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Stress-induced impairments in prefrontal-mediated behaviors and the role of the *N*-methyl-D-aspartate receptor

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Abstract

The prefrontal cortex (PFC) mediates higher-order cognitive and executive functions that subserve various complex, adaptable behaviors such as cognitive flexibility, attention and working memory. Deficits in these functions typify multiple neuropsychiatric disorders that are caused or exacerbated by exposure to psychological stress. Here we review recent evidence examining the effects of stress on executive and cognitive functions in rodents, and discuss an emerging body of evidence that implicates the *N*-methyl-D-aspartate receptor (NMDAR) as a potentially critical molecular mechanism mediating these effects. Future work in this area could open up new avenues for developing pharmacotherapies for ameliorating cognitive dysfunction in neuropsychiatric disease.

Introduction

Higher-order cognitive and executive functions encompass mental processes that allow for complex, adaptable behavior and include attention, working memory, behavioral inhibition, and cognitive flexibility. Deficits in executive functions are hallmarks of various neuropsychiatric disorders, such as schizophrenia, depression, obsessive compulsive disorder, and drug addictions (Murphy et al., 2003, McLean et al., 2004, Waltz and Gold, 2007). In recent years, the field has placed a growing focus on understanding the mechanisms underlying executive deficits as an approach to designing improved treatments for these disorders (Barnett et al., 2010).

An outstanding question in this context is how exposure to environmental insults such as stress, which is a known risk factor for these disorders (Sinha, 2008, Lupien et al., 2009), impacts executive functions. This then raises the corollary issue of which molecular mechanisms are involved and whether these offer targets for new pharmacotherapies. The goal of the current article is to provide an update on recent research that has attempted to address these questions using rodent preclinical models.

We first provide a brief overview of the literature on stress effects on two relatively well-studied prefrontal cortex (PFC)-mediated executive functions - working memory and cognitive flexibility, as well as on fear extinction, an important PFC-mediated form of

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emotional regulation. We then discuss preliminary evidence implicating the *N*-methyl-D-aspartate receptor (NMDAR) as one potential molecular mechanism mediating stress effects on cognition and fear extinction.

Stress effects on PFC-mediated behaviors

Stress, even when relatively mild and brief, can profoundly alter structure and neuronal morphology in rodent PFC (Arnsten, 2009, Holmes and Wellman, 2009, Shansky and Morrison, 2009). This in and of itself strongly implies that stress would impact behaviors that are dependent upon intact PFC functions. Stress effects on rodent cognitive and executive functions have been directly examined using a range of well-characterized behavioral assays (for more detailed descriptions of these tasks, see Robbins, 2007, Floresco et al., 2008, Holmes and Wellman, 2009, Brigman et al., 2010, Chudasama, 2011). Some of the main findings from this literature are summarized in Table 1.

Stress effects on working memory

Working memory is the transient storage of recently acquired information. Working memory impairments are produced by medial prefrontal cortex (mPFC) lesions encompassing the prelimbic and infralimbic cortices and occasionally extending to the anterior cingulate cortex (Fritts et al., 1998, Schwabe et al., 2004, Chudasama and Robbins, 2006, Gisquet-Verrier and Delatour, 2006, Sloan et al., 2006) or experimentally-induced alterations in mPFC neurotransmitters such as dopamine (Cools and Robbins, 2004, Arnsten and Pliszka, 2011, Gamo and Arnsten, 2011).

A number of studies have examined the effects of stress on working memory. Mice exposed to chronic cold water stress, or rats subjected to chronic unpredictable stress (CUS) exhibit impaired working memory in the Morris water maze (MWM), radial arm maze and delayed alternation T-maze (Diamond et al., 1999, Mizoguchi et al., 2000, Woodson et al., 2003, Cerqueira et al., 2007, Park et al., 2008, Trofimiuk and Braszko, 2008, Hains et al., 2009). Exposure to a single stress episode, such as fifteen minute exposure to a predator's odor, is sufficient to impair working memory on assays including the delayed, non-matching-to-sample object recognition task, delayed alternation water T-maze or delayed win-shift radial maze (Morrow et al., 2000, Del Arco et al., 2007, Buchanan et al., 2008, Butts et al., 2011, Del Arco et al., 2011). However there are also reports of no effect of stress (Choy et al., 2008) or even facilitation of working memory after exposure to two hour restraint stress or forced swim stress (Barha et al., 2007, Yuen et al., 2009, Yuen et al., 2011). The reason for these differences is not fully clear but may relate to differences in the type of stress, the duration and chronicity of its application, and the interval between stress and behavioral testing (Anisman and Matheson, 2005, Joels et al., 2006, Joels et al., 2007). Indeed, there remains much to be understood the degree to which these parameters determine the impact of stress on cognition in general.

Stress-induced working memory impairments can be mimicked by treatment with corticosterone or dexamethasone, implicating glucocorticoids in this effect (Cerqueira et al., 2005, Trofimiuk and Braszko, 2008). Indeed, a recent report found that acute tail pinch stress applied specifically during the working memory retention interval in a maze-based task impaired performance and, moreover, that this could be rescued by blocking glucocorticoid receptors in the mPFC (Butts et al., 2011). However, the contribution of other neural mechanisms, including NMDARs, to stress-induced working memory deficits is yet to be elucidated.

Stress effects on cognitive flexibility

Cognitive flexibility, the ability to modify previously learned behavior following changes that alter the outcome of that behavior, can be assayed in rodents in various ways. One simple measure of cognitive flexibility is reversal learning, in which the subject is required to switch responding from one cue or location to another in order to gain a reward or avoid a punishment. By contrast, set-shifting involves more complex stimuli with distinctly perceptible features, e.g. odor and texture, and requires the subject to attend to and switch between these relevant features. Lesions studies in rats and mice have typically demonstrated a dissociation between orbitofrontal cortex (OFC) mediation of reversal and mediation of set-shifting by the mPFC (Birrell and Brown, 2000, Chudasama and Robbins, 2006, Boulougouris et al., 2007, Bissonette et al., 2008).

Rats exposed to CUS or given glucocorticoid treatment subsequently exhibit deficits in reversal learning as measured in the MWM (Hill et al., 2004, Cerqueira et al., 2005, Cerqueira et al., 2007). CUS or chronic intermittent cold exposure also impairs reversal and set-shifting in an odor-texture attentional set-shifting task, an analogue of the human Wisconsin Card Sorting Task, in a manner that is reversible by treatment with the monoaminergic antidepressants desipramine, nomifensine, fluoxetine or citalopram block these effects (Liston et al., 2006, Bondi et al., 2008, Lapiz-Bluhm et al., 2009, Bondi et al., 2010, Danet et al., 2010, Furr et al., 2011, Nikiforuk and Popik, 2011).

