nucleus accumbens [NAcc]) with the GABA-A agonist, muscimol, impairs working memory to a comparable degree. Nonetheless, MPH has no effect when infused into the dmSTR (**B**) or vmSTR (**C**). Shown is the mean (± SEM) percent change from baseline in delayed alternation performance. $^{**}P < 0.01$ compared with vehicle-treated animals. From (1). VEH, vehicle.

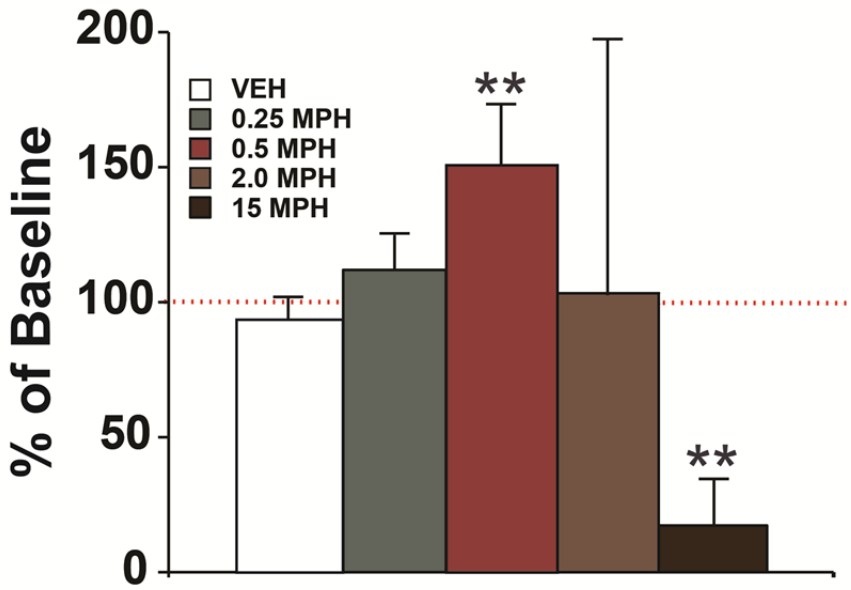

Figure S2. Methylphenidate (MPH) facilitates prefrontal cortex (PFC) neuronal signal processing. Shown are the effects of vehicle (VEH) and varying doses of MPH on evoked activity of neurons in the prelimbic subfield of the PFC of unanesthetized rats as measured by percent of baseline responding during the 30 minute epoch beginning 15-minutes following treatment. Evoked discharge was elicited by electrical activation of ventral subiculum afferents to the PFC. MPH elicited an inverted-U shaped facilitation of evoked responding, with maximal facilitation observed at the same clinically relevant dose that maximally improves working memory (0.5 mg/kg; see Figure 1). At a robustly locomotor activating and stereotypy-inducing dose (15 mg/kg), MPH profoundly suppressed PFC neuronal responsivity. Spontaneous discharge was relatively insensitive to MPH. $^{**}P < 0.01$ compared with vehicle treated animals. From (2).

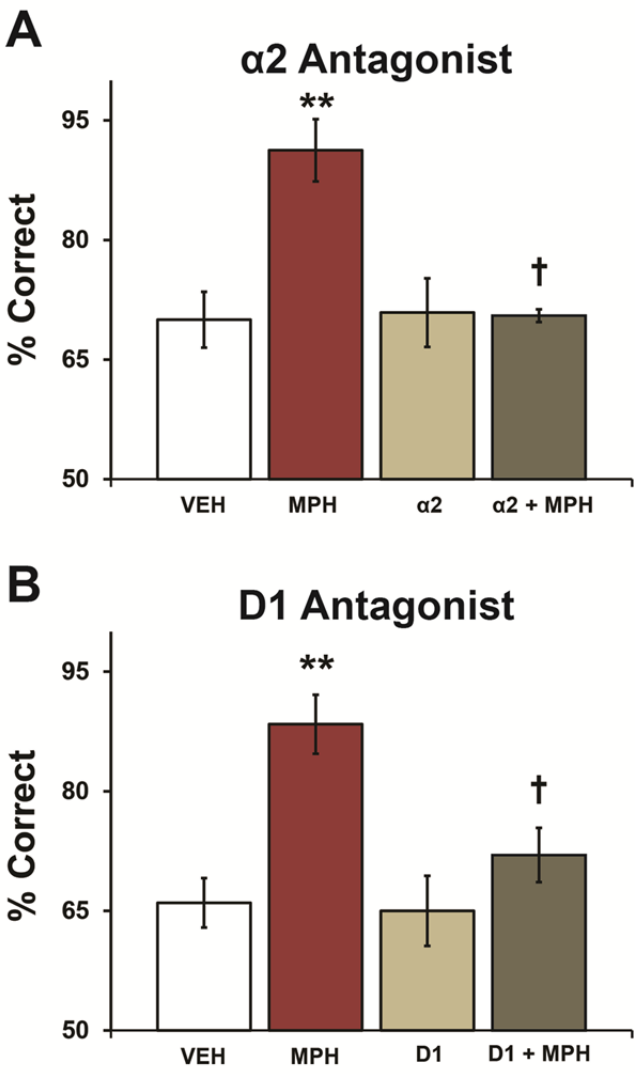

Figure S3. The cognition enhancing effects of methylphenidate (MPH) are dependent on dopamine D1 and norepinephrine α2 receptors. Cognitive enhancement from an optimal oral dose of MPH (1.0-2.0 mg/kg) was blocked with co-administration of (**A**) the norepinephrine α2 receptor antagonist Idazoxan (0.1 mg/kg), and (**B**) the dopamine D1 receptor antagonist, SCH23390 (0.01-0.1 mg/kg) at doses that had no effect on their own. Results represent mean (± SEM) percent correct on the delayed alternation task. ***P* < .01 compared to vehicle. †*P* < .01 compared to MPH. Modified from (3). VEH, vehicle.

Supplemental References

1. Rapport MD, Kelly, KL (1991): Psychostimulant effects on learning and cognitive function: findings and implications for children with attention deficit hyperactivity disorder. *Clin Psych Rev* 11:61-92.
2. Berridge CW (2006): Neural substrates of psychostimulant-induced arousal. *Neuropsychopharmacology* 31:2332-2340.
3. Devilbiss DM, Berridge CW (2008): Cognition-enhancing doses of methylphenidate preferentially increase prefrontal cortex neuronal responsiveness. *Biol Psychiatry* 64:626-635.