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Opioid Modulation of Cognitive Impairment in Depression

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Abstract

The failure of traditional antidepressant medications to adequately target cognitive impairment is associated with poor treatment response, increased risk of relapse and greater lifetime disability. Opioid receptor antagonists are currently under development as novel therapeutics for major depressive disorders (MDD) and other stress-related illnesses. Although it is known that dysregulation of the endogenous opioid system is observed in patients diagnosed with MDD, the impact of opioidergic neurotransmission on cognitive impairment has not been systematically evaluated. Here we review the literature indicating that opioid manipulations can alter cognitive functions in humans. Furthermore, we detail the preclinical studies that demonstrate the ability of mu opioid receptor (MOR) and kappa opioid receptor (KOR) ligands to modulate several cognitive processes. Specifically, this review focuses on domains within higher order cognitive processing, including attention and executive functioning, which can differentiate cognitive processes influenced by motivational state.

Keywords

Opioids; cognition; depression; stress; antidepressants

INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability and functional impairment worldwide (Global Burden of Disease Study, 2015). In addition to low mood, persistent anhedonia and cognitive dysfunction are core features of this debilitating and lifelong illness. Indeed, as many as 50% of depressed individuals report deficits in one or more cognitive domains, such as impaired memory, attention, executive function and processing speed (Albert et al., 2018, Cotrena et al., 2016, Lam et al., 2014, Marino et al., 2009). Although conventional antidepressants reduce depressive severity, they produce mixed results on cognitive processing outcomes, with many therapies failing to alter long-term cognitive dysfunction (Culpepper et al., 2017, Kaser et al., 2017).

In recent years, clinical studies have begun to explore the association between cognitive variables and functional impairment in MDD. Over the course of two years, the Prospective

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Epidemiological Research on Functioning Outcomes Related to Major depressive disorder (PERFORM) study followed depressed subjects from the beginning of a course of antidepressant monotherapy. Although functional impairment improved initially following treatment onset, persistent functional impairment due to depression (measured using the Work Productivity and Activity Impairment (WPAI) questionnaire) correlated positively with increased cognitive symptoms (measured by the five-item Perceived Deficit Questionnaire (PDQ-5)). These PERFORM data demonstrate the impact of cognitive symptoms on the chronicity and severity of depression. Similarly, the international Study to Predict Optimized Treatment for Depression (iSPOT-D), demonstrated that decreased accuracy in attention, processing speed, response inhibition and working memory were predictive of remission of symptoms in response to escitalopram (Etkin et al., 2015). In this study, melancholic MDD subjects exhibited greater impairment in processing speed and set-shifting tasks compared to non-melancholic MDD subjects and controls (Day et al., 2015). Moreover, cognitive impairment identified those patients with a history of greater adversity and maltreatment in childhood (Miller et al., 2015). Collectively, these reports illustrate how cognitive dysfunction in depression has been an untargeted contributor to disease chronicity, severity and incomplete treatment success.

Although executive dysfunction in depressed subjects may reflect distractibility due to negative affect and pronounced bias for negative stimuli, persistent levels of cognitive impairment even following remission suggest that other biological processes influence long-term cognitive deficits associated with MDD. These deficits are most apparent in emotion-dependent cognitive processes, such as decision-making, impulsive choice/action, sustained attention and psychomotor speed (Snyder, 2013), which are associated with blunted reward valuation (Fletcher et al., 2015, Roiser and Sahakian, 2013, Soskin et al., 2013, Treadway and Zald, 2011). Cognitive flexibility and goal directed cognitive processes are impacted by different subcomponents of reward processing: 1) motivation, the incentive salience or wanting associated with unconscious response to cues, or conscious responses for desires, 2) hedonic impact, or how much pleasure is derived from the reward, i.e. liking, which is influenced by the subjective awareness and salience of the reward, and 3) learning, the implicit and explicit associations with the rewarding or aversive stimulus (Berridge and Kringelbach, 2008). There is an extensive literature detailing the importance of dopaminergic neurotransmission in the context of wanting (Alcaro and Panksepp, 2011, Fletcher et al., 2015, Olney et al., 2018, Soskin et al., 2013). In contrast, dopamine (DA) does not alter core liking processes (Thomsen, 2015). Most conventional therapies modulate hedonic impact, or “wanting”. Thus, targeting “liking”, or the ability to learn about a reward may prove a beneficial strategy in the development of new antidepressant medications.

Emerging data suggest that opioid-based compounds targeting one or more of the four opioid receptor subtypes, mu (MOR), kappa (KOR), delta (DOR) and the nociceptin/orphaninFQ (NOP), may be effective therapeutics for stress-related psychiatric disorders (Lutz and Kieffer, 2013, Witkin et al., 2014). Moreover, endogenous opioid neurotransmission has been shown to affect all subcomponents of reward processing (DiFeliceantonio and Berridge, 2012) and cognitive processes. Therefore, this review will outline the importance of opioid receptors and their ligands in the pathophysiology of motivational and cognitive deficits associated with depression. Specially, the role of MORs

and KORs in cognitive processing domains will be discussed, providing an overview of the clinical and preclinical findings.

OPIOID LIGANDS AND COGNITIVE FUNCTION: CLINICAL EVIDENCE

There have been few clinical studies pertaining to the role of opioid neurotransmission in cognitive processing domains. Early studies conducted in healthy controls demonstrated that agonists of MOR (Saarialho-Kere et al., 1989, Walker et al., 2001) and KOR (MacLean et al., 2013) impair normal cognitive processes, primarily by increasing reaction time (psychomotor retardation), decreasing accuracy and impairing recall for episodic and spatial memory (Martin del Campo et al., 1992, Tariot et al., 1988). Conversely, high doses of the mixed opioid antagonist naltrexone were shown to reduce cue-induced responding and impulsivity in healthy subjects (Weber et al., 2016). In the context of disease, opioid antagonists appear to confer a beneficial effect; improved psychomotor responses, decision-making, and attention were detected in subjects diagnosed with Tourette's syndrome (Kurlan et al., 1991), binge-eating (Chamberlain et al., 2012) and gambling disorders (Porchet et al., 2013). In addition, MDD patients exhibited anterograde and retrograde amnesia when administered electroconvulsive therapy (ECT) to treat their depression. Naltrexone administered prior to ECT, greatly improved sustained attention compared with patients treated with ECT alone (Prudic et al., 1999). Although it can be difficult to attribute the effects of mixed opioid antagonists to one receptor subtype, additional evidence suggests that value-based decision-making is regulated by MORs, as low-dose morphine promotes responding to high-value rewards, whereas naltrexone decreases the preference for high versus low-value rewards (Eikemo et al., 2017). Moreover, healthy human carriers of the loss of function *OPRM1* A118G allele exhibited impaired reward responding compared to AA homozygotes on a probabilistic signal detection reward task, that was characterised by a decline in the response for rewarded stimuli (Lee et al., 2011). Since reduced reward responsiveness can predict anhedonia, it would be worthwhile to study this polymorphism within the clinical MDD population.

The importance of MORs in hedonic response to social anhedonia has been highlighted by recent imaging studies; avoidance of attachment in adulthood is negatively correlated with MOR availability or binding potential (BP) for the selective radiotracer [^{11}C] carfentanil in the thalamus, anterior cingulate cortex (ACC, amygdala, and insula of depressed subjects (Nummenmaa et al., 2015). Similarly, when asked to recount a sad experience, female MDD subjects exhibited decreased MOR BP in the anterior insular cortex (AIC), anterior and posterior thalamus, ventral basal ganglia, amygdala, and periamygdalar cortex compared to controls (Kennedy et al., 2006). Conversely, greater trait resilience to social rejection was positively correlated with MOR activation in the amygdala, periaqueductal gray and ACC (Hsu et al., 2013). Furthermore, depressed subjects showed exaggerated subjective wellbeing following acceptance and greater lowering of self-esteem after rejection compared to healthy controls (Hsu et al., 2015). In addition, individuals with the loss of function *OPRM1* A118G allele had greater reactivity to social rejection in the dorsal ACC and AIC as shown on fMRI, during an online ball-tossing game (Way et al., 2009). Together these data highlight the importance of MORs in social reward in MDD.

KORs may also play a role in regulating the response to social stimuli in depressed individuals. Social withdrawal may reflect a failure to inhibit aversive thoughts and actions. Humans (Pfeiffer et al., 1986, Ranganathan et al., 2012) and rodents exhibit significant dysphoria and aversion following KOR activation (Bals-Kubik et al., 1993, Bruchas et al., 2007, Chefer et al., 2013, del Rosario Capriles and Cancela, 2002, Land et al., 2008, Mori et al., 2002, Shippenberg and Herz, 1986, Zhang et al., 2005). Postmortem studies in suicide completers with a history of major depression revealed increased mRNA expression of prodynorphin (*PDYN*), the precursor of the endogenous KOR ligand dynorphin (DYN), in the patch compartment of the caudate, but not in the dorsolateral prefrontal, or cingulate cortices (Hurd et al., 1997, Peckys and Hurd, 2001). Conversely, decreased *PDYN* gene expression was evident in depressed subjects within the periamygdaloid complex (Anderson et al., 2013, Hurd, 2002). Moreover, childhood maltreatment, was associated with decreased expression of the *OPRK1* gene in the AIC of depressed suicides (Lutz et al., 2017), a brain region that is critical for both social bond formation and introspection. Subsequent neuroimaging studies in depressed patients have suggested that low KOR availability in amygdala-anterior cingulate cortex-ventral striatal circuit regulates the phenotypic expression of dysphoria in patients diagnosed with depression, anhedonia and PTSD (Pietrzak et al., 2014). It is proposed that reduced expression of KORs may ultimately lead to increased inhibitory gamma-aminobutyric acid (GABA) neurotransmission in the amygdala and insula, disrupting normal function and shifting responsivity towards a more stress-like state.

In relation to cognitive processes, opioid-dependent subjects treated with the mixed opioid compound buprenorphine performed better than subjects treated with the MOR agonist methadone in several cognitive tests, including N-back and spatial working memory (Baewert et al., 2007, Loeber et al., 2008, Pirastu et al., 2006, Rapeli et al., 2007, Rapeli et al., 2011). It was proposed that buprenorphine was superior to methadone in preserving working memory function due to KOR antagonism and downstream modulation of prefrontal DA tone. In healthy human subjects, robust anti-stress effects and improved emotional processing of stimuli were detected following low doses of buprenorphine, an effect that occurred in the absence of a subjective high (Bershad et al., 2015, Bershad et al., 2016). Together, these data implicate aberrant MOR and KOR tone, particularly in cortico-limbic structures, in the development of emotional dependent cognitive impairment. Now, as several selective compounds are currently under clinical development for affective disorders, the effects of selective MOR and KOR antagonists on executive function can be empirically tested. Despite the dearth of clinical data, preclinical evidence supports the hypothesis that cognitive processes are dramatically altered by opioid neurotransmission.