Extending these findings, recent work from our laboratory found that under some test conditions, stress can ‘paradoxically’ facilitate reversal learning. We found that mice exposed to three days of forced swim stress showed improved reversal learning in a touchscreen-based operant task, and that this effect was mimicked by lesions of the mPFC (Graybeal et al., 2011). Given lesions of the dorsolateral striatum (DLS) impair reversal learning in this task (Graybeal et al., 2011), one interpretation of these data is that stress-induced impairment of mPFC function disinhibits DLS-mediated learning. This hypothesis is in line with recent work from Dias-Ferreira and colleagues and Schwabe and Wolf showing that stress promotes DLS-mediated learning and the formation of habits (Dias-Ferreira et al., 2009, Schwabe and Wolf, 2009, 2011). Taken together, these studies underscore a key issue, which is that while the PFC may be a particularly sensitive target for stress, the consequences of resultant PFC dysfunction are complex and may not always simply be impairing. Rather, stress effects will manifest at the systems levels as shifts in the balance of control over behavior amongst parallel and even competing brain regions.

Stress effects on fear extinction

Fear extinction is not a measure of executive function but is very salient to the current discussion given the importance of the mPFC to fear extinction (Quirk and Mueller, 2008) and clinical evidence of deficient fear extinction in diseases such as schizophrenia, where PFC dysfunction is prominent (Holt et al., 2008).

In an early indication that stress impairs fear extinction, mice exposed to three days of forced swim were found to have slower extinction, which was coupled with dendritic retraction in mPFC pyramidal neurons (Izquierdo et al., 2006). More prolonged stress regimens involving chronic restraint or corticosterone treatment in adult rats, or maternal separation in neonatal rats, have also been shown to impair extinction and PFC-mediated neuronal encoding of extinction (Miracle et al., 2006, Baran et al., 2009, Gourley et al., 2009, Wilber et al., 2009, Green et al., 2011, Wilber et al., 2011).

Elegant work by Maier and colleagues has shown that the controllability of stress determines the nature of stress effects on the expression of learned fear (Maier and Watkins, 2010). For example, rats exposed to escapable stress subsequently exhibit reduced fear conditioning

and decreased fear during fear extinction training (Baratta et al., 2007). The apparent resilience conferred by a history of escapable stress extends to other behaviors (social and depression-related) (Amat et al., 2006, Christianson et al., 2008, Christianson et al., 2009, Amat et al., 2010). Interestingly, this resiliency is dependent upon mPFC (specifically infralimbic cortex) function, as demonstrated by the finding that infralimbic inactivation during stress or testing prevents the fear-reducing effect of escapable stress on fear expression (Baratta et al., 2008), apparently due to loss of regulation of midbrain serotonergic signaling (Amat et al., 2005). However, the potential contribution of glutamatergic signaling, either in mPFC or at the midbrain level, to this effect has not been determined and remains an interesting question for future work.

NMDARs in PFC-mediated behaviors

Glutamate, the main excitatory neurotransmitter, binds to multiple metabotropic receptors and three families of ionotropic receptors: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), kainate receptors and NMDARs. While all three families have been found to play a role in cognitive and stress-related behaviors, NMDARs represent a particularly intriguing mechanism mediating stress-induced changes in prefrontal-mediated behaviors for a number of reasons.

NMDARs and PFC-mediated cognition

Pharmacological blockade of NMDARs can have profound effects on PFC-mediated cognitive processes discussed above (Floresco et al., 2008, Brigman et al., 2010, Neill et al., 2010). A number of studies have shown that either acute or chronic treatment with NMDAR antagonists such as ketamine (Nikiforuk et al., 2010, Kos et al., 2011), phencyclidine (Abdul-Monim et al., 2006, Didriksen et al., 2007) or MK-801 (Bardgett et al., 2003, van der Meulen et al., 2003, Watson and Stanton, 2009c, b, a) impairs cognitive flexibility. For example, phencyclidine administration disrupts reversal learning (Abdul-Monim et al., 2006, Abdul-Monim et al., 2007) and ketamine treatment impairs extra-dimensional set-shifting (Nikiforuk et al., 2010, Kos et al., 2011). A similar disruptive effect of ketamine is observed in humans tested in the Wisconsin card sorting task (Krystal et al., 2000). Further reinforcing the translational relevance of the rodent data, clinically efficacious antipsychotics including sertindole, clozapine or risperidone rescue these cognitive-impairing effects NMDAR antagonists (Amitai et al., 2007, Didriksen et al., 2007, Kos et al., 2011).

Systemic treatment with NMDAR antagonists also disrupts working memory (Jentsch et al., 1997, Aura and Riekkinen, 1999, Ko and Evenden, 2009, Willmore et al., 2009, Smith et al., 2011) and produces deficits in attentional performance that reflect increased impulsivity (Higgins et al., 2003, Higgins et al., 2005, Baviera et al., 2008, Amitai and Markou, 2009, 2010, Murphy et al., 2011, Thomson et al., 2011). These effects can be recapitulated by direct infusion of NMDAR antagonists into the mPFC (Aura and Riekkinen, 1999, Baviera et al., 2008), consistent with the hypothesis that NMDARs in this brain region are key mediators of these behaviors.

NMDAR subunits and PFC-mediated cognition

An important functional characteristic of NMDARs is their heteromeric structure: obligatory GluN1 subunits and one or more GluN2 (GluN2A-GluN2D) or GluN3 subunits (Rosenmund et al., 1998). GluN2A and GluN2B are modulatory in that their inclusion influences receptor kinetics (Cull-Candy et al., 2001). NMDARs containing GluN2A and/or GluN2B are widely expressed in corticolimbic regions, including the mPFC, where they are localized on both pyramidal and interneurons (Cull-Candy et al., 2001).

The behavioral role of GluN2B-containing NMDARs has been studied using GluN2B-selective antagonists such as ifenprodil and Ro 25-6981. Studies utilizing these agents have shown, for example, that systemic GluN2B antagonist treatment impaired reversal learning as assayed in a rat lever pressing task (Dalton et al., 2011a) and in the mouse MWM test (Duffy et al., 2008), and produced impulsivity in an attentional task (Higgins et al., 2003, Higgins et al., 2005). While parallel studies on GluN2A are hampered by a lack of selective drugs for this subunit (Neyton and Paoletti, 2006), the pharmacological literature on this and the other subunits has been extended using mutant mice in which a NMDAR subunit is genetically deleted.

Mice with constitutive genetic inactivation of GluN2A exhibit impairments in operant discrimination and reversal learning (Brigman et al., 2008) and spatial working, but not reference, memory (Bannerman et al., 2008). This working memory deficit phenocopies the effects of deleting GluN1 in a subpopulation of forebrain parvalbumin-expressing GABAergic interneurons (Belforte et al., 2010) or deleting GluN2B in hippocampal principal neurons (von Engelhardt et al., 2008). More pronounced effects are produced by forebrain-wide or corticohippocampal deletion of GluN2B in principal neurons, which produces deficits in object recognition, maze-based spatial working and reference memory, and discrimination learning (Brigman et al., 2008, von Engelhardt et al., 2008).

