Published in final edited form as:

Brain Res. 2016 June 15; 1641(Pt B): 189–196. doi:10.1016/j.brainres.2015.11.024.

Differential Cognitive Actions of Norepinephrine $\alpha 2$ and $\alpha 1$ Receptor Signaling in the Prefrontal Cortex

Craig W. Berridge and Robert C. Spencer

Dept. Psychology, University of Wisconsin-Madison, Madison, WI 53706

Abstract

The prefrontal cortex (PFC) supports cognitive and behavioral processes that guide goal directed behavior. Moreover, dysregulated prefrontal cognitive dysfunction is associated with multiple psychiatric disorders. Norepinephrine (NE) signaling in the PFC is a critical modulator of prefrontal cognition and is targeted by a variety of drugs used to treat PFC-dependent cognitive dysfunction. Noradrenergic modulation of PFC-dependent cognition is complex, with concentration and receptor-specific actions that are likely dependent on neuronal activity state. Recent studies indicate that within the PFC, noradrenergic $\alpha 1$ and $\alpha 2$ receptors exert unique modulatory actions across distinct cognitive processes that allow for context-dependent modulation of cognition. Specifically, high affinity post-synaptic $\alpha 2$ receptors, engaged at moderate rates of NE release associated with moderate arousal levels, promote working memory. In contrast, lower affinity $\alpha 1$ receptors, engaged at higher rates of release associated with high arousal conditions (e.g. stress), impair working memory performance while promoting flexible attention. While these and other observations were initially interpreted to indicate high rates of NE release promotes the transition from focused to flexible/scanning attention, recent findings indicate that $\alpha 1$ receptors promote *both* focused and flexible attention. Collectively, these observations indicate that while $\alpha 2$ and $\alpha 1$ receptors in the PFC differentially modulate distinct cognitive processes, this cannot be simply ascribed to differential roles of these receptors in ‘focused’ vs. ‘flexible’ cognitive processes. Translationally, this information indicates that: 1) not all tests of prefrontal cognitive function may be appropriate for preclinical programs aimed at specific PFC-dependent disorders and 2) the treatment of specific PFC cognitive deficits may require the differential targeting of noradrenergic receptor subtypes.

Introduction

The prefrontal cortex (PFC) supports a coordinated set of cognitive and behavioral processes that guide goal-directed behavior, particularly under distracting and/or ambiguous conditions. These include working memory, planning, and various attentional processes (Robbins, 1996). Extensive research demonstrates that the catecholamine neurotransmitter,

Correspondence: Dr. Craig Berridge, University of Wisconsin-Madison, Department of Psychology, 1202 West Johnson Street, Madison, WI 53706, Phone: 608-265-5938, ; Email: berridge@wisc.edu

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norepinephrine (NE), is an important modulator of PFC function. Consistent with this, NE is targeted by pharmacological treatments used to treat PFC dysfunction associated with a range of psychopathologies, including attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder and depression. Research over the past few decades has provided significant insight into the receptor and intracellular signaling mechanisms that underlie noradrenergic modulation of distinct PFC-dependent cognitive processes. An important outcome of this research is the discovery that NE signaling in the PFC exerts differential actions across cognitive processes that are both concentration- and receptor-dependent. In the following sections we review the general features of the PFC noradrenergic system and evidence regarding noradrenergic receptor modulation of PFC-dependent cognition.

NE and the PFC

From humans to rodents, the PFC displays a functional topographic organization with dorsal subfields associated with higher cognitive function and ventral regions associated with affect- and motivation-related processes (Price et al., 1996). Thus, in the rat, the dorsal portion of the medial PFC, encompassing the dorsal anterior cingulate and dorsal prelimbic subfields, serves a critical role in higher cognitive function (Kesner, 2000), while the ventromedial PFC, comprised of the infralimbic and ventral prelimbic subfields, participates in affective/motivational processes (Dalley et al., 2004; Vertes, 2004). This functional heterogeneity within the PFC involves, in part, topographically-organized projections to downstream striatal subfields, forming distinct functional frontostriatal circuits (Haber, 2003; Haber and Calzavara, 2009).