OPIOID LIGANDS AND COGNITIVE FUNCTION – PRECLINICAL EVIDENCE

Chronic stress exposure is associated with increased risk for development of depression. In animal models of chronic stress, cognition has been demonstrably altered by stress exposure (Campeau et al., 2011, Conrad and Bimonte-Nelson, 2010, Darcet et al., 2016, Holmes and Wellman, 2009, Hurtubise and Howland, 2017, Sandi and Pinelo-Nava, 2007). Preclinical analogues of the behavioral tasks used to explore cognitive processing domains in humans are noted in Table 1. Stress-induced cognitive impairments are overwhelmingly and reliably

observed in tasks assessing higher order processes of cognitive functioning (Darcet et al., 2016, Holmes and Wellman, 2009, Hurtubise and Howland, 2017), such as those included under the cognitive constructs of attention and executive function. These tasks rely more on prefrontal cortex engagement, rather than hippocampal processes. On the other hand, impairments on tasks related more closely to learning and memory, such as those included under the constructs of declarative memory and working memory, which are more hippocampal based, are less reliably observed following exposure to chronic stress (Conrad and Bimonte-Nelson, 2010). Additionally, these tasks are not employed as often in humans and overall have less translational value. To our knowledge, no preclinical study has assessed the influence of the opioid system in response to chronic stress exposure on performance of higher order cognitive processes and executive functioning. Therefore, this section of the review will highlight those preclinical tests in which administration of opioid ligands and genetic deletion of opioid receptors have yielded valuable information regarding opioids and cognition, regardless of any impairments due to a stress-induced depressive-like phenotype, including the 5-choice serial reaction time test, select behavioral control tasks, attentional set shifting, reversal learning, prepulse inhibition, and latent inhibition (Table 1). Moreover, the following section will evaluate the capacity of these tests to differentiate motivational state and cognitive impairment.

5-choice serial reaction time task (5-CSRTT).

The 5-CSRTT has been used to measure many facets of attention, decision-making, and response inhibition that are differentially affected by opioid ligands. Briefly, rodents must divide and sustain their attention to detect a brief visual target presented randomly in one of five locations, where they then must respond appropriately at that specific location within a limited time period to receive a food reward (Bari et al., 2008, Robbins, 2002). The 5-CSRTT is analogous to the continuous performance task (CPT) in humans (Robbins, 2002), the performance of which is impaired in patients with depression (Canpolat et al., 2014). Attention is primarily measured by assessing correct responses, omissions, and total accuracy. Omissions are trials in which no response is made, or a response is made too late. Accuracy is how subjects perform on trials in which they make any response. Premature and anticipatory responses during inappropriate times terminate the trial, making it possible to also measure inhibitory control, or impulsive action. Decision-making, and processing speed can be assessed by latency to respond to the stimulus presentation. Motivation can be parsed out by assessing latency to retrieve the reward. In rodents, administration of KOR and MOR agonists decreased performance on several measures of attention in the 5-CSRTT, and pretreatment with mixed opioid antagonists blocked impairments induced by opioid and non-opioid ligands, Table 2.

The systemic administration of opioid agonists, including U50,488, U69,593, GR89,69, salvinorin A, and morphine impair attention (Maguire et al., 2016, Nemeth et al., 2010, Pattij et al., 2009, Shannon et al., 2007). These ligands typically decreased correct responding, but did not affect overall accuracy (Maguire et al., 2016, Nemeth et al., 2010, Paine et al., 2007, Pattij et al., 2009). Additionally, opioid agonists increased omissions (Boyette-Davis et al., 2008, Koffarnus and Katz, 2011, Maguire et al., 2016, Nemeth et al., 2010, Paine et al., 2007, Pattij et al., 2009, Shannon et al., 2007), which is a measure linked

not only to attention, but also to motivation. Typically, no effects have been reported on the latency to retrieve the reward in response to opioid ligands (Boyette-Davis et al., 2008, Nemeth et al., 2010, Paine et al., 2007), although this parameter is not measured in all studies. Overall, increased omissions with no increase in reward latency is indicative of impaired attention rather than a deficit in motivation (Robbins, 2002).

As summarized in Table 2, the non-selective opioid antagonist naltrexone (Shannon et al., 2007) and selective KOR antagonist JDTC (Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012) did not affect any 5-CSRTT measures at baseline, but reversed all impairments induced by U69,593 (Shannon et al., 2007), salvinorin A (Nemeth et al., 2010), and morphine (Shannon et al., 2007). Opioid receptor antagonists can also attenuate impaired performance on the 5-CSRTT induced by other ligands. Administration of ketamine produced comparable impairment to that produced by salvinorin A (Nemeth et al., 2010). JDTC decreased responding and increased omissions in ketamine impaired rats, but had no effect on response latency (Nemeth et al., 2010). Surprisingly, administration of both JDTC and ketamine synergistically led to an increase in premature responding, an effect that was absent in rats administered either compound alone (Nemeth et al., 2010). Amphetamine also decreases accuracy and response latency, while increasing premature responses, all of which can be reversed by naloxone but not the KOR antagonists, norbinaltorphimine (nor-BNI), or naltrindole, a selective delta opioid receptor antagonist, suggesting the effects are driven by MORs (Wiskerke et al., 2011). Moreover, naloxone blocked the increase in premature responses induced by the selective DA transporter inhibitor GBR 12909 (Wiskerke et al., 2011) although naloxone did not affect behavioral impairments produced by nicotine (Wiskerke et al., 2012). Taken together, these data suggest a MOR-selective mechanism may be involved in the restoration of normal attention in the 5-CSRTT. This is supported by studies of both opioid and non-opioid mediated attention deficits, which report better outcomes following naloxone administration compared with administration of selective KOR antagonists, or the mixed opioid antagonist naltrexone.

Performance deficits on measures of the 5-CSRTT induced by opioids are most likely centrally mediated, as the peripherally restricted KOR agonist ICI-204,448 had no effect on any measure of performance (Shannon et al., 2007). One of the brain regions controlling the motivational components of 5-CSRTT is the nucleus accumbens (NAc). Infusions of naloxone, morphine, the selective MOR agonist DAMGO, and the selective MOR antagonist CTAP into the NAc shell and core, indicate that the NAc shell is more important for premature responding in this task (Wiskerke et al., 2011). It is proposed that MOR-mediated effects on premature responses are dependent on DA transmission within the NAc shell (Wiskerke et al., 2011). However, Lister Hooded rats bred for low, or high impulsivity based on their premature responses on the 5-CSRTT displayed comparable MOR binding in the ventral striatum (Jupp et al., 2013). Additionally, high impulsive rats exhibited lower binding for the DA transporter (DAT) and D2/D3 receptors in NAc shell. Although, MORs are clearly of importance in modulating inhibitory control on this task, it is likely that MOR sensitive brain regions other than the NAc shell, are involved in behavioral inhibition.

To date no studies have directly assessed the ability of opioid antagonists to attenuate deficits in 5-CSRTT following stress exposure. However, multiple reports have studied the

effects of opioid antagonists on behavioral deficits induced by stress neuropeptides. Corticotropin releasing factor (CRF) and pituitary adenylate cyclase-activating polypeptide (PACAP), play important roles in regulating stress responses (Donahue et al., 2016, Van't Veer et al., 2012). Administration of both CRF and PACAP can mimic direct stress exposure, and PACAP can even increase CRF expression. Intracerebroventricular (ICV) infusions of PACAP impaired performance in the 5-CSRTT, as measured by lower correct responses, increased omissions, reduced accuracy, and reduced post error accuracy (Donahue et al., 2016). Similarly, ICV infusions of CRF decreased correct responses, accuracy and premature responses, while increasing omissions, reward latencies, and the total time to complete the session (Van't Veer et al., 2012). Moreover, JDTC reversed CRF-induced impairments in correct responses, omissions, response latency and session time (Van't Veer et al., 2012). Overall these data suggest that opioid antagonists may attenuate stress-induced alterations in 5-CSRTT behavioral parameters.

Post error accuracy is affected by how performance changes following an incorrect response. In a negative emotional state such as that experienced during a depressive episode, cognitive control deficits continue to worsen following errors, or negative feedback. Across a number of cognitive tasks, following an incorrect, but not correct response, performance decreased in depressed patients (Holmes and Pizzagalli, 2007, Steffens et al., 2001). Replication of stress induced impairments in post error adjustments in rats was observed following administration of CRF (Beard et al., 2015) or PACAP-38 (Donahue et al., 2016). Post error accuracy on the 5-CSRTT decreased in response to these hormones, this effect was reversed with pre-treatment of the KOR antagonist, JDTC (Beard et al., 2015). Since a KOR antagonist improved post error accuracy in rats, it is possible that KOR signaling may be part of the mechanism underlying deficits in post error accuracy in humans (Beard et al., 2015). However, it is important to keep in mind that acute administration of CRF, or PACAP is not the same as chronic stress exposure. Support for the role of opioidergic signaling in performance monitoring has also been reported in healthy humans, where naltrexone given acutely in healthy female humans had no effect on post error accuracy, but increased post error slowing in a Stroop-like task (van Steenbergen et al., 2017). Post error slowing, and post error accuracy are not mutually exclusive entities. Slower responses post error may indicate a subject's effort in ensuring the accuracy of the subsequent response, therefore likely increasing post error slowing while not effecting post error accuracy. However, in depressed patients undergoing cognitive behavioral therapy (CBT) in conjunction with antidepressant treatment, both post correct and post error adjustments in reaction time were decreased following treatment (Beard et al., 2015). This effect was replicated in rats, where CRF increased response latencies, and was reversed by a KOR antagonist (Beard et al., 2015). Additionally, in healthy individuals with a gain of function polymorphism in the *PDYN* gene, assessed on the arrow flanker task while undergoing electroencephalogram (EEG) recordings, determined that those with higher *PDYN* expression showed higher neural error processing compared to those with lower *PDYN* expression (Pfabigan and Tran, 2015). This finding suggests that high DYN levels may enhance performance monitoring in healthy controls. However, the effect of elevated DYN levels induced by persistent exposure to stressful stimuli on cognitive processes are unknown and may actually be detrimental to behavioral performance. In remitted depressed individuals, an acute stress manipulation

decreased post error accuracy in an arrow flanker task, as expected, but this corresponded with decreased frontocingulate activation shown by event related potentials (Whitton et al., 2017). Performance monitoring involves learning processes driven by reward prediction errors (RPEs), which are most commonly linked with DA neurotransmission (Schultz, 1997). It is therefore likely that these effects are mediated by an interaction between both opioid and DA neurotransmission. Whether activity is enhanced or diminished is debated and requires more research, nevertheless these studies provide evidence for a role of the endogenous opioid system in performance monitoring and RPEs (Beard et al., 2015, Pfabigan and Tran, 2015, Whitton et al., 2017). Together these studies support the claim that blocking opioid function increases adaptive control following errors.