Conversely, transgenic overexpression of GluN2B throughout the forebrain facilitates fear extinction (Tang et al., 1999) and working memory performance on multiple tasks in concert with enhanced plasticity (long-term potentiation) at PFC synapses (Cui et al., 2011). These data suggest that GluN2B can exert bidirectional control over cognition, although the precise contribution of GluN2B to these effects remains to be determined. The same limitation applies to current understanding of the role of GluN2A given the absence of studies that specifically manipulate the subunit (either genetically or pharmacologically) in the PFC. Nonetheless, given the nature of the deficits on PFC-dependent tasks it is reasonable to hypothesize that NMDARs mediate forms of cognition that are subserved by this brain region.

NMDARs and PFC-mediated extinction

A number of findings establish a role for PFC NMDARs in fear extinction. Pre-extinction treatment with the NMDAR partial agonist D-cycloserine facilitates fear extinction when given systemically (Matsuda et al., Walker et al., 2002, Lee et al., 2006) and facilitates re-extinction when given directly into the mPFC (Chang and Maren, 2009). Systemic administration of NMDAR antagonists also impairs both the acquisition and consolidation of fear extinction if administered before or after extinction training, respectively (Santini et al., 2001, Lee et al., 2006, Sotres-Bayon et al., 2007, Sotres-Bayon et al., 2009). This consolidation impairment is mimicked by mPFC-infusion of a NMDAR antagonist, possibly via reductions in the post-extinction burst firing of mPFC neurons (Burgos-Robles et al., 2007).

As with the PFC-mediated cognition, an important issue around the role of NMDARs in extinction is whether specific receptor subunits can be implicated. In this context, systemic treatment with GluN2B-specific antagonists (Rodrigues et al., 2001, Sotres-Bayon et al., 2007, Sotres-Bayon et al., 2009, Dalton et al., 2011b), as well as disruption of phosphorylation sites on the subunit (Nakazawa et al., 2006), impairs fear extinction. The effect of direct infusion of GluN2B antagonists on fear extinction has not been reported, although GluN2B inactivation, via antagonism or RNA interference, in dorsal regions of the mPFC (i.e., anterior cingulate) impairs the acquisition of contextual (but not cued) fear memory (Zhao et al., 2005).

NMDARs and antidepressant-like actions

It is notable that while NMDAR antagonists such as ketamine have impairing effects on fear extinction and cognition, the same drugs have fast-acting antidepressant and anxiolytic effects in patients (Krystal et al., 1994, Berman et al., 2000, Zarate et al., 2006, Preskorn et al., 2008). When delivered systemically, these compounds also reduce anxiety-like (reviewed in Cryan and Dev, 2008, Barkus et al., 2010) and 'depression-related' behaviors in rats and mice at baseline and following stress (Maeng et al., 2008, Li et al., 2010, Li et al., 2011). These effects are linked to the PFC, by the finding that they occur in parallel with various changes in this region, including enhanced mammalian target of rapamycin (mTOR) signaling, increased expression of synaptic proteins (synapsin, PSD-95, AMPA GluA1) and dendritic spinogenesis (Li et al., 2010). Moreover, intra-PFC blockade of mTOR is sufficient to prevent some of these behavioral and neuronal effects of systemically-delivered NMDAR antagonists (Li et al., 2010). These findings reveal a key role for NMDARs, via effects in PFC, in mediating rodent antidepressant-like actions, expanding the role of this mechanism beyond 'classic' PFC-mediated extinction and cognition behaviors which we have focused on in the current review.

There is growing evidence that, as with cognition and extinction, the GluN2B subunit is critical to NMDAR antagonist antidepressant-like effects. The above mentioned effects of ketamine, including the reversal of CUS-induced depression-related behaviors, are replicated by systemic treatment with the GluN2B-selective antagonist Ro 25-6981 (Li et al., 2010, Li et al., 2011). Moreover, gene deletion of GluN2B on principal neurons in the cortex, as well dorsal CA1 hippocampus, leads to an attenuated despair-like response to repeated swim stress, but normal baseline anxiety-behavior (Kiselycznyk et al., 2011). This phenotype contrasts with the more generalized anxiolytic-like effects of either more widespread forebrain GluN2B deletion (von Engelhardt et al., 2008) or systemic GluN2B antagonist treatment (Fraser et al., 1996, Maeng et al., 2008, Li et al., 2010). This would be consistent with a preferential role for cortical GluN2B in regulating adaptive responses to stress, although this remains to be shown.

Do NMDARs mediate stress-induced changes in PFC?

Taken together, the literature discussed thus far comes raises the intriguing possibility that stress acts via NMDARs in the PFC to produce changes in a variety of behaviors that are regulated by this brain region. There remains, however, a paucity of evidence directly testing this hypothesis.

What has been shown is that stress produces changes in the expression of NMDARs that parallel alterations in PFC-mediated behaviors. For example, rats subjected to neonatal maternal separation have decreased levels of GluN1 in the infralimbic cortex, and show impaired fear extinction, as adults (Wilber et al., 2009). Along similar lines, chronic corticosterone administration in adult rats impairs fear extinction, in tandem with decreased mPFC expression of the GluN2B NMDAR subunit (Gourley et al., 2009). Acute forced swim stress (also in rats), on the other hand, has been found to transiently (one day) increase the cell surface expression of GluN1, GluN2A and GluN2B in mPFC and improve working memory in a T-maze task (Yuen et al., 2009). Thus, changes in mPFC NMDAR expression appear to be closely (and bidirectionally) tied to stress-induced shifts in behaviors mediated by the region.

As mentioned above, chronic stress causes dendritic retraction in PFC neurons. Dendritic atrophy is also seen in CA3 hippocampus following chronic stress (Roozendaal et al., 2009). Systemic administration of drugs blocking glutamate release (phenytoin) (Watanabe et al., 1992), or NMDARs (but not AMPA) can block this morphological effect (Magarinos and

McEwen, 1995). Deletion of GluN1 on CA3 principal neurons mimicked this effect but, importantly, was not sufficient to prevent stress-induced increases in anxiety-like behavior – indicating the behavioral effects were not a consequence of dendritic changes in this region and likely resided elsewhere (Christian et al., 2011). Indeed, if GluN2A (but not AMPA GluA1) is deleted brain-wide, restraint-stress-induced changes in anxiety-like behavior can be prevented (Boyce-Rustay and Holmes, 2006; Mozhui et al., 2010).

Studies that examine the consequences of blockade or deletion of NMDARs specifically within the PFC for stress-induced behavioral alterations have not yet been conducted. One recent study found that the reduced PFC synaptic potentiation observed in mice exposed to postnatal footshock stress could be partially ameliorated by systemic injection of the NMDAR partial agonist D-cycloserine (Judo et al., 2010). In addition, an important recent study by Martin and Wellman found that rats given systemic NMDAR antagonist treatment failed to show mPFC dendritic atrophy (Martin and Wellman, 2011). These authors also showed that NMDAR antagonistic treatment in the presence of stress (but not NMDAR antagonist treatment alone) produced dendritic hypertrophy. This demonstrates that NMDARs mediate stress-induced morphological changes in PFC and suggest that neuronal morphology in this region is under tonic control of NMDAR activity.