Noradrenergic fibers are found throughout the PFC (Lewis and Morrison, 1989). While there are multiple brainstem noradrenergic nuclei, the pontine nucleus, locus coeruleus (LC), is the primary source of cortical NE (Foote et al., 1983). Historically, tract-tracing studies have indicated little topographical organization of LC projections, with individual LC neurons branching extensively to target multiple functionally distinct terminal fields (Berridge and Waterhouse, 2003). However, recent observations suggest that, at least in the rat, individual LC neurons preferentially target functionally distinct cortical regions (Chandler et al., 2014), potentially permitting regionally- and functionally-selective modulation of PFC vs. other cortical regions. In the PFC and other noradrenergic terminal fields, NE acts at three families of receptors: α_1 , α_2 , and β receptors, each comprised of multiple subtypes. All three families are found throughout the PFC (Nicholas et al., 1993a; Nicholas et al., 1993b; Pieribone et al., 1994). α_2 receptors display a higher affinity for NE relative to α_1 and β receptors and are thus preferentially engaged at lower rates of release (Arnsten, 2000). There are three subtypes of α_2 receptors, α_2A , α_2B , and α_2C , with post-synaptic α_2A receptors playing a critical role in the regulation of PFC-dependent cognition (see below; MacDonald et al., 1997; Wang et al., 2007). Importantly, the 'dopamine (DA)' D4 receptor binds both NE and DA and thus should be considered a generalized catecholamine receptor, likely playing a role in noradrenergic function (Van Tol et al., 1991). While evidence strongly implicates D4 receptor signaling in cognition (Furth et al., 2013; Yuen et al., 2013; Zhong and Yan, 2014), our understanding of the cognitive actions of *NE signaling* at this receptor is limited.

Noradrenergic Modulation of PFC-Dependent Cognition

1. Working Memory: Opposing Actions of $\alpha 2$ and $\alpha 1$ Receptors

The role of PFC NE in cognition has been extensively studied using delayed response tests of working memory (Arnsten, 2000; Arnsten, 2011). This research demonstrates that NE acts within the PFC to exert an inverted-U shaped modulation of performance in tests of working memory such that *both* inadequate and excessive NE signaling is associated with an impairment in working memory performance while moderate levels of NE signaling is associated with optimal performance (Figure 1; Robbins and Arnsten, 2009). This inverted-U shaped function reflects the differential activation of NE receptor subtypes within the PFC. Thus, under low arousal conditions associated with low rates of NE release or other conditions associated with reduced NE signaling in the PFC (e.g. NE lesions in the PFC, aging) working memory is impaired (Arnsten et al., 1996). These deficits in working memory are reversed by selective activation of high-affinity $\alpha 2$ receptors (Figure 1; Arnsten et al., 1996). Conversely, under conditions associated with moderate arousal levels and moderate rates of NE release, $\alpha 2$ receptor blockade degrades optimal working memory (Figure 1; Arnsten, 2000). In contrast to that seen with PFC $\alpha 2$ receptors, stimulation of $\alpha 1$ receptors in the PFC elicits a stress-like impairment in working memory (Arnsten and Castellanos, 2002). Moreover, while blockade of PFC $\alpha 1$ receptors has no effect on working memory under optimal conditions associated with moderate rates of NE release (Li and Mei, 1994), this reverses working memory impairment associated with high rates of NE release (e.g. stress; Figure 1; Arnsten and Castellanos, 2002; Birnbaum et al., 1999). For β -receptors, limited evidence indicates that $\beta 1$ and $\beta 2$ receptors in the PFC exert opposing actions on working memory; blockade of $\beta 1$ or stimulation of $\beta 2$ receptors in the PFC improves working memory (Figure 1; Ramos et al., 2005; Ramos et al., 2008).

Evidence suggests that pyramidal cell networks in the PFC maintain information required for successful completion of working memory tasks (Goldman-Rakic, 1995). This, in part, involves recurrent excitation of pyramidal neurons through glutamatergic NMDA receptor signaling on dendritic spines (Wang et al., 2007). Electrophysiological studies indicate that pyramidal cells receive excitatory inputs from neighboring pyramidal cells with shared properties ("signals"), as well as input from neurons with dissimilar properties ("noise"; Goldman-Rakic, 1995). Response to "noisy" input is reduced by lateral inhibition from GABAergic interneurons (Goldman-Rakic, 1995). Whereas, response to 'signals' is modulated, in part, through hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels) located on dendritic spines adjacent to excitatory synapses. When HCN channels are open, connectivity and neuronal firing are decreased (Arnsten et al., 2012).