In the 5-CSRTT, animals are typically deprived of food to increase motivation to perform operant behavior and therefore the motivational level is a potential confound in interpretation of the data. Opioid neurotransmission, particularly within the NAc, plays a key role in food-motivated behaviors (Berridge, 2009, Cota et al., 2006, Morales et al., 2016, Pecina and Smith, 2010). As stated above, there have been mixed results reported on factors related to motivation in this task, where there is sometimes an increased failure to respond overall but latency to retrieve the food reward does not differ. If performance were governed by food motivation, changing motivation to eat would result in altering retrieval of the food reward. Previous studies have shown that neither pre-feeding before sessions nor increasing the levels of food deprivation influence the effects of many drugs, including amphetamine, nicotine, and caffeine, on accuracy (Bizarro and Stoleran, 2003, Grottick and Higgins, 2002), arguably the most valuable measure of attention in this task. When vehicle-treated rats were pre-fed an entire daily ration of food 30 minutes prior to testing, correct responses were reduced, omissions and correct response latency increased, but there was no effect on accuracy (Nemeth et al., 2010). These effects of pre-feeding were similar, but much smaller in magnitude, to the effects seen following administration of KOR and MOR agonists. Further, pre-feeding also reduced premature responding and increased the latency to collect the food reward (Nemeth et al., 2010), two effects not observed with opioid ligands. Thus, pre-feeding elicits behaviors both different in magnitude and not observed with opioid ligands. This observation, together with the findings that most opioidergic ligands do not alter reward latency, provides evidence that the deficits in attention observed on the 5-CSRTT are likely independent of motivation.

In summary, MOR and KOR agonists can impair attention on the 5-CSRTT. While MOR and KOR antagonists have no effect on baseline 5-CSRTT behaviors, they ameliorate deficits induced by other ligands. All the reports on 5-CSRTT mentioned earlier were conducted in male rats and mice. No studies have compared how females perform on this task when given opioid ligands, nor how DYN/KOR knock-out animals may perform on the task. Overall, the mechanisms by which opioidergic ligands regulate attention and impulsivity on the 5-CSRTT are unknown, and they may act indirectly through effects on other neurotransmitter systems. Notably, the 5-CSRTT has the capacity to differentiate impaired cognitive processes from motivational deficits on attention and the potential of opioids to modulate these processes and behavioral endpoints.

Impulsivity.

Decision-making deficits and impulsivity are primary risk factors associated with suicide. Although animals models cannot address suicidality, impulsivity can be measured in the 5-CSRTT and may offer a potential avenue for preclinical studies to address the risk for suicidal behavior (Gould et al., 2017). Impulsivity can also be considered a construct of impaired cognitive control, consisting of two distinct entities: impulsive choice and impulsive action, Table 1. Also known as inhibitory control, or response inhibition, impulsive action can be measured using several behaviors, such as the differential reinforcement of low rates of responding schedule (DRL) test, stop signal reaction time task (SSRT), Go/NoGo test, Stroop test and 5-CSRTT (Bari and Robbins, 2013, Dalley et al., 2011). Impulsive choice can be considered risky decision-making, the tendency to accept smaller and more immediate rewards instead of larger, delayed, and sometimes even less predictable rewards. Impulsive choice can be measured on delayed reward tasks, such as delay discounting, or gambling tasks (Bari and Robbins, 2013, Bechara et al., 2005, Dalley et al., 2011). Impulsivity in general was not the focus of this review, and thus the following section does not review these topics thoroughly. Instead, emphasis is placed on tasks that measure impulsive action rather than impulsive choice, while tasks related to gambling and reward learning are excluded, Table 3.

In line with the pro-depressive effects associated with KOR activation, latency to respond in the 5-CSRTT to the stimulus was increased in response to opioid agonists, salvinorin A (Nemeth et al., 2010), U69,593 (Paine et al., 2007), and morphine (Koffarnus and Katz, 2011, Pattij et al., 2009), suggesting impaired decision-making and processing speed. However, in a separate study, only modest increases in response latency were measured following treatment with the KOR agonists U69,593, U50,488, and GR89,696 (Shannon et al., 2007), effects that were blocked by opioid antagonist administration (Nemeth et al., 2010, Pattij et al., 2009). Impulse control, measured as premature responding, did not differ in response to KOR agonists (Nemeth et al., 2010, Paine et al., 2007, Shannon et al., 2007), but was increased by the MOR agonists, morphine (Pattij et al., 2009, Wiskerke et al., 2011) and DAMGO (Wiskerke et al., 2011). However, it should be noted that the effects of MOR agonists on premature responses are uncertain, as other studies found no effect (Maguire et al., 2016), or decreased premature responding following morphine administration (Koffarnus and Katz, 2011). Despite the sparse evidence, the findings reported herein suggest a role for KORs in decision-making and MORs in impulsivity. In summary, opioidergic agonists disrupt attention as characterized by decreased correct responses, increased omissions, decreased processing speed, but intact accuracy.

Like the 5-CSRTT, response inhibition tasks provide an opportunity to assess premature responses, response latencies, and omissions. In rats tested in a response inhibition task with fixed delays between signal presentations, morphine increased premature responses and omissions (Mahoney et al., 2013), but when rats were tested in the same response inhibition task with variable delays between signal presentations, morphine had no effect on any measure (Befort et al., 2011). Further, in the SSRT, a similar task which also has variable delays, morphine had no effect on any measure (Pattij et al., 2009). Collectively, these findings stress the importance of delay period on morphine's ability to effect response

inhibition,. Perhaps MOR agonism only alters impulsive action when the delay is constant and predictable, but in an unpredictable paradigm other factors influence responding. In contrast to the lack of effect of MOR agonism the SSRT (Pattij et al., 2009), the KOR agonist, U50,488 increased impulsive action (reduced number of correct trials), but had no effect on omissions and total response rate, which are measures of motivation on this task (Walker and Kissler, 2013). The opioid antagonists naloxone (Befort et al., 2011, Mahoney et al., 2013, Pattij et al., 2009) and nor-BNI (Walker and Kissler, 2013) had no effects on these tasks related to impulsive action when administered alone, but blocked increased impulsive action induced by both morphine (Mahoney et al., 2013) and U50 (Walker and Kissler, 2013). Even though pharmacological blockade of MOR signaling had no effect on motor impulsivity (Mahoney et al., 2013), MOR knockout mice performed better on and had lower levels of motor impulsivity in a signaled nose poke task (Olmstead et al., 2009). Amphetamine produced similar effects as morphine on the 5-CSRTT, which were blocked with administration of opioid antagonists (Wiskerke et al., 2011). The underlying mechanism of MOR signaling increasing impulsive action is unknown, but it is likely to involve DAergic neurotransmission.

Opioid agonists also increase impulsive responding on impulsive choice tests, where subjects prefer a smaller and more immediate reward more often than a larger delayed reward, Table 3. The KOR agonist, U50,488 had no effect on delay discounting (Walker and Kissler, 2013), but morphine increased impulsive decision-making on several delay discounting tasks (Kieres et al., 2004, Maguire et al., 2016, Pattij et al., 2009, Pitts and McKinney, 2005). On the other hand, in a risky decision-making task where rats had to choose between a safe but small food reward, and a large but risky food reward associated with foot shock, a moderate dose of morphine increased the preference for the large and risky reward, but lower and higher doses had no effect (Mitchell, 2011). These impairments by morphine were blocked by prior administration of naloxone (Pattij et al., 2009) and naltrexone (Kieres et al., 2004). Although amphetamine produced deficits on impulsive action, it reduced impulsive choice on delayed reward tasks, as shown by an increased preference for the larger delayed reward (Wiskerke et al., 2011). Whereas naloxone restored amphetamine-induced impairments on impulsive action, it had no effect on the improvements in impulsive choice (Wiskerke et al., 2011). Additionally, naltrindole alone and with amphetamine had no additional effects. On the other hand, nor-BNI partially reversed the effects of amphetamine on the delayed reward task. Rats given both nor-BNI and amphetamine had lower preferences for the larger reward at longer delays, more like vehicle animals, compared to amphetamine only animals. Thus, MORs mediate amphetamine-induced deficits in impulsive action, whereas KORs may be involved in the effects of amphetamine on impulsive choice (Wiskerke et al., 2011). Lastly, the opioid antagonists naloxone (Pattij et al., 2009, Wiskerke et al., 2011), naltrexone (Kieres et al., 2004), and nor-BNI (Wiskerke et al., 2011) had no effect on impulsive choice when administered alone.

In humans, no effect of acute oxycodone was reported in healthy volunteers across several impulsivity tasks, including delay and probability discounting, balloon analogue risk task (BART), go/no-go task, stop task, and simple reaction time tasks (Zacny and de Wit, 2009). Moreover, in a modified delay discounting procedure that allowed measurement of motor

impulsivity, naltrexone enhanced inhibitory motor control in healthy human volunteers (Mitchell et al., 2007). In the same task, naloxone reduced impulsive decisions in abstinent alcoholics based on a locus of control personality trait (Mitchell et al., 2007). This contrasts with preclinical studies that found acute morphine increased impulsivity on similar tasks (Kieres et al., 2004, Maguire et al., 2016, Mahoney et al., 2013, Mitchell, 2011, Pattij et al., 2009, Pitts and McKinney, 2005). However, preclinical studies did replicate the capacity of opioid antagonists to attenuate elevated impulsivity (Abraham et al., 2018, Kieres et al., 2004, Walker and Kissler, 2013, Wiskerke et al., 2011). In summary, KOR activation may impair impulsive action while having no effect on impulsive choice. MOR activation impairs both measures of impulsivity, and opioid antagonists can alleviate these deficits. More research is necessary in humans regarding the effects of acute opioids and whether genetic variations in opioid receptors have an impact on these specific measures.

Reversal Learning and Attentional Set Shifting.