Conclusions and future directions

The current literature sets up a number of critical questions going forward. For example, would systemic NMDAR blockade be sufficient to prevent stress-induced alterations in PFC-mediated behaviors, such as cognitive flexibility and fear extinction? If so, would these effects be recapitulated by blockade or gene deletion of NMDARs specifically within the PFC, or are they instead driven by NMDARs localized in other brain regions? What are the specific NMDAR subunits and critical downstream signaling processes involved in these effects? The development and refinement of pharmacological and genetic experimental tools should greatly aid preclinical research addressing these questions.

Ultimately, the question will be whether the findings made in rodents can illuminate novel therapeutic targets for alleviating cognitive deficits resulting from stress. A number of issues already present themselves in translating the rodent work to potential clinical application. One issue relates to the fact that on the one hand NMDAR antagonists have cognitive impairing effects, but have antidepressant actions likely via effects in the PFC. Preclinical evidence that chronic stress impairs cognition via reductions in mPFC NMDAR might predict that stimulation, rather than blockade, of NMDARs would work to rebalance mPFC functions. This could turn out to be the case for certain cognitive processes (e.g., see fear extinction and the case of D-cycloserine). In terms of antidepressant effects, one pertinent factor may be timing, with cognitive deficits occurring acutely and then waning, but antidepressant activity being more sustained due to long-lasting plastic changes in PFC. Indeed, patients given ketamine scored high on the Brief Psychiatric Rating Scale for positive symptoms of psychosis only 40 minutes after infusion, while alleviation of depressive symptoms occurred 2 hours to 7 days after treatment (Zarate et al., 2006). This echoes to some degree data in rats showing ketamine changes in spine growth and synaptic protein expression were delayed until 24 hours after injection (Li et al., 2010). Precisely delineating the temporal dynamics of NMDAR antagonist effects will be one important area for future study as this exciting field moves forward.

Highlights

1. Executive dysfunctions are hallmarks of many stress-related neuropsychiatric disorders.

2. Rodent studies demonstrate stress-induced impairments in prefrontal-mediated cognitive functions.
3. N-methyl-D-aspartate receptors (NMDARs) are key mediators of cognition and stress responses.
4. Preclinical studies implicate NMDARs in stress-induced prefrontal cognitive deficits.
5. Targeting NMDAR functions may offer novel therapeutics to alleviate stress-related cognitive deficits.

References

- Abdul-Monim Z, Neill JC, Reynolds GP. Sub-chronic psychotomimetic phencyclidine induces deficits in reversal learning and alterations in parvalbumin-immunoreactive expression in the rat. *J Psychopharmacol*. 2007; 21:198–205. [PubMed: 17329300]
- Abdul-Monim Z, Reynolds GP, Neill JC. The effect of atypical and classical antipsychotics on sub-chronic PCP-induced cognitive deficits in a reversal-learning paradigm. *Behav Brain Res*. 2006; 169:263–273. [PubMed: 16500717]
- Amat J, Alekseyev RM, Paul E, Watkins LR, Maier SF. Behavioral control over shock blocks behavioral and neurochemical effects of later social defeat. *Neuroscience*. 2010; 165:1031–1038. [PubMed: 19909791]
- Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat Neurosci*. 2005; 8:365–371. [PubMed: 15696163]
- Amat J, Paul E, Zarza C, Watkins LR, Maier SF. Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex. *J Neurosci*. 2006; 26:13264–13272. [PubMed: 17182776]
- Amitai N, Markou A. Increased impulsivity and disrupted attention induced by repeated phencyclidine are not attenuated by chronic quetiapine treatment. *Pharmacol Biochem Behav*. 2009; 93:248–257. [PubMed: 18809428]
- Amitai N, Markou A. Disruption of performance in the five-choice serial reaction time task induced by administration of N-methyl-D-aspartate receptor antagonists: relevance to cognitive dysfunction in schizophrenia. *Biol Psychiatry*. 2010; 68:5–16. [PubMed: 20488434]
- Amitai N, Semenova S, Markou A. Cognitive-disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. *Psychopharmacology (Berl)*. 2007; 193:521–537. [PubMed: 17497138]
- Anisman H, Matheson K. Stress, depression, and anhedonia: caveats concerning animal models. *Neurosci Biobehav Rev*. 2005; 29:525–546. [PubMed: 15925696]
- Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci*. 2009; 10:410–422. [PubMed: 19455173]
- Arnsten AF, Pliszka SR. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. *Pharmacol Biochem Behav*. 2011; 99:211–216. [PubMed: 21295057]
- Aura J, Riekkinen P Jr. Blockade of NMDA receptors located at the dorsomedial prefrontal cortex impairs spatial working memory in rats. *Neuroreport*. 1999; 10:243–248. [PubMed: 10203316]
- Bannerman DM, Niewoehner B, Lyon L, Romberg C, Schmitt WB, Taylor A, Sanderson DJ, Cottam J, Sprengel R, Seeburg PH, Kohr G, Rawlins JN. NMDA receptor subunit NR2A is required for rapidly acquired spatial working memory but not incremental spatial reference memory. *J Neurosci*. 2008; 28:3623–3630. [PubMed: 18385321]