Under conditions associated with moderate arousal and moderate rates of NE release, high affinity $\alpha 2A$ receptors located on dendritic spines of PFC pyramidal neurons are engaged, inhibiting cAMP signaling and reducing HCN channel activation. This results in a strengthening of pyramidal neuronal firing to task-relevant "signals", improving PFC working memory function (Wang et al., 2007). Blockade of $\alpha 2A$ activity elicits opposite actions, increasing HCN channel activity, decreasing task-related network firing and

impairing working memory (Li and Mei, 1994; Ma et al., 2003; Ma et al., 2005; Wang et al., 2007). Under stressful and high arousal conditions associated with high rates of release, NE signaling at $\alpha 1$ receptors in the PFC engages calcium-protein kinase C signaling, leading to a suppression of neuronal firing and an impairment of working memory performance (Arnsten, 2009). These actions of $\alpha 1$ receptors are thought to involve an opening of Ca^{2+} -activated/ K^{+} channels (SK channels) located in the cell body (Arnsten, 2009). It should be noted that the majority of these electrophysiological observations were made in cognitively tested monkeys. Limited, *in vitro* data from rodents indicate that in contrast to the suppressive actions of $\alpha 1$ receptors on delay-related activity observed in monkeys, $\alpha 1$ receptor activation increased glutamate release within rat PFC (Marek and Aghajanian, 1999; Zhang et al., 2013). These observations could reflect species differences in terms of $\alpha 1$ action in the PFC; inhibitory in primates and excitatory in rodents. However, we recently observed in rats tested in a working memory task that while stress suppresses the discharge activity of neurons displaying strongly tuning to delay, reward and error - similar to that seen in monkeys - while the larger population of neurons displaying weak task-related activity were activated under stressful conditions (Devilbiss and Berridge, 2014). This is consistent with evidence suggesting that the neuromodulatory actions of noradrenergic signaling is likely dependent on the activity state of the neuron (Berridge and Waterhouse, 2003). Thus, the differences observed across awake behaving and *in vitro* studies may reflect state-dependent actions of $\alpha 1$ receptors rather than species differences in receptor action.

To summarize, at the level of working memory, $\alpha 2$ and $\alpha 1$ receptors residing within the PFC exert opposing effects, with $\alpha 2$ receptors promoting and $\alpha 1$ receptors impairing PFC network and cognitive function.

2. Flexible Attention: Attentional Set Shifting

Successful attainment of distal goals can require the ability to readily switch attention between cues depending on context and experience. The regulation of attentional shifts is highly dependent on the PFC (Birrell and Brown, 2000). In humans, the Wisconsin Card Sort Task is a commonly used test of attentional flexibility. In this task, the cue that predicts success is changed without being signaled to the subject and success is measured by the time taken to learn the new rule. In rodents, an attentional set shifting task is similarly used to measure the ability to switch attention from a previously rewarded cue to a new reward predicting cue when the shift in cue is unsignaled to the subject (Birrell and Brown, 2000; Owen et al., 1991). Shifting attention to a cue of a different sensory modality (e.g. olfaction to texture), referred to as an extra-dimensional shift, requires greater attentional flexibility than intra-dimensional shifts (e.g. from one odor to a different odor).

Similar to that seen with working memory, depletion of NE within the PFC impairs attentional set shifting (McGaughy et al., 2008). However, in distinct contrast to that seen in tests of working memory, activation of $\alpha 1$ receptors in the PFC improves attentional set shifting, while PFC $\alpha 2$ and β receptors have minimal modulatory effects in this task (Lapiz and Morilak, 2006). The effects of NE manipulations are largely limited to extradimensional shifts, and not observed with intra-dimensional shifts or reversal learning (Lapiz and Morilak, 2006; McGaughy et al., 2008). Thus, the observed effects of NE manipulations on

attentional set shifting do not reflect general alterations in motivation, learning or perception and instead are unique to shifting attention across sensory modalities (Lapiz and Morilak, 2006; McGaughy et al., 2008).

The ability of PFC $\alpha 1$ receptors to improve attention set shifting contrasts with their working memory impairing effects. It was initially posited that the discrepancy between the actions of PFC $\alpha 1$ receptors across these tasks reflected the fact that working memory required a more focused form of attention relative to attentional set shifting. This hypothesis was largely based on results obtained in earlier LC recording studies in monkeys engaged in a vigilance task, a form of focused and sustained attention that does not require flexible shifts of attention. It was observed that optimal performance in the vigilance/sustained attention task was associated with moderate rates of tonic LC discharge activity. In contrast, when tonic LC activity was elevated, the animals displayed elevated indices of arousal and visual scanning and impaired vigilance/sustained attention (Rajkowski et al., 1994). Combined, the observations across these different studies suggested the hypothesis that under conditions of stress/arousal, higher rates of NE signaling within the PFC activate $\alpha 1$ receptors which drives the transition from focused attention to a more flexible mode of scanning attention (Usher et al., 1999; Lapiz and Morilak, 2006). Consistent with this, attentional set shifting in rats is improved by activation of LC neurons by the stress-related neuropeptide, corticotropin releasing factor (Snyder et al., 2012).