Opioid involvement on behavioral flexibility using attentional set shifting and reversal learning, in rodents and humans alike, has been studied across multiple tests, Table 1. Attentional set-shifting measures the ability of subjects to shift between rules. In rodents, aged male rats performed worse than young rats during the extradimensional shift, but not during the intradimensional shift or during reversal. This impairment was rescued with prior naltrexone administration, and naltrexone had no other effect on performance (Rodefer and Nguyen, 2008). In an attentional set-shifting test conducted in humans, an acute dose of morphine (10 mg) in healthy male participants given 75 minutes prior to testing, reduced the rates of intradimensional and extradimensional errors, but had no effect on reversal learning (Quednow et al., 2008). Similarly, aging studies assessed KOR neurotransmission in relationship to reversal learning (Menard et al., 2014a, Rodefer and Nguyen, 2008). Briefly, aged mice with higher levels of *Pdyn* gene expression showed impaired reversal learning on the Morris water maze relative to aged mice with lower levels of DYN. The impairments were rescued by nor-BNI, (Menard et al., 2014a, Menard et al., 2014b, Menard et al., 2013) suggesting that the increased DYN impaired reversal learning. Clinical data suggest that KOR agonists can induce similar deficits in healthy humans tested on a probabilistic reversal learning task; those with higher DYN had impaired reversal learning measured as an increase in the number of perseverative errors compared with subjects with lower levels of PDYN expression (Votinov et al., 2015). Using fMRI, during reversal learning and processing of negative feedback, the group with higher PDYN expression exhibited lower left orbitofrontal cortex (OFC) activity, engagement of corticostriatal circuitry, and connectivity of the OFC with other regions including the AIC and ventrolateral PFC (Votinov et al., 2015). Thus, both preclinical and clinical studies provide evidence that higher DYN levels contribute to impaired reversal learning, and impaired monitoring and adapting to changes in reward contingencies.

Modulation of reversal learning in preclinical research has been predominantly investigated using hippocampal dependent spatial learning tasks. In male rats, administration of low dose DAMGO injected directly into the dorsal striatum, enhanced spatial acquisition and reversal learning on the Morris water maze (Holahan et al., 2008). Conversely, high doses of DAMGO caused overall impairments on the task (Holahan et al., 2008). Moreover, impaired

reversal learning on the Barnes maze following three days of social defeat stress in male California mice was accompanied by downregulated MOR BP in the lateral OFC (Laredo et al., 2015). In contrast, behavioral flexibility was unaffected in female stressed mice (Laredo et al., 2015). Morphine reversed the stress-induced deficit in reversal learning (Laredo et al., 2015). However, beta-funaltrexamine (β -FNA), an irreversible MOR antagonist, given 24 hours prior to acquisition testing and again 24 hours before reversal testing, increased perseverative errors during reversal in male mice. Unstressed females receiving β -FNA also made fewer errors during reversal (Laredo et al., 2015). In a different form of a reversal learning task conducted on the radial arm maze, acute oxycodone impaired spatial reversal learning when reward rules were changed quickly, but not when they changed slowly (Seip-Cammack and Shapiro, 2014). Overall, these data indicate a role for MORs and KORs in the modulation of behavioral flexibility, but further research is required using more complex cortical dependent tasks.

Prepulse inhibition (PPI).

PPI is a measure of pre-attentive sensory filtering or sensorimotor gating, which is often measured by inhibition of the acoustic startle response (ASR) following the brief presentation of an auditory stimulus (Kohl et al., 2014). PPI is reduced in patients with schizophrenia and post-traumatic stress disorder (Takahashi et al., 2011). Moreover, in humans, the antidepressants sertraline and reboxetine, habituated ASR and decreased PPI respectively (Quednow et al., 2004), suggesting that serotonergic and noradrenergic neurotransmission differentially regulate these behavioral endpoints in MDD subjects. As MOR and KOR agonist binding is associated with Gi coupled opioid receptor inhibition, and subsequent reductions in monoamine release (De Vries et al., 1990, Margolis et al., 2003), these receptors are ideally placed to modulate sensorimotor gating. PPI is an ideal behavioral task for the study of opioidergic function since it is relatively easy to implement, requires no extensive training, and has little to no interaction with motivation.

PPI tends to be impaired across studies in humans with MDD, but overall studies have determined that PPI is unaffected by depressive severity (Ludewig et al., 2003, Perry et al., 2004, Quednow et al., 2006). Conversely, PPI levels were correlated with cognitive performance and this relationship is mediated by attentional processes (Scholes and Martin-Iverson). In rats, MOR agonists, including morphine and heroin, reduced PPI at high doses but not at low doses (Leitner, 1989, Ouagazzal et al., 2001, Rorick-Kehn et al., 2014, Swerdlow et al., 1991, Ukai and Okuda, 2003). However, lower doses of morphine effectively disrupted PPI in SD rats during withdrawal following chronic administration (Lee et al., 2017, Meng et al., 2010), but not when the MOR agonist was present, suggesting a marker of opioid withdrawal. On the other hand, in humans, an acute dose of morphine (10 mg) in healthy male participants given 75 minutes prior to testing, enhanced sensorimotor gating by increasing PPI, but had no effect on ASR and habituation (Quednow et al., 2008). Inconsistencies regarding the effect of KOR agonists on PPI are reflected in the literature. In male SD rats, both U50,488 (2.5 or 5 mg/kg) (Bortolato et al., 2005) and U69,593 (3 mg/kg) (Rorick-Kehn et al., 2014) reduced PPI. However, under similar testing conditions U50,488, U69,593 and Salvinorin A failed to effect PPI in male SD rats (Tejeda et al., 2010). In mice, higher doses of the KOR agonist U50,488 were not shown to impair PPI (Halberstadt et al.,

2016). Similarly, no inhibition of PPI was evident in rats and mice treated systemically with the non-selective opioid receptor antagonist naloxone (Swerdlow et al., 1991), the selective MOR antagonist naloxonazine (35 mg/kg) (Ukai and Okuda, 2003) and centrally with the MOR antagonist β -Funaltrexamine (β -FNA) (5 μ g) (Ukai and Okuda, 2003) alone. Neither did the selective KOR antagonists CERC-501 (3, 10, or 30 mg/kg) and nor-BNI (10 mg/kg) (Bortolato et al., 2005, Halberstadt et al., 2016, Rorick-Kehn et al., 2014, Tejada et al., 2010) reduce PPI when given alone. However, low-dose naltrexone (0.03, 0.1, or 0.3 mg/kg) attenuated morphine induced PPI reductions (Rorick-Kehn et al., 2014) whereas the selective KOR antagonist CERC-501 (10 or 30 mg/kg) did not attenuate morphine induced reduction of PPI (Rorick-Kehn et al., 2014). Conversely, when PPI was reduced by the KOR agonist U69,593 (3 mg/kg), both CERC-501 (0.1, 0.3, or 1 mg/kg) and naltrexone (1 mg/kg) restored PPI to normal levels (Rorick-Kehn et al., 2014). Furthermore, in rats nor-BNI (10 mg/kg) restored normal PPI following U69,593 administration, but did not affect PPI disruptions produced by other compounds, such as apomorphine (0.25 mg/kg) (Bortolato et al., 2005), the NMDA antagonist dizocilpine (0.1 mg/kg) (Bortolato et al., 2005), or following central administration of the stress hormone CRF (Tejada et al., 2010). To our knowledge the study by Tejada and colleagues is the only one that has examined the interaction of stress (exogenous CRF) and endogenous opioid function on the effects of PPI. Finally, naloxone blocked the reduction of PPI by the indirect DA agonist amphetamine (Swerdlow et al., 1991), suggesting that sensorimotor gating may represent a functional interaction between opioid receptors and DA transmission.

In summary, there is a substantial amount of information on the effects of both MOR and KOR ligands on PPI. High doses of MOR agonists are required to reduce PPI. Lower doses of KOR agonists appear the most effective in modulating PPI. Opioid antagonists do not alter basal PPI but can restore PPI impairment induced by MOR or KOR activation. PPI may also be used to study the interaction between opioid receptors and DA transmission or stress. PPI has analogous methods in humans allowing parallel studies to be conducted to examine the effects of opioid ligands in humans. Going forward, additional systematic research is necessary to gain a clearer understanding of the functional effects of both MOR and KOR systems on sensorimotor gating as measured by PPI.

Latent Inhibition.

Latent inhibition measures the ability to learn to ignore irrelevant stimuli. This form of behavioral inhibition occurs when prior exposure to a stimulus not associated with reinforcement leads subsequently to slower conditioning to the stimulus when it is later paired with reinforcement. Latent inhibition is most often assessed using fear conditioning procedures. Opioid receptor antagonists, such as naloxone (2.5 mg/kg), blocked latent inhibition of fear conditioning in male Wistar rats (Leung et al., 2013). Interestingly, although nor-BNI prevented the renewal of fear in response to a conditioned stimulus, nor-BNI failed to affect context-dependent latent inhibition of fear (Cole et al., 2011). This was an unexpected finding, as the KOR agonist Salvinorin A (160 μ g/kg) was shown to impair taste aversion for lithium hydrochloride in a sucrose solution, another rodent model of latent inhibition (Braida et al., 2011), suggesting that increased KOR signaling was detrimental for learning and memory, and that antagonism of KOR could improve outcomes. A likely

mechanism underlying impaired latent inhibition in response to opioid ligands is decreased DA neurotransmission, which has been shown to be essential for the emergence of latent inhibition (Braida et al., 2011, Ellenbroek et al., 1997). Overall, these data suggest that latent inhibition paradigms could be helpful in differentiating the effects of opioid ligands on latent inhibition independent of motivational deficits.

OPIOIDS, COGNITION AND AGING

Augmentation of antidepressant therapy with a cognitive enhancer improved executive function deficits in unremitting late-life depression (Butters et al., 2000, Cotrena et al., 2016, Cristancho et al., 2018, Devanand et al., 2003, Kaneriyia et al., 2016, Koenig et al., 2014, Pelton et al., 2016, Pimontel et al., 2016). Regardless of any psychiatric disorder diagnosis, aging in general is associated with changes in endogenous opioid functioning and cognitive deficits. The decline of cognitive function with aging (Harada et al., 2013, Samson and Barnes, 2013) occurs in parallel with increased MOR BP in the frontal cortex and putamen (Zubieta et al., 1999). DYN expression increases with age and is associated with cognitive dysfunction in natural aging, shown in both humans (Kolsch et al., 2009) and nonhuman animal models of aging (Jiang et al., 1989, Menard et al., 2014a, Menard et al., 2013, Nguyen et al., 2005, Zhang et al., 1991). Elevated DYN in aged rats was observed in the frontal cortex (Jiang et al., 1989), whereas no age-related differences were observed in the hypothalamus, basal forebrain, parietal cortex striatum and nucleus of the solitary tract (Jiang et al., 1989, Kotz et al., 2004, Zhang et al., 1991). As such, cortical regions are proposed as key regions of interest for future studies exploring the involvement of MORs in cognitive function in later life depression.

On the other hand, decreased *Pdyn* in aged rats was observed in the arcuate nucleus and amygdala (Kotz et al., 2004), which parallels reduced *PDYN* expression detected in MDD subjects. Importantly, in rats, age-related increases in hippocampal DYN A (Jiang et al., 1989, Zhang et al., 1991) and increased hippocampal *Pdyn* gene expression (Jiang et al., 1989, Kotz et al., 2004) were associated with impaired performance on the Morris water maze. Additionally, in LOU/C/Jall (LOU) rats, a strain model of healthy aging, lower levels of *Pdyn* expression were observed in the hippocampus relative to age-matched SD rats (Menard et al., 2014b), and this finding correlated with intact novel object recognition memory in LOU rats. Conversely, acquisition, retention, and even reversal learning on the Morris water maze, was similar between old and young LOU rats (Menard et al., 2014b).