- Baran SE, Armstrong CE, Niren DC, Hanna JJ, Conrad CD. Chronic stress and sex differences on the recall of fear conditioning and extinction. *Neurobiol Learn Mem.* 2009; 91:323–332. [PubMed: 19073269]
- Baratta MV, Christianson JP, Gomez DM, Zarza CM, Amat J, Masini CV, Watkins LR, Maier SF. Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. *Neuroscience.* 2007; 146:1495–1503. [PubMed: 17478046]
- Baratta MV, Lucero TR, Amat J, Watkins LR, Maier SF. Role of the ventral medial prefrontal cortex in mediating behavioral control-induced reduction of later conditioned fear. *Learn Mem.* 2008; 15:84–87. [PubMed: 18235108]
- Bardgett ME, Boeckman R, Krochmal D, Fernando H, Ahrens R, Csernansky JG. NMDA receptor blockade and hippocampal neuronal loss impair fear conditioning and position habit reversal in C57Bl/6 mice. *Brain Res Bull.* 2003; 60:131–142. [PubMed: 12725901]
- Barha CK, Pawluski JL, Galea LA. Maternal care affects male and female offspring working memory and stress reactivity. *Physiol Behav.* 2007; 92:939–950. [PubMed: 17716698]
- Barkus C, McHugh SB, Sprengel R, Seeburg PH, Rawlins JN, Bannerman DM. Hippocampal NMDA receptors and anxiety: at the interface between cognition and emotion. *Eur J Pharmacol.* 2010; 626:49–56. [PubMed: 19836379]
- Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell AD. Assessing cognitive function in clinical trials of schizophrenia. *Neurosci Biobehav Rev.* 2010; 34:1161–1177. [PubMed: 20105440]
- Baviera M, Invernizzi RW, Carli M. Haloperidol and clozapine have dissociable effects in a model of attentional performance deficits induced by blockade of NMDA receptors in the mPFC. *Psychopharmacology (Berl).* 2008; 196:269–280. [PubMed: 17940750]
- Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, Quinlan EM, Nakazawa K. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat Neurosci.* 2010; 13:76–83. [PubMed: 19915563]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* 2000; 47:351–354. [PubMed: 10686270]
- Birrell JM, Brown VJ. Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J Neurosci.* 2000; 20:4320–4324. [PubMed: 10818167]
- Bissonette GB, Martins GJ, Franz TM, Harper ES, Schoenbaum G, Powell EM. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. *J Neurosci.* 2008; 28:11124–11130. [PubMed: 18971455]
- Blundell J, Blaiss CA, Lagace DC, Eisch AJ, Powell CM. Block of glucocorticoid synthesis during reactivation inhibits extinction of an established fear memory. *Neurobiol Learn Mem.* 2011; 95:453–460. [PubMed: 21333745]
- Bondi CO, Jett JD, Morilak DA. Beneficial effects of desipramine on cognitive function of chronically stressed rats are mediated by [alpha]1-adrenergic receptors in medial prefrontal cortex. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2010; 34:913–923. [PubMed: 20417676]
- Bondi CO, Rodriguez G, Gould GG, Frazer A, Morilak DA. Chronic unpredictable stress induces a cognitive deficit and anxiety-like behavior in rats that is prevented by chronic antidepressant drug treatment. *Neuropsychopharmacology.* 2008; 33:320–331. [PubMed: 17406647]
- Boulougouris V, Dalley JW, Robbins TW. Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. *Behav Brain Res.* 2007; 179:219–228. [PubMed: 17337305]
- Boyce-Rustay JM, Holmes A. Genetic inactivation of the NMDA receptor NR2A subunit has anxiolytic- and antidepressant-like effects in mice. *Neuropsychopharmacology.* 2006; 31:2405–2414. [PubMed: 16482087]
- Brenhouse HC, Andersen SL. Nonsteroidal anti-inflammatory treatment prevents delayed effects of early life stress in rats. *Biol Psychiatry.* 2011; 70:434–440. [PubMed: 21679927]
- Brigman JL, Feyder M, Saksida LM, Bussey TJ, Mishina M, Holmes A. Impaired discrimination learning in mice lacking the NMDA receptor NR2A subunit. *Learn Mem.* 2008; 15:50–54. [PubMed: 18230672]

- Brigman JL, Graybeal C, Holmes A. Predictably irrational: assaying cognitive inflexibility in mouse models of schizophrenia. *Front Neurosci.* 2010; 4
- Brinks V, de Kloet ER, Oitzl MS. Corticosterone facilitates extinction of fear memory in BALB/c mice but strengthens cue related fear in C57BL/6 mice. *Exp Neurol.* 2009; 216:375–382. [PubMed: 19162011]
- Buchanan JB, Sparkman NL, Chen J, Johnson RW. Cognitive and neuroinflammatory consequences of mild repeated stress are exacerbated in aged mice. *Psychoneuroendocrinology.* 2008; 33:755–765. [PubMed: 18407425]
- Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron.* 2007; 53:871–880. [PubMed: 17359921]
- Butts KA, Weinberg J, Young AH, Phillips AG. Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. *Proc Natl Acad Sci U S A.* 2011; 108:18459–18464. [PubMed: 22032926]
- Callaghan BL, Richardson R. Maternal separation results in early emergence of adult-like fear and extinction learning in infant rats. *Behav Neurosci.* 2011; 125:20–28. [PubMed: 21319883]
- Cerqueira JJ, Mailliet F, Almeida OF, Jay TM, Sousa N. The prefrontal cortex as a key target of the maladaptive response to stress. *J Neurosci.* 2007; 27:2781–2787. [PubMed: 17360899]
- Cerqueira JJ, Pego JM, Taipa R, Bessa JM, Almeida OF, Sousa N. Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. *J Neurosci.* 2005; 25:7792–7800. [PubMed: 16120780]
- Chang CH, Maren S. Early extinction after fear conditioning yields a context-independent and short-term suppression of conditional freezing in rats. *Learn Mem.* 2009; 16:62–68. [PubMed: 19141467]
- Choy KH, de Visser Y, Nichols NR, van den Buuse M. Combined neonatal stress and young-adult glucocorticoid stimulation in rats reduce BDNF expression in hippocampus: effects on learning and memory. *Hippocampus.* 2008; 18:655–667. [PubMed: 18398848]
- Christian KM, Miracle AD, Wellman CL, Nakazawa K. Chronic stress-induced hippocampal dendritic retraction requires CA3 NMDA receptors. *Neuroscience.* 2011; 174:26–36. [PubMed: 21108993]
- Christianson JP, Paul ED, Irani M, Thompson BM, Kubala KH, Yirmiya R, Watkins LR, Maier SF. The role of prior stressor controllability and the dorsal raphe nucleus in sucrose preference and social exploration. *Behav Brain Res.* 2008; 193:87–93. [PubMed: 18554730]
- Christianson JP, Thompson BM, Watkins LR, Maier SF. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. *Stress.* 2009; 12:445–450. [PubMed: 19051125]
- Chudasama Y. Animal models of prefrontal-executive function. *Behav Neurosci.* 2011; 125:327–343. [PubMed: 21639603]
- Chudasama Y, Robbins TW. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol Psychol.* 2006; 73:19–38. [PubMed: 16546312]
- Cools R, Robbins TW. Chemistry of the adaptive mind. *Philos Transact A Math Phys Eng Sci.* 2004; 362:2871–2888. [PubMed: 15539374]
- Cryan, JF.; Dev, KK. Role of glutamate in anxiety. In: Blanchard, DC.; Blanchard, RM., editors. *Handbook of fear and anxiety.* London: Elsevier; 2008. p. 269–301.
- Cui Y, Jin J, Zhang X, Xu H, Yang L, Du D, Zeng Q, Tsien JZ, Yu H, Cao X. Forebrain NR2B overexpression facilitating the prefrontal cortex long-term potentiation and enhancing working memory function in mice. *PLoS One.* 2011; 6:e20312. [PubMed: 21655294]
- Cull-Candy S, Brickley S, Farrant M. NMDA receptor subunits: diversity, development and disease. *Curr Opin Neurobiol.* 2001; 11:327–335. [PubMed: 11399431]
- Dalton GL, Ma LM, Phillips AG, Floresco SB. Blockade of NMDA GluN2B receptors selectively impairs behavioral flexibility but not initial discrimination learning. *Psychopharmacology (Berl).* 2011a; 216:525–535. [PubMed: 21384103]