While this hypothesis was consistent with data available at the time, as described in the following section, recent observations with the ADHD-related drug, methylphenidate, suggest that PFC $\alpha 1$ receptors do not differentially modulate focused vs. flexible attention and instead improve both forms of attention.

3. Focused Attention: Sustained Attention

Psychostimulants are the first-line treatment of ADHD (Greenhill, 2001; Wilens et al., 2004). The therapeutic effects of these drugs are closely linked to their ability to improve PFC-dependent cognition (Spencer et al., 2015). Importantly, the procognitive effects of these drugs are not restricted to ADHD patients; low doses that elicit clinically relevant plasma concentrations improve PFC-dependent cognitive processes in healthy human and animal subjects (Arnsten and Dudley, 2005; Berridge et al., 2006; Rapoport et al., 1980; Rapoport and Inoff-Germain, 2002). Similar to that described for NE (and DA), psychostimulants exert an inverted-U shaped modulation of working memory, with clinically-relevant doses improving and supra-clinical doses impairing (Figure 2; Arnsten and Dudley, 2005; Berridge et al., 2006; Spencer et al., 2015). Also similar to that seen with catecholamines, psychostimulants exert an inverted-U shaped modulation of PFC neuronal signaling, with clinically relevant doses strengthening and supra-clinical doses suppressing PFC signaling (Devilbiss and Berridge, 2008; Gamo et al., 2010).

Neurochemically, methylphenidate inhibits NE and DA reuptake (Kuczenski and Segal, 1997). At high and abuse-relevant doses, this and other psychostimulants robustly elevate extracellular catecholamines widely throughout the brain (Kuczenski et al., 1991; Kuczenski and Segal, 1997). In contrast, at clinically relevant doses methylphenidate preferentially targets PFC catecholamines, eliciting moderate increases in extracellular NE and DA within

the PFC (100-250%) and significantly smaller increases in cortical and subcortical regions outside the PFC (25%-50%; Berridge et al., 2006; Drouin et al., 2006; Kuczenski and Segal, 2002). Collectively, these observations suggest the hypothesis that psychostimulant action within the PFC contributes to the cognition-enhancing and therapeutic effects of these drugs. Consistent with this, infusion of low concentrations of methylphenidate into the dorsomedial, but not ventromedial, PFC of rats improves working memory performance (Spencer et al., 2012).

Clinically-relevant doses of psychostimulants also improve performance in sustained attention tasks in humans and animals (Berridge et al., 2006; Solanto, 1998). However, in contrast to the narrow inverted-U dose response curve observed with working memory tasks, the sustained attention-improving actions are observed across a broader dose range. Specifically, in rats, maximal improvement in sustained attention is observed at a dose 4-fold higher than the dose that maximally-improves working memory, a dose that in fact impairs working memory (Figure 2; Berridge et al., 2012b). A similar shift in dose response curves across these two tasks is observed with MPH infusion directly into the dmPFC (Spencer et al., 2014). A comparable divergence of dose-response curves has been observed in ADHD patients for methylphenidate-induced improvements in working memory and response inhibition (narrow) vs. suppression of hyperactivity (broad; Sprague and Sleator, 1977; Tannock et al., 1989).

To assess whether this divergence in dose response curves is unique to tasks requiring high focused attention, additional studies examined the dose-dependent actions of methylphenidate in the attentional set shifting task (Berridge et al., 2012b). The doses at which methylphenidate improved performance in this task were identical to those identified as improving sustained attention (Figure 6; Berridge et al., 2012b). Collectively, these observations indicate that differing PFC-dependent cognitive processes display differing dose sensitivity to methylphenidate that are not predicted by the degree to which they are associated with cognitive flexibility.