The effects of aging on KOR/DYN signaling in rats is conserved across species, with many similar reports in mice. Poor performance on the Morris water maze was correlated with elevated DYN levels in the frontal cortex (Menard et al., 2013, Nguyen et al., 2005) and hippocampus (Menard et al., 2013) of aged wildtype mice. Conversely, aged *Pdyn* knockout (KO) mice exhibited enhanced learning and memory relative to aged wildtype mice on the Morris water maze (Menard et al., 2013, Nguyen et al., 2005). Furthermore, cognitive impairment in aged wildtype mice was rescued by administration of the KOR antagonist nor-BNI. In addition, aged *Pdyn* KO mice exhibited increased levels of GluR1 protein and NMDA NR2B subunits in the hippocampus relative to wildtype controls (Menard et al., 2014a), indicating a possible mechanistic link mGluR function and opioid

neurotransmission in impaired cognition in aging (Menard et al., 2013). In relation to more complex cognitive tasks, aged male SD rats performed worse than younger animals during the extradimensional phase of an attentional set-shifting test without exhibiting differences during the intradimensional shift phase of reversal learning (Rodefer and Nguyen, 2008). Furthermore, naltrexone (2 mg/kg) given 30 minutes prior to testing, attenuated the impairments in extradimensional shifting without any other effect on performance (Rodefer and Nguyen, 2008). How opioid receptor blockade may enhance cognition during aging is unclear, but it may involve opioid modulation of DA and acetylcholine release in cortical regions, or at the level of mesolimbic structures. In summary, DYN levels can increase during aging and result in cognitive dysfunction in the aged population alone. When combined with additional psychiatric disorders also associated with increased DYN, such as depression, the impact on cognitive function may be debilitating.

OPIOID MECHANISMS OF COGNITIVE AND MOTIVATIONAL DEFICITS

Opioid receptors belong to the superfamily of 7-transmembrane-spanning G-protein-coupled receptors (GPCRs), coupled to inhibitory heterotrimeric G α i/o proteins (Al-Hasani and Bruchas, 2011). Activation of MOR is mediated by enkephalin and β -endorphin, while activation of KOR is mediated by dynorphin (Al-Hasani and Bruchas, 2011, Belcheva et al., 2005). Following opioid receptor activation, G $\beta\gamma$ dissociation upregulates K $^{+}$ conductance through the inwardly-rectifying K $^{+}$ channel K $_{ir}$ 3, while down-regulating voltage-dependent Ca $^{2+}$ channel activity (Clayton et al., 2009, Henriksen and Willoch, 2008, Liu et al., 2000, Nagi and Pineyro, 2014, Rusin et al., 1997, Toth et al., 1996). G $\beta\gamma$ also induces the upregulation of mitogen activated protein kinases (MAPK) including c-Jun N-terminal Kinase (JNK) and extracellular signal-regulated kinase 1/2 (ERK1/2). In a calcium dependent process, the G $\beta\gamma$ dissociation following KOR activation (Figure 1.), pyruvate dehydrogenase kinase 1 (PDK-1) phosphorylation of phosphoinositide-3-kinase (PI3K) activates protein kinase C zeta (PKC ζ), which in turn phosphorylates ERK1/2 (Belcheva et al., 2005, Bruchas and Chavkin, 2010, Chou et al., 1998). MOR activation upregulates ERK1/2 phosphorylation via PKC ϵ in a Ca $^{2+}$ -independent manner (Belcheva et al., 2005). Figure 2. Depicts MOR-induced PKC ϵ activation through phospholipase C (PLC)-mediated upregulation of diacyl glycerol (DAG), which has been shown to facilitate PKC ϵ phosphorylation (Belcheva et al., 2005). pERK1/2 is a well-studied regulator of phosphorylated cAMP response element-binding protein (pCREB), which regulates the transcription of genes within the nucleus such as the neuropeptides such as brain-derived neurotrophic factor (BDNF) and endogenous opioid peptides (Carlezon et al., 2005). pERK is a highly conserved MAPK, that modulates synaptic plasticity and is upregulated in response to many antidepressant therapies including novel opioid compounds (Almeida et al., 2006, First et al., 2013, Gourley et al., 2008, Lepack et al., 2016, Qi et al., 2008, Rorick-Kehn et al., 2014). Moreover, the motivational deficits induced by chronic administration of the stress hormone corticosterone (the rodent equivalent of human cortisol) on an operant conditioning food reward task were attenuated by amitriptyline in an ERK1/2 dependent manner (Gourley et al., 2008). Induction of BDNF and subsequent neurogenesis by pERK1/2 is another molecular correlate of antidepressant efficacy. BDNF deficits were restored following chronic, but not acute administration with conventional antidepressants,

and were also normalized following acute administration of rapid acting compounds such as ketamine (First et al., 2013, Lepack et al., 2016, Martinowich et al., 2007, Pilar-Cuellar et al., 2014). In the context of increased opioid tone, sustained MOR and KOR activation have divergent effects on ERK. Acute activation by the MOR agonist DAMGO resulted in a highly transient pERK1/2 upregulation lasting under 30 minutes; in contrast, chronic MOR activation produced a 30–40% decrease in pERK1/2 (Belcheva et al., 2005). Conversely, chronic activation by KOR agonist U69,593 maintained ERK1/2 upregulation (Belcheva et al., 2005). Overall, these data demonstrate that opioid compounds administered acutely, modulate ERK 1/2 in a manner similar to that of chronic treatment with conventional antidepressants and the acute effects of rapid acting novel therapeutics.

These changes in receptor specific ERK phosphorylation also modulate in the levels of proBDNF and mature (m)BDNF which respectively facilitate long-term depression (LTD) and long-term potentiation (LTP) (Martinowich et al., 2007). Moreover, at the level of the ventral tegmental area (VTA) and nucleus accumbens (NAc), BDNF induction within VTA-NAc projecting DAergic cells produced anhedonia and motivational deficits, whereas in the hippocampus (Hipp), BDNF knockdown induced behavioral despair (Martinowich et al., 2007). Overall, as opioid receptors are highly localized in both these regions they are perfectly poised to modulate the divergent and region-specific effects of BDNF. It has been systematically demonstrated that KOR upregulation of pCREB mediates the increases in BDNF and DYN expression in the NAc, which ultimately promotes depression-like behavior in sucrose preference, forced swim tests, and learned helplessness paradigms (Bruchas and Chavkin, 2010, Carlezon et al., 2005), but research on the executive functioning effects of NAc KOR outputs is not currently available. In contrast with these findings, KOR-mediated BDNF increases in the hippocampus attenuated depression-like behavior. Similarly, upregulation of KOR activity in the amygdala produced timing-dependent effects on depression-like behavior in a learned helplessness paradigm, where KOR agonist pretreatment elevated “despair-like,” behavior and KOR agonist administration post-testing diminished “despair” behavior (Carlezon et al., 2005). All of these effects were mediated by CREB-induced transcriptional control (Bruchas and Chavkin, 2010).

Separate from the GPCR MAPK signaling cascade, opioid activation leads to G-protein coupled receptor kinase 3 (GRK3) mediated arrestin dependent internalization (Bruchas and Chavkin, 2010, Loh et al., 2017) and KOR agonist desensitization (Loh et al., 2017, Williams et al., 2013). A large body of evidence exists detailing the complex, ligand specific effects of MOR activation and β -arrestin dependent internalization particularly in relation to analgesic tolerance (Dang and Christie, 2012, Melief et al., 2010, Raehal and Bohn, 2011). Arrestin binding also facilitates the phosphorylation of p38 α MAPK, a regulator of pCREB, transcription factor zif268, and SERT reuptake (Bruchas et al., 2011, Loh et al., 2017, Schindler et al., 2012). Zif268 is implicated in brain plasticity and memory consolidation (Maroteaux et al., 2014, Penke et al., 2014, Veyrac et al., 2013), and has also been proposed as a necessary intermediary in the phospho-p38 α MAPK-mediated acquisition of conditioned place aversion and increased immobility during forced swim stress (Belcheva et al., 2005, Bruchas et al., 2007). Furthermore, in presynaptic serotonergic neurons, p38 α MAPK upregulation of synaptic SERT expression leads to a decrease in 5-HT availability, suggested as one of the potential underlying mechanisms promoting conditioned place

aversion and behavioral despair (immobility) in the forced swim test, demonstrated in p38 α MAPK and SERT knockout mice and in mice treated with citalopram (Belcheva et al., 2005, Bruchas et al., 2007, Bruchas et al., 2011, Land et al., 2009, Schindler et al., 2012). Additionally, the KOR antagonist U69,593 decreased synaptic SERT expression and activity by increasing SERT membrane delivery (Samuvel et al., 2005). Although it has not been empirically tested, the induction of phospho-p38 α MAPK may also underlie many of the cognitive deficits induced following chronic stress and elevated DYN/KOR signaling.

Collectively, the preclinical data indicate the capacity of opioid receptors to modulate monoaminergic neurotransmission to influence cognitive outcomes. Activation of opioid receptors by their endogenous ligands reduces neurotransmitter release in a cell-type specific manner in discrete brain nuclei implicated in motivational and cognitive deficits, Figure 3. It is proposed that KOR activation may disrupt performance during attention tasks by decreasing DA neurotransmission (Spanagel et al., 1992). MOR acts in opposition to KOR on the DA system, upregulating mesolimbic DA (Gulley et al., 2002) and 5-HT (Samuvel et al., 2005, Spanagel et al., 1992, Tao and Auerbach, 2002) neurotransmission. The functioning of the PFC is highly correlated with attention, behavioral flexibility, and overall executive functioning (Tejeda et al., 2015). DAergic VTA projections to the mPFC but not the NAc are inhibited following KOR upregulation (Margolis et al., 2006). Moreover, within the mPFC, ERK 1/2 dependent KOR-mediated decreases in synaptic DA availability was demonstrated to be necessary for normal development (Kivell et al., 2014, Sirohi and Walker, 2015), indicating that KO-mediated mPFC DA may be of importance in cognitive processing during aging. Systemically injected KOR agonist U69,593 inhibited glutamatergic inputs to the mPFC from the basolateral amygdala (BLA) but not the Hipp, suggesting a gating effect of KOR activation in BLA-mPFC glutamatergic signaling (Tejeda et al., 2015). In presynaptic DAergic neurons, acute KOR activation decreased phasic DAergic (DA) firing, precipitated by increased DA transporter (DAT) reuptake which was reversed by administration of nor-BNI, (Carlezon et al., 2005, Ebner et al., 2010, Grilli et al., 2009, Gulley and Zahniser, 2003, Kivell et al., 2014, Tejeda et al., 2013). Both KOR agonists and antagonists exhibited greatest effects 40–60 minutes post infusion, which is consistent with the timeline of pCREB regulation (Muschamp and Carlezon, 2013, Spanagel et al., 1992). Decreases in DA release have been shown following pCREB-mediated upregulation of DYN (Muschamp and Carlezon, 2013). Conversely, conditional DA neuron KOR knockouts display increased DA release and decreased anxiety-like behavior in open field and light/dark box tests (Van't Veer et al., 2013). One proposed pathway for KOR upregulation of DA is that KOR inhibition of GABA exocytosis in GABAergic neurons, as evidenced by KOR agonist-mediated inhibition of LTP_{GABA} in VTA DA neurons, results in the disinhibition of DA neurons (Graziane et al., 2013).