- Dalton GL, Wu DC, Wang YT, Floresco SB, Phillips AG. NMDA GluN2A and GluN2B receptors play separate roles in the induction of LTP and LTD in the amygdala and in the acquisition and extinction of conditioned fear. *Neuropharmacology*. 2011b
- Danet M, Lapiz-Bluhm S, Morilak DA. A cognitive deficit induced in rats by chronic intermittent cold stress is reversed by chronic antidepressant treatment. *Int J Neuropsychopharmacol*. :1–13.
- Danet M, Lapiz-Bluhm S, Morilak DA. A cognitive deficit induced in rats by chronic intermittent cold stress is reversed by chronic antidepressant treatment. *Int J Neuropsychopharmacol*. 2010; 13:997–1009. [PubMed: 20149267]
- Del Arco A, Segovia G, de Blas M, Garrido P, Acuna-Castroviejo D, Pamplona R, Mora F. Prefrontal cortex, caloric restriction and stress during aging: studies on dopamine and acetylcholine release, BDNF and working memory. *Behav Brain Res*. 2011; 216:136–145. [PubMed: 20655333]
- Del Arco A, Segovia G, Garrido P, de Blas M, Mora F. Stress, prefrontal cortex and environmental enrichment: studies on dopamine and acetylcholine release and working memory performance in rats. *Behav Brain Res*. 2007; 176:267–273. [PubMed: 17097747]
- Diamond DM, Park CR, Heman KL, Rose GM. Exposing rats to a predator impairs spatial working memory in the radial arm water maze. *Hippocampus*. 1999; 9:542–552. [PubMed: 10560925]
- Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, Costa RM, Sousa N. Chronic stress causes frontostriatal reorganization and affects decision-making. *Science*. 2009; 325:621–625. [PubMed: 19644122]
- Didriksen M, Skarsfeldt T, Arnt J. Reversal of PCP-induced learning and memory deficits in the Morris' water maze by sertindole and other antipsychotics. *Psychopharmacology (Berl)*. 2007; 193:225–233. [PubMed: 17406859]
- Duffy S, Labrie V, Roder JC. D-serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. *Neuropsychopharmacology*. 2008; 33:1004–1018. [PubMed: 17625504]
- Farrell MR, Sayed JA, Underwood AR, Wellman CL. Lesion of infralimbic cortex occludes stress effects on retrieval of extinction but not fear conditioning. *Neurobiol Learn Mem*. 2010; 94:240–246. [PubMed: 20538067]
- Floresco SB, Zhang Y, Enomoto T. Neural circuits subserving behavioral flexibility and their relevance to schizophrenia. *Behav Brain Res*. 2008
- Francis DD, Zaharia MD, Shanks N, Anisman H. Stress-induced disturbances in Morris water-maze performance: interstrain variability. *Physiol Behav*. 1995; 58:57–65. [PubMed: 7667428]
- Fraser CM, Cooke MJ, Fisher A, Thompson ID, Stone TW. Interactions between ifenprodil and dizocilpine on mouse behaviour in models of anxiety and working memory. *Eur Neuropsychopharmacol*. 1996; 6:311–316. [PubMed: 8985715]
- Fritts ME, Asbury ET, Horton JE, Isaac WL. Medial prefrontal lesion deficits involving or sparing the prelimbic area in the rat. *Physiol Behav*. 1998; 64:373–380. [PubMed: 9748107]
- Furr A, Lapiz-Bluhm MD, Morilak DA. 5-HT_{2A} receptors in the orbitofrontal cortex facilitate reversal learning and contribute to the beneficial cognitive effects of chronic citalopram treatment in rats. *Int J Neuropsychopharmacol*. 2011:1–11. [PubMed: 22008191]
- Gamo NJ, Arnsten AF. Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. *Behav Neurosci*. 2011; 125:282–296. [PubMed: 21480691]
- Gisquet-Verrier P, Delatour B. The role of the rat prelimbic/infralimbic cortex in working memory: not involved in the short-term maintenance but in monitoring and processing functions. *Neuroscience*. 2006; 141:585–596. [PubMed: 16713111]
- Goswami S, Cascardi M, Rodriguez-Sierra OE, Duvarci S, Pare D. Impact of predatory threat on fear extinction in Lewis rats. *Learn Mem*. 2010; 17:494–501. [PubMed: 20929713]
- Gourley SL, Kedves AT, Olausson P, Taylor JR. A history of corticosterone exposure regulates fear extinction and cortical NR2B, GluR2/3, and BDNF. *Neuropsychopharmacology*. 2009; 34:707–716. [PubMed: 18719621]
- Graybeal C, Feyder M, Schulman E, Saksida LM, Bussey TJ, Brigman JL, Holmes A. Paradoxical reversal learning enhancement by stress or prefrontal cortical damage: rescue with BDNF. *Nat Neurosci*. 2011; 14:1507–1509. [PubMed: 22057192]

- Green MK, Rani CS, Joshi A, Soto-Pina AE, Martinez PA, Frazer A, Strong R, Morilak DA. Prenatal stress induces long term stress vulnerability, compromising stress response systems in the brain and impairing extinction of conditioned fear after adult stress. *Neuroscience*. 2011; 192:438–451. [PubMed: 21723377]
- Hains AB, Vu MA, Maciejewski PK, van Dyck CH, Gottron M, Arnsten AF. Inhibition of protein kinase C signaling protects prefrontal cortex dendritic spines and cognition from the effects of chronic stress. *Proc Natl Acad Sci U S A*. 2009; 106:17957–17962. [PubMed: 19805148]
- Higgins GA, Ballard TM, Enderlin M, Haman M, Kemp JA. Evidence for improved performance in cognitive tasks following selective NR2B NMDA receptor antagonist pre-treatment in the rat. *Psychopharmacology (Berl)*. 2005; 179:85–98. [PubMed: 15759152]
- Higgins GA, Ballard TM, Huwyler J, Kemp JA, Gill R. Evaluation of the NR2B-selective NMDA receptor antagonist Ro 63–1908 on rodent behaviour: evidence for an involvement of NR2B NMDA receptors in response inhibition. *Neuropharmacology*. 2003; 44:324–341. [PubMed: 12604092]
- Hill MN, Patel S, Carrier EJ, Rademacher DJ, Ormerod BK, Hillard CJ, Gorzalka BB. Downregulation of Endocannabinoid Signaling in the Hippocampus Following Chronic Unpredictable Stress. *Neuropsychopharmacology*. 2004; 30:508–515. [PubMed: 15525997]
- Holmes A, Wellman CL. Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neurosci Biobehav Rev*. 2009; 33:773–783. [PubMed: 19111570]
- Holt DJ, Lebron-Milad K, Milad MR, Rauch SL, Pitman RK, Orr SP, Cassidy BS, Walsh JP, Goff DC. Extinction Memory Is Impaired in Schizophrenia. *Biol Psychiatry*. 2008
- Izquierdo A, Wellman CL, Holmes A. Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. *J Neurosci*. 2006; 26:5733–5738. [PubMed: 16723530]
- Jentsch JD, Tran A, Le D, Youngren KD, Roth RH. Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. *Neuropsychopharmacology*. 1997; 17:92–99. [PubMed: 9252984]
- Joels M, Karst H, Krugers HJ, Lucassen PJ. Chronic stress: implications for neuronal morphology, function and neurogenesis. *Front Neuroendocrinol*. 2007; 28:72–96. [PubMed: 17544065]
- Joels M, Pu Z, Wiegert O, Oitzl MS, Krugers HJ. Learning under stress: how does it work? *Trends Cogn Sci*. 2006; 10:152–158. [PubMed: 16513410]
- Judo C, Matsumoto M, Yamazaki D, Hiraide S, Yanagawa Y, Kimura S, Shimamura K, Togashi H. Early stress exposure impairs synaptic potentiation in the rat medial prefrontal cortex underlying contextual fear extinction. *Neuroscience*. 2010; 169:1705–1714. [PubMed: 20600655]
- Kiselycznyk CL, Svenningsson P, Delpire E, Holmes A. Genetic, pharmacological and lesion analyses reveal a selective role for corticohippocampal GLUN2B in a novel repeated swim stress paradigm. *Neuroscience*. 2011
- Ko T, Evenden J. The effects of psychotomimetic and putative cognitive-enhancing drugs on the performance of a n-back working memory task in rats. *Psychopharmacology (Berl)*. 2009; 202:67–78. [PubMed: 18825373]
- Kos T, Nikiforuk A, Rafa D, Popik P. The effects of NMDA receptor antagonists on attentional set-shifting task performance in mice. *Psychopharmacology (Berl)*. 2011; 214:911–921. [PubMed: 21161188]
- Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS. Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. *Biol Psychiatry*. 2000; 47:137–143. [PubMed: 10664830]
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994; 51:199–214. [PubMed: 8122957]
- Lapiz-Bluhm MD, Soto-Pina AE, Hensler JG, Morilak DA. Chronic intermittent cold stress and serotonin depletion induce deficits of reversal learning in an attentional set-shifting test in rats. *Psychopharmacology (Berl)*. 2009; 202:329–341. [PubMed: 18587666]