As reviewed above, noradrenergic $\alpha 2$ receptors improve, while $\alpha 1$ -receptors impair, working memory (Arnsten and Li, 2005). In contrast, $\alpha 1$ receptors improve attentional set shifting while $\alpha 2$ receptors have little impact in this task (Lapiz and Morilak, 2006). Collectively, these observations suggest the hypothesis that the narrow vs. broad inverted-U shaped actions of methylphenidate across working memory vs. focused *and* flexible attention tasks reflect differential actions of $\alpha 2$ vs. $\alpha 1$ receptors, respectively. Consistent with this hypothesis, while methylphenidate-induced improvement in *working memory* is dependent on $\alpha 2$ receptors (Arnsten and Li, 2005; Spencer et al., 2014) MPH-induced improvement in *sustained attention* is dependent on $\alpha 1$ receptors (Berridge et al., 2012b). Moreover, ongoing studies in our laboratory indicate that direct infusion of an $\alpha 1$ agonist into the dorsomedial PFC improves sustained attention similar to that seen with attentional set shifting, while improvement in sustained attention induced with intra-PFC infusion of MPH is prevented by $\alpha 1$ receptor blockade locally within the PFC (data not shown). Combined, these observations indicate that PFC $\alpha 1$ receptors, activated at high rates of NE release, facilitate both focused and flexible attention.

Noradrenergic Modulation of Sensorimotor Gating

We are bombarded by sensory information irrelevant to goal attainment. Thus, effective goal-directed behavior requires pre-attentive gating of sensory information. Prepulse inhibition (PPI) is a commonly used measure of sensorimotor gating. In this test, a low intensity auditory stimulus (prepulse), applied immediately before a high-intensity and startle-eliciting auditory stimulus, reduces the musculoskeletal startle response to the high-intensity stimulus. Deficits in sensorimotor gating as measured with PPI have been associated with varying psychopathologies, including schizophrenia (Geyer et al., 2001; Swerdlow et al., 1998; Swerdlow et al., 1999). NE acts in a variety of brain regions to modulate sensorimotor gating, including the PFC (Alsene and Bakshi, 2011; Alsene et al., 2011). In particular, studies in rats demonstrate that activation of $\alpha 1$ (and β) receptors in the caudal dorsomedial PFC *impairs* sensorimotor gating. This action contrasts with the attention-promoting effects of $\alpha 1$ receptors described above (Berridge et al., 2012b; Lapiz and Morilak, 2006). These observations indicate that noradrenergic $\alpha 1$ receptors exert opposing actions on pre-attentive vs. attention-related processes. While a deficit in pre-attentive sensory information filtering could contribute to working memory deficits elicited by PFC $\alpha 1$ receptor activation, much of the research with $\alpha 1$ receptor-dependent modulation of working memory involves the rostral PFC, a region in which $\alpha 1$ receptor activation has no effect on sensorimotor gating (Alsene et al., 2011).

Summary

The available evidence indicates that $\alpha 2$ and $\alpha 1$ receptors in the PFC modulate distinct cognitive processes. Specifically, $\alpha 2$ receptors promote and $\alpha 1$ receptors impair performance in tests of working memory. In rats, these actions of $\alpha 2$ and $\alpha 1$ receptor manipulations are observed within the rostral aspect of the dorsomedial PFC. As with working memory, $\alpha 1$ receptors also impair sensorimotor gating as measured in PPI. However, this appears to be associated with more caudal portions of the dorsomedial PFC. Combined, these findings indicate that NE action in the PFC displays functional topography in both the dorsoventral and rostrocaudal axes. In contrast, to that seen in working memory, the available evidence indicates that PFC $\alpha 1$ receptors promote while $\alpha 2$ receptors exert minimal effects on flexible attention as measured in an attentional set shifting task. Moreover, recent observations indicate that the differential actions of $\alpha 2$ vs. $\alpha 1$ receptors across working memory and attentional set shifting tasks cannot be simply ascribed to differential roles of these receptors in 'focused' vs. 'flexible' cognitive processes. Specifically, the available evidence indicates that $\alpha 1$ receptor signaling in the PFC promotes *both* flexible (attentional set shifting) and focused attention (sustained attention). A key difference between working memory tasks and the tests of attention described above is the need in working memory tests for the maintenance of information 'on-line' in the presence of distractors to guide subsequent response selection. The available data indicate that $\alpha 2$ receptors support while $\alpha 1$ receptors degrade this process in part through opposing actions on the sustained activation of PFC neurons during the delay interval of working memory tasks.