The impact of opioid mediated DA release on cognitive function was recently illustrated on impulsive action tested on the DRL task (Abraham et al., 2018). In this task, subjects must refrain from making a reinforced response for a specific period. Systemic administration of the KOR agonist U50,488 and the G protein-biased KOR agonist nalfurafine, both independently disrupted performance on the DRL task in male and female mice (Abraham et al., 2018). Impaired performance in both sexes was typified by an increase in the number of non-reinforced responses, increased errors, and increased burst responding. A 2-day forced-

swim stress procedure also impaired DRL performance in male mice, and systemic administration of the KOR antagonist nor-BNI restored this stress-induced impairment (Abraham et al., 2018). Additionally, nor-BNI administered directly into the VTA, but not the infralimbic PFC, or the dorsal raphe nucleus, restored percent error on the DRL task. Thus, KOR activation within the VTA is required for disruptions in DRL performance. Further, Cre-dependent genetic excision of KOR from DA neurons, blocked U50,488-induced disruption in performance, but genetic excision of KOR from 5-HT neurons had no effect. Lastly, KOR-mediated disruptions on the DRL task did not require GRK3/arrestin-dependent intracellular signaling pathways since mice with conditional knockouts of p38 MAPK from DA neurons and GRK3 knockout mice independently did not influence U50,488-induced impairment. Therefore, the mechanisms underlying KOR-activated impairments in DRL performance are still unknown, but are likely not dependent on GRK3/arrestin pathways (Abraham et al., 2018). To date, this is the only study to clearly examine the mechanisms of and the direct interactions between KOR signaling, stress exposure, and cognition. Although the study did not directly assess chronic stress, it can be inferred that KOR antagonism during periods of chronic stress may decrease cognitive deficits. Going forward determining the molecular underpinnings of the behavioral effects of opioid ligands across a variety of tasks is recommended.

CONCLUSION

Therapeutics that effectively target cognitive impairment in depression could greatly enhance daily functioning in patients and improve long-term outcomes. This review has provided a synopsis of the current knowledge regarding opioid modulation of cognitive processes. Although a great deal more work is required to comprehensively examine the impact of endogenous opioidergic tone in cognition, it is clear from the literature that in addition to the beneficial effects of opioid based antagonists on depressed mood and anxiety, these compounds may effectively target cognitive dysfunction potentially by modulating DA neurotransmission within the mesolimbic circuit.

For many patients, resolution of functional impairment is as important as relief from depression. As such there is a growing recognition among clinicians and researchers that more thorough examination of cognitive processing during depressive episodes and remission is required. These deficits are primarily self-reported, so they may be under-recognized. When assessed clinically using the most common depression rating scales, recognition of cognitive impairment may be limited by the lack of questions related to cognition - only a single item is covered in the MADRS, processing speed, and the HAM-D includes only one item rating slowness of thought and speech and impaired ability to concentrate. To address these limitations in the assessment of cognitive symptoms, basic assessment of cognitive function such as the mini-mental status examination, and more complex batteries of neurocognitive domains such as CANTAB are being used to demonstrate the importance of cognition in illness severity and treatment outcomes. As reported in this review, these neurocognitive batteries are highly translatable to preclinical studies in rodents, where stress and pharmacotherapy produce similar effects on cognitive processes that are analogous to those performed by humans.

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Figure 1.

Increased dynorphin secretion following stress exposure activates G_i-coupled KOR signaling. Depicted here are the potential downstream effectors that modulate responses to stress and impact behavior. Following ligand binding the $\beta\gamma$ subunit dissociates from the receptor complex to facilitate potassium channel activity and decreased calcium channel activity, ultimately hyperpolarizing the cell to suppressed neurotransmission. Arrestin-dependent internalization of KOR is mediated by GRK3, resulting in the recycling of KORs, or the induction of JNK, ERK and p-38 MAPK signaling, which ultimately elevates the expression of CREB and increased dynorphin release in a positive feedback loop.

Figure 2.

Increased phosphorylation of enkephalin activates G_i-coupled MOR signaling. Dissociation of the βγ subunit and calmodulin (CaM) leads to an increase in GRK3 activity and inhibition of Ca²⁺ channel activity, which suppress neurotransmission of glutamate and GABA and increases signaling by 5-HT and DA. In addition, subunit dissociation leads to an upregulation of JNK, ERK, and CREB signaling.

Figure 3.

Stress induced alterations in KOR and MOR expression in brain regions that impact motivational and cognitive processes. Relative expression levels of kappa (red) and mu (blue) opioid receptors as measured by radioautography ligand binding, mRNA expression analysis, and immunohistochemical staining. Grey indicates some conflicting evidence over expression levels. Solid arrows indicate dopaminergic (black), glutamatergic (green), and GABAergic (orange) neurotransmission between regions. Dotted arrows indicate effects of stress-induced alterations of KOR and MOR. mPFC – medial prefrontal cortex; AIC – anterior insular cortex; ACC – anterior cingulate cortex; Hipp – hippocampus; PAG – periaqueductal grey; Thalamus; Hypothalamus; VTA – ventral tegmentum area; LC – locus coeruleus; CeA – central nucleus of the amygdala; BLA – basolateral nucleus of the amygdala; VP – ventral pallidum; PPN- pedunculopontine nucleus; NAc – nucleus accumbens; DS – dorsal striatum; LHb – lateral habenula; DRN – dorsal raphe nucleus.

Table 1 –

Selection of clinical and preclinical tasks used to assess the cognitive domains of attention, executive control/behavioral control, declarative memory and working memory. ASST – attentional set shifting task; CPT – continuous performance task; DRL – differential reinforcement of low response rate task; IGT – Iowa gambling task; PPI – prepulse inhibition; SAT – sustained attention task; WCST – Wisconsin card sorting task; 5-CSRTT – 5-Choice serial reaction time task.

Cognitive Construct	Cognitive Measure	Clinical Assessment	Preclinical Assessment
Attention	Sustained attention	CPT	5-CSRTT
		SAT	SAT
		Signal detection task	Signal detection task
	Inattention	WCST, ASST	ASST
			Sand-digging task
		Latent Inhibition	Latent Inhibition
	Sensorimotor gating	PPI	PPI
	Processing speed	Attentional blink	Attentional blink
		CPT, Symbol-Digit Modality	5-CSRTT
		Reaction time tasks	Choice reaction time tasks
Reasoning / Problem solving		Dichotic listening	Lateralized reaction-time task
		Immediate and delayed memory tasks	Immediate and delayed memory tasks
		Dual task paradigms	Olfactory discrimination
		Spatial and non-spatial cueing	Delayed match/non-match to sample tasks
		Visual search tasks	Visual search tasks
		WCST/ASST	ASST & Reversal learning (spatial tasks)
	Cognitive flexibility	CPT	5-CSRTT
	Performance monitoring	Arrow flanker test	5-CSRTT
		CPT	5-CSRTT
		Response inhibition	Response inhibition signaled nose task
Executive function/Behavioral control	Impulsive action/Inhibitory control/Response inhibition	Stroop test	Stroop analog tests, three-choice visual or olfactory discrimination
		Go/NoGo test	Go/NoGo test
		DRL	DRL

Cognitive Construct	Cognitive Measure	Clinical Assessment	Preclinical Assessment
		Stop signal task	Stop signal task
		IGT	Rodent IGT
	Impulsive choice	Immediate and delayed reward tasks	Immediate and delayed reward tasks
		Delay discounting	Delay discounting
Declarative memory	Episodic memory	Visual paired associations	Novel object recognition Object location recognition
	Visual learning/Memory	Field and virtual reality spatial navigation tasks	Spatial learning Social recognition Social interaction
		Delayed match-to-sample (or non-sample)	Delayed match-to-sample (or non-sample)
Working Memory	Visual recognition/ Source memory	Delayed alteration	Delayed alteration (Y or T maze)
	Spatial learning/memory	Field and virtual reality spatial navigation tasks, spatial working memory tasks	Barnes maze, Morris water maze, Radial arm maze/ radial arm water maze
	Associative memory	Cued or contextual fear conditioning and extinction	Cued or contextual fear conditioning and extinction; passive or active avoidance

Opioid mediated alterations in cognitive domains assessed in the 5-choice serial reaction time test (5-CSRTT). Doses included are those found effective for each finding and are only those systematically administered. Admin – administration; CRF – Corticotropin releasing factor; FR – fixed ratio; H – hour; ICV – intracerebroventricular; IP – intraperitoneal injection; Min – minute, N/A – not applicable; PACAP – Pituitary adenylate cyclase-activating peptide; SC – subcutaneous injection; SD – Sprague Dawley