- Lee SY, Kang JS, Song GY, Myung CS. Stress induces the expression of heterotrimeric G protein beta subunits and the phosphorylation of PKB/Akt and ERK1/2 in rat brain. *Neurosci Res.* 2006; 56:180–192. [PubMed: 16949170]
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science.* 2010; 329:959–964. [PubMed: 20724638]
- Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS. Glutamate N-methyl-D-aspartate Receptor Antagonists Rapidly Reverse Behavioral and Synaptic Deficits Caused by Chronic Stress Exposure. *Biol Psychiatry.* 2011
- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci.* 2006; 26:7870–7874. [PubMed: 16870732]
- Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* 2009; 10:434–445. [PubMed: 19401723]
- Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, Manji HK. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry.* 2008; 63:349–352. [PubMed: 17643398]
- Magarinos AM, McEwen BS. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience.* 1995; 69:89–98. [PubMed: 8637636]
- Maier SF, Watkins LR. Role of the medial prefrontal cortex in coping and resilience. *Brain Res.* 2010; 1355:52–60. [PubMed: 20727864]
- Martin KP, Wellman CL. NMDA Receptor Blockade Alters Stress-Induced Dendritic Remodeling in Medial Prefrontal Cortex. *Cereb Cortex.* 2011
- Matsuda S, Matsuzawa D, Nakazawa K, Sutoh C, Ohtsuka H, Ishii D, Tomizawa H, Iyo M, Shimizu E. d-serine enhances extinction of auditory cued fear conditioning via ERK1/2 phosphorylation in mice. *Prog Neuropsychopharmacol Biol Psychiatry.* 34:895–902. [PubMed: 20416352]
- Matsumoto M, Togashi H, Konno K, Koseki H, Hirata R, Izumi T, Yamaguchi T, Yoshioka M. Early postnatal stress alters the extinction of context-dependent conditioned fear in adult rats. *Pharmacol Biochem Behav.* 2008; 89:247–252. [PubMed: 18262260]
- McLean A, Dowson J, Toone B, Young S, Bazanis E, Robbins TW, Sahakian BJ. Characteristic neurocognitive profile associated with adult attention-deficit/hyperactivity disorder. *Psychol Med.* 2004; 34:681–692. [PubMed: 15099422]
- Mehta M, Schmauss C. Strain-specific cognitive deficits in adult mice exposed to early life stress. *Behav Neurosci.* 2011; 125:29–36. [PubMed: 21319884]
- Mineur YS, Belzung C, Crusio WE. Functional implications of decreases in neurogenesis following chronic mild stress in mice. *Neuroscience.* 2007; 150:251–259. [PubMed: 17981399]
- Miracle AD, Brace MF, Huyck KD, Singler SA, Wellman CL. Chronic stress impairs recall of extinction of conditioned fear. *Neurobiol Learn Mem.* 2006; 85:213–218. [PubMed: 16337411]
- Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T. Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. *J Neurosci.* 2000; 20:1568–1574. [PubMed: 10662846]
- Morrow BA, Roth RH, Elsworth JD. TMT, a predator odor, elevates mesoprefrontal dopamine metabolic activity and disrupts short-term working memory in the rat. *Brain Res Bull.* 2000; 52:519–523. [PubMed: 10974491]
- Mozhuy K, Karlsson RM, Kash TL, Ihne J, Norcross M, Patel S, Farrell MR, Hill EE, Graybeal C, Martin KP, Camp M, Fitzgerald PJ, Ciobanu DC, Sprengel R, Mishina M, Wellman CL, Winder DG, Williams RW, Holmes A. Strain differences in stress responsivity are associated with divergent amygdala gene expression and glutamate-mediated neuronal excitability. *J Neurosci.* 2010; 30:5357–5367. [PubMed: 20392957]