Clinically, this information indicates that the choice of drug treatment for PFC dysfunction may be guided by the specific cognitive deficits associated with a disorder. Preclinically, the

above-described observations indicate that not all PFC-dependent cognitive tasks may be well suited for drug discovery programs focused on specific disorders. For example, extensive evidence demonstrates that the pharmacology of working memory mirrors the pharmacology of ADHD: all approved ADHD-related drugs, including α_2 agonists (Arnsten, 2010), low-dose psychostimulants (Arnsten and Dudley, 2005; Berridge and Devilbiss, 2011) and selective NE reuptake blockers (e.g. atomoxetine; Gamo et al., 2010) improve performance in tests of working memory. Moreover, in the case of psychostimulants, their beneficial effects on working memory only occur across a narrow range of doses that produce clinically-relevant plasma concentrations (Arnsten, 2010; Berridge, 2006; Kuczenski and Segal, 2001; Kuczenski and Segal, 2002). Thus, delayed response tests of working memory are well-suited for preclinical identification of potentially efficacious compounds for use in ADHD. In contrast, in sustained attention and attentional set shifting tasks, maximal beneficial actions of methylphenidate occur at doses that produce plasma concentrations above the clinically-relevant range and that exert arousing and behaviorally activating effects (Berridge, 2006; Kuczenski and Segal, 2002; Navarra et al., 2008). Additionally, where examined, clinically efficacious α_2 agonists have minimal effects on performance in these tasks. Thus these tests may have less utility in an ADHD-focused preclinical program. Identifying the degree to which drug-induced improvement in these attention tests predicts clinical efficacy for other disorders is an important topic for future studies.

Acknowledgments

This work and research described was supported by PHS grants MH098631, MH081843 and the University of Wisconsin-Madison Graduate School. We gratefully acknowledge permission by Dr. Amy Arnsten to adapt her schematic figure depicting inverted-U modulatory actions of catecholamines for use in this article.

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highlights

Norepinephrine acts in the prefrontal cortex to modulate higher cognitive function.

Norepinephrine exerts differential actions across distinct cognitive processes.

The differential actions reflect differential participation of receptor subtypes.

High affinity $\alpha 2$ receptors promote working memory.

Lower affinity $\alpha 1$ receptors promote both focused and flexible forms of attention.

Figure 1.

Differential actions of noradrenergic receptor subtypes on working memory. Under low rates of norepinephrine (NE) release in the prefrontal cortex (PFC) associated with sedation or following lesions, working memory is impaired. This impairment is reversed by selective stimulation of α_2 receptors in the PFC. As rates of NE release increase, lower affinity α_1 receptor are engaged resulting in a decrease in working memory function. Blockade of these receptors reverses stress-related working memory impairment. Limited evidence suggests that β_2 receptors facilitate while β_1 receptors degrade working memory function. Adapted from (Berridge et al., 2012a)

Figure 2.

Low dose methylphenidate (Ritalin) exerts differential actions across working memory and attentional processes. Panel A. The psychostimulant, methylphenidate (MPH) exerts a relatively narrow inverted-U shaped facilitation of working memory performance (A, dotted line), with maximal improvement seen at the clinically-relevant dose of 0.5 mg/kg (intraperitoneally) and impairment seen at a dose four-fold higher (2.0 mg/kg). This contrasts with the right-shifted dose-response curve seen with MPH-induced improvement in sustained attention, with maximal improvement seen at 2.0 mg/kg. This does not reflect a differential sensitivity of 'flexible' vs. 'focused' attentional/cognitive function as attentional set shifting (B) shows a dose sensitivity identical to that seen with sustained attention (i.e. maximal improvement seen with the 2.0 mg/kg dose). * $P < 0.05$; ** $P < 0.01$ compared to vehicle treatment. Data from (Berridge et al., 2012b).

Figure 3.

Sustained attention is improved by α_1 receptors. Shown are the effects of the α_1 receptor antagonist, prazosin (PRAZ), on the sustained attention improving effects of methylphenidate (MPH). When administered systemically alone at 2.0 mg/kg, MPH improves sustained attention (left bar). Coadministration of PRAZ at a dose that on its own does not affect sustained at a dose (0.5 mg/kg, middle bar), prevents the sustained attention improving action of MPH (right bar). These data indicate that sustained attention is improved by α_1 receptor activation, similar to attentional set shifting. Bars indicate mean change in d' from baseline. ** $P < 0.01$ vs. baseline; + $P < 0.05$ vs. vehicle.