Table 2 –

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Attention	Correct responses (%) (correct responses/correct + incorrect + omitted responses)	Agonist	Salvinorin A	2, 4 mg/kg, IP	10 min	Decreased	(Nemeth et al., 2010)
			U69,593	0.25, .5, 1, 2 mg/kg, IP	30 min	N/A	(Paine et al., 2007)
			(+) U69,593	0.3, 0.56 mg/kg, SC	30 min	Decreased	(Shannon et al., 2007)
			(±) U50,488	3, 5.6 mg/kg, SC	30 min	Decreased	(Shannon et al., 2007)
			GR89,696	0.003, 0.01 mg/kg, SC	30 min	Decreased	(Shannon et al., 2007)
			ICI-204,488	1–10 mg/kg, SC	30 min	No effect	(Shannon et al., 2007)
			Morphine	3, 5.6 mg/kg, SC	30 min	Decreased	(Shannon et al., 2007)
			Morphine	1, 3, 6 mg/kg, SC	20 min	No effect	(Boyette-Davis et al., 2008)
			Morphine	0.1, 0.3, 1, 3, 10 mg/kg, IP	5 min	N/A	(Koffarnus and Katz, 2011)
			Morphine	0.3 – 10 mg/kg, IP	30 min	N/A	(Maguire et al., 2016, Pattij et al., 2009)
		Antagonist	Naltrexone	0.3, 1, 3 mg/kg, SC	30 min	No effect in vehicle animals	(Shannon et al., 2007)
			Naltrexone	0.1, 0.3, 1 mg/kg, SC	30 min	Dose-dependent attenuation of U69 (0.56 mg/kg) impairment	(Shannon et al., 2007)
			Naltrexone	0.01, 0.03, 0.1, 0.3 mg/kg, SC	30 min	Dose-dependent attenuation of morphine (5.6 mg/kg) impairment	(Shannon et al., 2007)
			Naloxone	0.3, 1, 3 mg/kg, IP	30 min	N/A	(Pattij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			JD/Tic	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
		Agonist	Male SD rat	10 mg/kg, IP	24 h	Blocked effect of salvinorin A (2 mg/kg)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	96 h	Blocked effect of ketamine (20 mg/kg, IP)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	48 h	No effect on PACAP (0.5, 1 µg, i.c.v.) impairment	(Donahue et al., 2016)
			Male SD rat	10 mg/kg, IP	24 h	Blocked CRF (0.5 µg, i.c.v.) impairment. No effect of JD1c at 1 µg CRF	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	N/A	(Wiskerke et al., 2011)
			Male SD rat	0.125, 0.25, 0.5, 1, 2, 4 mg/kg, IP	10 min	No effect	(Nemeth et al., 2010)
			Male SD rat	0.003–10 mg/kg, IP & SC	10 or 30 min	No effect	(Paine et al., 2007, Shannon et al., 2007)
			Male SD rat	1, 3, 5, 6, 6 mg/kg, SC	20 or 30 min	N/A	(Boyette-Davis et al., 2008, Shannon et al., 2007)
			Male SD rat	0.1–10 mg/kg, IP	30 min	No effect	(Maguire et al., 2016)
			Male SD rat	10 mg/kg, IP	5 min	Decreased at FR 3	(Koffarnus and Katz, 2011)
			Male Wistar rat	0.3, 1, 3, 6 mg/kg, IP	30 min	No effect	(Pattij et al., 2009)
			Male SD rat	0.01–1 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male C57BL/6J mice	10 mg/kg, SC	25 min	Time-dependent increase in vehicle animals	(Sanchez-Roige et al., 2015)
			Male DBA/2J mice	10 mg/kg, SC	25 min	No effect in vehicle animals	(Sanchez-Roige et al., 2015)
		Antagonist	Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect in vehicle animals & w/ morphine or nicotine	(Pattij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	1, 3 mg/kg, IP	30 min	Dose-dependent attenuation of amphetamine impairment (0.5 mg/kg, IP)	(Wiskerke et al., 2011)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Attention, motivation, locomotor effects	Omissions (total omissions/number of trials)	Agonist	Male SD rat	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg IP	48 h	No effect of PACAP-38 (0.5, 1 µg, i.c.v.) impairment	(Donahue et al., 2016)
			Male SD rat	10 mg/kg, IP	24 h	No effect on CRF impairment, although data table suggests improvement	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	No effect in vehicle or amphetamine treated animals	(Wiskerke et al., 2011)
			Male SD rat	2, 4 mg/kg, IP	10 min	Increased	(Nemeth et al., 2010)
			Male SD rat	1, 2 mg/kg, IP	30 min	Increased	(Paine et al., 2007)
			Male SD rat	0.56 mg/kg, SC	30 min	Increased	(Shannon et al., 2007)
			Male SD rat	3, 5.6 mg/kg, SC	30 min	Increased	(Shannon et al., 2007)
			Male SD rat	0.003, 0.01 mg/kg, SC	30 min	Increased	(Shannon et al., 2007)
			Male SD rat	1–10 mg/kg, SC	30 min	No effect	(Shannon et al., 2007)
			Male SD rat	3 mg/kg, SC	20 min	Decreased	(Boyette-Davis et al.)
			Male SD rat	6 mg/kg, SC	20 min	Increased	(Boyette-Davis et al.)
			Male SD rat	3, 5.6 mg/kg, SC	30 min	Increased	(Shannon et al., 2007)
			Male SD rat	3, 10 mg/kg, IP	5 min	Increased	(Koffarnus and Katz, 2011)
			Male SD rat	1, 3.2, 10 mg/kg, IP	30 min	Increased	(Maguire et al., 2016)
			Male Wistar rat	6 mg/kg, IP	30 min	Increased	(Patij et al., 2009)
		Antagonist	Male SD rat	0.3, 1, 3 mg/kg, SC	30 min	No effect in vehicle animals	(Shannon et al., 2007)
			Male SD rat	0.3, 1 mg/kg, SC	30 min	Dose-dependent attenuation of U69,593 (0.56 mg/kg) impairment	(Shannon et al., 2007)
			Male SD rat	0.01, 0.03, 0.1, 0.3 mg/kg, SC	30 min	Dose-dependent attenuation of morphine (5.6 mg/kg) impairment	(Shannon et al., 2007)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Motivation	Reward latency	Agonist	Male C57BL/6J & DBA2/J mice	10 mg/kg, SC	25 min	Increased omissions in vehicle animals	(Sanchez-Roige et al., 2015)
			Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect in vehicle and nicotine treated animals.	(Patij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	0.3, 1 mg/kg, IP	30 min	Blocked effect of morphine (3 mg/kg, IP)	(Patij et al., 2009)
			Male SD rat	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg, IP	24 h	Blocked effect of salvinorin A (2 mg/kg)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	96 h	Blocked effect of ketamine (20 mg/kg, IP)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	48 h	No effect of PACAP (0.5, 1 µg, i.c.v.) impairment	(Donahue et al., 2016)
			Male SD rat	10 mg/kg, IP	24 h	Blocked CRF (0.5 µg, i.c.v.) and attenuated CRF (1 µg, i.c.v.) impairment	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	No effect in vehicle animals	(Wiskerke et al., 2011)
			Male Wistar rat	10 mg/kg, IP	22–24 h	Increased. Synergistic effect with amphetamine (0.5 mg/kg, IP)	(Wiskerke et al., 2011)
			Male SD rat	0.125, 0.25, 0.5, 1, 2, 4 mg/kg, IP	10 min	No effect	(Nemeth et al., 2010)
			Male SD rat	0.25, 0.5, 1, 2 mg/kg, IP	30 min	No effect	(Paine et al., 2007)
			Male SD rat	0.003–10 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male SD rat	1, 3, 6 mg/kg, SC	20 min	No effect	(Boyette-Davis et al., 2008)
			Male SD rat	0.1, 0.3, 1, 3, 10 mg/kg, IP	5 min	N/A	(Koffarnus and Katz, 2011)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Decision-making, processing speed, motivation	Response latency	Antagonist	Male Wistar rat	0.3, 1, 3, 6 mg/kg, IP	30 min	No effect	(Pattij et al., 2009)
			Male SD rat	0.01–1 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male C57BL/6J & DBA2/J mice	10 mg/kg, SC	25 min	Increased latency in vehicle animals	(Sanchez-Roige et al., 2015)
			Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect in vehicle animals or with amphetamine, GBR 12909, or nicotine	(Pattij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	0.3, 1 mg/kg, IP	30 min	Blocked increased latency in morphine (3 mg/kg, IP)	(Pattij et al., 2009)
			Male SD rat	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg, IP	48 h	No effect on CRF impairment	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	No effect in vehicle and amphetamine treated animals	(Wiskerke et al., 2011)
			Male SD rat	2, 4 mg/kg, IP	10 min	Increased	(Nemeth et al., 2010)
			Male SD rat	1, 2 mg/kg, IP	30 min	Increased	(Paine et al., 2007)
			Male SD rat	0.175, 0.3, 0.56 mg/kg, SC	30 min	Increased	(Shannon et al., 2007)
			Male SD rat	0.003–10 mg/kg, SC	30 min	No effect	(Shannon et al., 2007)
			Male SD rat	1, 3, 5, 6, 6 mg/kg, SC	20 or 30 min	N/A	(Boyette-Davis et al., 2008, Shannon et al., 2007)
			Male SD rat	10 mg/kg, IP	5 min	Increased at FR 3	(Kofarnus and Katz, 2011)
			Male Wistar rat	6 mg/kg, IP	30 min	Increased	(Pattij et al., 2009)
		Antagonist	Male SD rat	0.01–1 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male C57BL/6J & DBA2/J mice	10 mg/kg, SC	25 min	No effect in vehicle animals	(Sanchez-Roige et al., 2015)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Response inhibition (impulse control), motivation	Premature (anticipatory) responses	Agonist	Male Wistar rat	3 mg/kg, IP	30 min	Increased in vehicle animals	(Pattij et al., 2009)
			Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect in vehicle animals	(Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	3 mg/kg, IP	30 min	Blocked decreased latency in amphetamine (0.5 mg/kg, IP)	(Wiskerke et al., 2011)
			Male Wistar rat	0.3, 1 mg/kg, IP	30 min	Blocked increased latency in morphine (3 mg/kg, IP)	(Pattij et al., 2009)
			Male SD rat	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg, IP	24 h	Blocked effect of salvinorin A (2 mg/kg)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	96 h	No effect on increased latency by ketamine (20 mg/kg, IP)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	48 h	No effect on increased latency by PACAP-38 (0.5, 1 µg, i.c.v.)	(Donahue et al., 2016)
			Male SD rat	10 mg/kg, IP	24 h	Blocked CRF (0.5 µg, i.c.v.) impairment	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	No effect in vehicle or amphetamine treated animals	(Wiskerke et al., 2011)
			Male SD rat	0.125, 0.25, 0.5, 1, 2, 4 mg/kg, IP	10 min	No effect	(Nemeth et al., 2010)
			Male SD rat	0.25–5.6 mg/kg, IP & SC	10 or 30 min	No effect	(Paine et al., 2007, Shannon et al., 2007)
			Male SD rat	0.003–10 mg/kg, SC	30 min	No effect	(Shannon et al., 2007)
			Male SD rat	1, 3, 5.6, 6 mg/kg, SC	20 or 30 min	N/A	(Boyette-Davis et al., 2008, Shannon et al., 2007)
			Male SD rat	1–10 mg/kg, IP	30 min	No effect	(Maguire et al., 2016)
			Male SD rat	3, 10 mg/kg, IP	5 min	Decreased	(Koffarnus and Katz, 2011)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Overall performance	Time to complete session	Antagonist	Male Wistar rat	3, 6 mg/kg, IP	30 min	Increased	(Pattij et al., 2009)
			Male SD rat	0.01–1 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male C57BL/6J & DBA2/J mice	10 mg/kg, SC	25 min	Decreased responses in vehicle animals	(Sanchez-Roige et al., 2015)
			Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect in vehicle or amphetamine treated animals	(Pattij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	0.3, 1 mg/kg, IP	30 min	Blocked effect of morphine (3 mg/kg, IP)	(Pattij et al., 2009)
			Male Wistar rat	1, 3 mg/kg, IP	30 min	Dose-dependent attenuation of amphetamine (0.5 mg/kg, IP) and GBR 12909 (5 mg/kg, IP) impairment	(Wiskerke et al., 2011)
			Male SD rat	10 mg/kg, IP	24, 48, or 72 h	No effect in vehicle animals	(Donahue et al., 2016, Nemeth et al., 2010, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg, IP	96 h	Increased responses, synergistic effect with ketamine (20 mg/kg, IP)	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	24 h	No effect on decreased responses by CRF (0.5, 1 µg, i.c.v.)	(Van't Veer et al., 2012)
			Male Wistar rat	10 mg/kg, IP	22–24 h	No effect alone & w/ amphetamine	(Wiskerke et al., 2011)
			Male SD rat	0.125, 0.25, 0.5, 1, 2, 4 mg/kg, IP	10 min	N/A, 90 trials or 30 min	(Nemeth et al., 2010)
			Male SD rat	0.25, .5, 1, 2 mg/kg, IP	30 min	N/A, 90 trials or 30 min	(Paine et al., 2007)
			Male SD rat	0.1, 0.175, 0.3, 0.56 mg/kg, SC	30 min	Ended at 30 min regardless	(Shannon et al., 2007)
			Male SD rat	0.003–10 mg/kg, SC	30 min	Ended at 30 min regardless	(Shannon et al., 2007)
			Male SD rat	1, 3, 6 mg/kg, SC	20 min	Ended at 60 min (250 trials) regardless	(Boyette-Davis et al.)
			Male SD rat	1–10 mg/kg, IP	30 min	N/A, 100 trials or 30 min	(Maguire et al., 2016)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Decision-making	Post-error accuracy	Antagonist	Male SD rat	0.1, 0.3, 1, 3, 10 mg/kg, IP	5 min	N/A, 50 trials or 15–40 min	(Koffarnus and Katz, 2011)
			Male Wistar rat	0.3, 1, 3, 6 mg/kg, IP	30 min	N/A, 100 trials or 30 min	(Pattij et al., 2009)
			Male SD rat	0.01–1 mg/kg, SC	30 min	N/A, Ended at 30 min regardless	(Shannon et al., 2007)
			Male Wistar rat	0.3–10 mg/kg, IP	30 min or 22–24 h	N/A, Ended at 100 trials or 30 min	(Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male Wistar rat	3 mg/kg, IP	30 min	N/A, Ended at 100 trials or 30 min	(Pattij et al., 2009)
			Male C57BL/6J & DBA2/J mice	10 mg/kg, SC	25 min	N/A	(Sanchez-Roige et al., 2015)
			Male SD rat	10 mg/kg, IP	24, 72, or 96 h	N/A, 90 trials or 30 min	(Nemeth et al., 2010)
			Male SD rat	10 mg/kg, IP	48 h	No effect in vehicle animals	(Donahue et al., 2016, Van't Veer et al., 2012)
			Male SD rat	10 mg/kg, IP	24 h	Blocked increased time by CRF (0.5, 1 µg, i.c.v.)	(Van't Veer et al., 2012)
			Male SD rat	0.125, 0.25, 0.5, 1, 2, 4 mg/kg, IP	10 min	N/A	(Nemeth et al., 2010)
			Male SD rat	0.003–10 mg/kg, IP & SC	20 or 30 min	N/A	(Boyette-Davis et al., 2008, Paine et al., 2007, Shannon et al., 2007)
			Male SD rat	0.1–10 mg/kg, IP	30 min	N/A	(Maguire et al., 2016)
			Male SD rat	0.1, 0.3, 1, 3, 10 mg/kg, IP	5 min	N/A	(Koffarnus and Katz, 2011)
			Male Wistar rat	0.3, 1, 3, 6 mg/kg, IP	30 min	N/A	(Pattij et al., 2009)
Decision-making	Post-error accuracy	Antagonist	Male SD rat	0.01–1 mg/kg, SC	30 min	N/A	(Shannon et al., 2007)
			Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	N/A	(Pattij et al., 2009, Wiskerke et al., 2011, Wiskerke et al., 2012)
			Male SD rat	10 mg/kg, IP	24 h	No effect in vehicle animals	(Beard et al., 2015, Donahue et al., 2015)
			Male SD rat	10 mg/kg, IP	72 h	N/A	(Nemeth et al., 2010)

Behavioral Measure	5-CSRTT Measure	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
			Male SD rat	10 mg/kg, IP	48 h	Blocked impairment by PACAP-38 (0.25, 0.5, 1 µg, i.c.v.)	(Donahue et al., 2016)
			Male SD rat	10 mg/kg, IP	24 h	Attenuated impairment by CRF (0.5, µg, i.c.v.)	(Beard et al., 2015)
			Male Wistar rat	10 mg/kg, IP	22–24 h	N/A	(Wiskerke et al., 2011)

Table 3 –

Opioid-induced changes in impulsivity, measured across multiple behavioral tasks. Doses included are those found effective for the findings. DRL – differential reinforcement of low response rate; DRN – dorsal raphe nucleus; H – hour; ICV – intracerebroventricular; IP – intraperitoneal injection; min – minute; nor-BNI – nor-binaltorphimine; PFC – prefrontal cortex; SC – subcutaneous injection; SD – Sprague Dawley; SSRT – stop signal reaction time; VTA – ventral tegmental area.

Cognitive Measure	Cognitive Test	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Impulsive Action	SSRT	U50,488	Male Wistar rat	0.25, 2.5 µg, ICV	5 min	Reduced number of correct trials, no effect on omissions & total response rate	(Walker and Kissler, 2013)
	DRL	(±)U50,488	Male & female C57BL/6 mice	5, 10 mg/kg, IP	Immediate	Increased non-reinforced responses, increased errors, increased burst responding	(Abraham et al., 2018)
	DRL	Nalfurafine	Male & female C57BL/6 mice	50 µg/kg, IP	Immediate	Increased non-reinforced responses, increased errors, increased burst responding	(Abraham et al., 2018)
	Response inhibition with fixed delay	Morphine	Male Long-Evans rat	3, 6 mg/kg, SC	20 min	Increased premature responses and omissions	(Mahoney et al., 2013)
	Response inhibition with variable delay	Morphine	Male Long-Evans rat	0.5, 1, 2, 4, 6, 8 mg/kg, SC	30 min	No effect	(Befort et al., 2011)
	SSRT	Morphine	Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect	(Pattij et al., 2009)
	SSRT	Naloxone	Male Wistar rat	0.3, 1, 3 mg/kg, IP	30 min	No effect	(Pattij et al., 2009)
	Response inhibition with fixed delay	Naloxone	Male Long-Evans rat	0.3, 1, 3 mg/kg, SC	30 min	No effect in vehicle animals	(Mahoney et al., 2013)
	Response inhibition with fixed delay	Naloxone	Male Long-Evans rat	0.3, 1, 3 mg/kg, SC	30 min	Blocked morphine-induced (6 mg/kg, SC) increases in premature responses and omissions	(Mahoney et al., 2013)
	Response inhibition with variable delay	Naloxone	Male Long-Evans rat	1 mg/kg, SC	30 min	No effect in vehicle animals and in combination with morphine	(Befort et al., 2011)
	DRL	nor-BNI	Male C57/BL6 mice	10 mg/kg, IP	24 h	Restored swim stress induced impairments	(Abraham et al., 2018)
	DRL	nor-BNI	Male C57/BL6 mice	2.5 µg/ml	3 d	Restored U50,488 induced impairments when injected into VTA, but not infralimbic PFC or DRN	(Abraham et al., 2018)
	SSRT	nor-BNI	Male Wistar rat	8 µg, ICV	48 h	No effect in vehicle animals	(Walker and Kissler, 2013)
	SSRT	nor-BNI	Male Wistar rat	8 µg, ICV	48 h	Blocked U50,488 induced (0.25 µg, ICV) impairment	(Walker and Kissler, 2013)

Cognitive Measure	Cognitive Test	Ligand	Species	Dose & Route	Test post admin	Finding	Reference
Impulsive Choice	Delay discounting	U50,488	Male Wistar rat	0.25, 2.5, 50 µg, ICV	5 min	No effect	(Walker and Kissler, 2013)
	Delayed reward paradigm	Morphine	Male Wistar rat	6 mg/kg, IP	30 min	Decreased preference for the larger delayed reward	(Pattij et al., 2009)
	Delay discounting adjusting amount procedure	Morphine	Male SD rat	1, 1.8 mg/kg SC	20 min	Dose-dependently increased the rate of delay discounting	(Kieres et al., 2004)
	Delay discounting	Morphine	Male SD rat	1 – 17 mg/kg, IP	15 min	Dose-dependently increased the rate of delay discounting	(Pitts and McKinney, 2005)
	Risky decision-making task	Morphine	Male Long-Evans rat	3 mg/kg, SC	15 min	Increased preference for large risky reward	(Mitchell, 2011)
	Delay discounting	Morphine	Male rhesus monkey	0.1–5.6 mg/kg, SC	15 min	Increased trial omissions, Small doses decreased & large doses increased preference of larger delayed reward	(Maguire et al., 2016)
	Delay discounting/ Delayed reward paradigms	Naloxone	Male Wistar rat	1, 3 mg/kg, IP	30 min	No effect in vehicle animals	(Pattij et al., 2009, Wiskerke et al., 2011)
	Delay discounting adjusting amount procedure	Naloxone	Male Wistar rat	1, 3 mg/kg, IP	30 min	No effect on improvements induced by amphetamine (0.5 mg/kg, IP)	(Wiskerke et al., 2011)
	Delayed reward paradigm	Naloxone	Male Wistar rat	1 mg/kg, IP	30 min	Blocked effect of morphine (6 mg/kg, IP)	(Pattij et al., 2009)
	Delay discounting	Naltrexone	Male SD rat	0.01, 0.1, 1, 10 mg/kg, SC	40 min	No effect in vehicle animals	(Kieres et al., 2004)
	Delay discounting	Naltrexone	Male SD rat	0.1 mg/kg, SC	40 min	Blocked effect of morphine (1.8 mg/kg, SC)	(Kieres et al., 2004)
	Delayed reward paradigm	nor-BNI	Male Wistar rat	10 mg/kg, IP	22–24 h	No effect in vehicle animals	(Wiskerke et al., 2011)
	Delayed reward paradigm	nor-BNI	Male Wistar rat	10 mg/kg, IP	22–24 h	Attenuated amphetamine-induced (0.5 mg/kg, IP) improvements	(Wiskerke et al., 2011)