- Murphy ER, Fernando AB, Urcelay GP, Robinson ES, Mar AC, Theobald DE, Dalley JW, Robbins TW. Impulsive behaviour induced by both NMDA receptor antagonism and GABA(A) receptor activation in rat ventromedial prefrontal cortex. *Psychopharmacology (Berl)*. 2011
- Murphy FC, Michael A, Robbins TW, Sahakian BJ. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychol Med*. 2003; 33:455–467. [PubMed: 12701666]
- Nakazawa T, Komai S, Watabe AM, Kiyama Y, Fukaya M, Arima-Yoshida F, Horai R, Sudo K, Ebine K, Delawary M, Goto J, Umemori H, Tezuka T, Iwakura Y, Watanabe M, Yamamoto T, Manabe T. NR2B tyrosine phosphorylation modulates fear learning as well as amygdaloid synaptic plasticity. *EMBO J*. 2006; 25:2867–2877. [PubMed: 16710293]
- Neill JC, Barnes S, Cook S, Grayson B, Idris NF, McLean SL, Snigdha S, Rajagopal L, Harte MK. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. *Pharmacol Ther*. 2010; 128:419–432. [PubMed: 20705091]
- Neyton J, Paoletti P. Relating NMDA receptor function to receptor subunit composition: limitations of the pharmacological approach. *J Neurosci*. 2006; 26:1331–1333. [PubMed: 16452656]
- Nikiforuk A. Selective blockade of 5-HT7 receptors facilitates attentional set-shifting in stressed and control rats. *Behav Brain Res*. 2012; 226:118–123. [PubMed: 21925545]
- Nikiforuk A, Golembiowska K, Popik P. Mazindol attenuates ketamine-induced cognitive deficit in the attentional set shifting task in rats. *Eur Neuropsychopharmacol*. 2010; 20:37–48. [PubMed: 19729284]
- Nikiforuk A, Popik P. Long-lasting cognitive deficit induced by stress is alleviated by acute administration of antidepressants. *Psychoneuroendocrinology*. 2011; 36:28–39. [PubMed: 20580164]
- Ohmura Y, Yamaguchi T, Futami Y, Togashi H, Izumi T, Matsumoto M, Yoshida T, Yoshioka M. Corticotropin releasing factor enhances attentional function as assessed by the five-choice serial reaction time task in rats. *Behav Brain Res*. 2009; 198:429–433. [PubMed: 19084036]
- Park CR, Zoladz PR, Conrad CD, Fleshner M, Diamond DM. Acute predator stress impairs the consolidation and retrieval of hippocampus-dependent memory in male and female rats. *Learn Mem*. 2008; 15:271–280. [PubMed: 18391188]
- Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol*. 2008; 28:631–637. [PubMed: 19011431]
- Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology*. 2008; 33:56–72. [PubMed: 17882236]
- Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci*. 2007; 362:917–932. [PubMed: 17412678]
- Rodrigues SM, Schafe GE, LeDoux JE. Intra-amygdala blockade of the NR2B subunit of the NMDA receptor disrupts the acquisition but not the expression of fear conditioning. *J Neurosci*. 2001; 21:6889–6896. [PubMed: 11517276]
- Roosendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci*. 2009; 10:423–433. [PubMed: 19469026]
- Rosenmund C, Stern-Bach Y, Stevens CF. The tetrameric structure of a glutamate receptor channel. *Science*. 1998; 280:1596–1599. [PubMed: 9616121]
- Sandstrom NJ. Sex differences in the long-term effect of preweanling isolation stress on memory retention. *Horm Behav*. 2005; 47:556–562. [PubMed: 15811357]
- Sandstrom NJ, Hart SR. Isolation stress during the third postnatal week alters radial arm maze performance and corticosterone levels in adulthood. *Behav Brain Res*. 2005; 156:289–296. [PubMed: 15582115]
- Santini E, Muller RU, Quirk GJ. Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. *J Neurosci*. 2001; 21:9009–9017. [PubMed: 11698611]
- Schwabe K, Enkel T, Klein S, Schutte M, Koch M. Effects of neonatal lesions of the medial prefrontal cortex on adult rat behaviour. *Behav Brain Res*. 2004; 153:21–34. [PubMed: 15219703]

- Schwabe L, Wolf OT. Stress prompts habit behavior in humans. *J Neurosci*. 2009; 29:7191–7198. [PubMed: 19494141]
- Schwabe L, Wolf OT. Stress-induced modulation of instrumental behavior: From goal-directed to habitual control of action. *Behav Brain Res*. 2011
- Shansky RM, Morrison JH. Stress-induced dendritic remodeling in the medial prefrontal cortex: effects of circuit, hormones and rest. *Brain Res*. 2009; 1293:108–113. [PubMed: 19361488]
- Sinha R. Chronic stress, drug use, and vulnerability to addiction. *Ann N Y Acad Sci*. 2008; 1141:105–130. [PubMed: 18991954]
- Sloan HL, Good M, Dunnett SB. Double dissociation between hippocampal and prefrontal lesions on an operant delayed matching task and a water maze reference memory task. *Behav Brain Res*. 2006; 171:116–126. [PubMed: 16677723]
- Smith JW, Gastambide F, Gilmour G, Dix S, Foss J, Lloyd K, Malik N, Tricklebank M. A comparison of the effects of ketamine and phencyclidine with other antagonists of the NMDA receptor in rodent assays of attention and working memory. *Psychopharmacology (Berl)*. 2011; 217:255–269. [PubMed: 21484239]
- Snyder K, Wang WW, Han R, McFadden K, Valentino RJ. Corticotropin-Releasing Factor in the Norepinephrine Nucleus, Locus Coeruleus, Facilitates Behavioral Flexibility. *Neuropsychopharmacology*. 2011
- Sotres-Bayon F, Bush DE, LeDoux JE. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. *Neuropsychopharmacology*. 2007; 32:1929–1940. [PubMed: 17213844]
- Sotres-Bayon F, Diaz-Mataix L, Bush DE, LeDoux JE. Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: NR2B contribution. *Cereb Cortex*. 2009; 19:474–482. [PubMed: 18562331]
- Stevenson CW, Meredith JP, Spicer CH, Mason R, Marsden CA. Early life programming of innate fear and fear learning in adult female rats. *Behav Brain Res*. 2009a; 198:51–57. [PubMed: 18996416]
- Stevenson CW, Spicer CH, Mason R, Marsden CA. Early life programming of fear conditioning and extinction in adult male rats. *Behav Brain Res*. 2009b; 205:505–510. [PubMed: 19682501]
- Tagliari B, Scherer EB, Machado FR, Ferreira AG, Dalmaz C, Wyse AT. Antioxidants prevent memory deficits provoked by chronic variable stress in rats. *Neurochem Res*. 2011; 36:2373–2380. [PubMed: 21822921]
- Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ. Genetic enhancement of learning and memory in mice. *Nature*. 1999; 401:63–69. [PubMed: 10485705]
- Thomson DM, McVie A, Morris BJ, Pratt JA. Dissociation of acute and chronic intermittent phencyclidine-induced performance deficits in the 5-choice serial reaction time task: influence of clozapine. *Psychopharmacology (Berl)*. 2011; 213:681–695. [PubMed: 20878519]
- Trofimiuk E, Braszko JJ. Alleviation by *Hypericum perforatum* of the stress-induced impairment of spatial working memory in rats. *Naunyn Schmiedeberg's Arch Pharmacol*. 2008; 376:463–471. [PubMed: 18094960]
- van der Meulen JA, Bilbija L, Joosten RN, de Bruin JP, Feenstra MG. The NMDA-receptor antagonist MK-801 selectively disrupts reversal learning in rats. *Neuroreport*. 2003; 14:2225–2228. [PubMed: 14625452]
- von Engelhardt J, Doganci B, Jensen V, Hvalby O, Gongrich C, Taylor A, Barkus C, Sanderson DJ, Rawlins JN, Seeburg PH, Bannerman DM, Monyer H. Contribution of hippocampal and extra-hippocampal NR2B-containing NMDA receptors to performance on spatial learning tasks. *Neuron*. 2008; 60:846–860. [PubMed: 19081379]
- Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J Neurosci*. 2002; 22:2343–2351. [PubMed: 11896173]
- Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr Res*. 2007; 93:296–303. [PubMed: 17482797]
- Wang L, Jiao J, Dulawa SC. Infant maternal separation impairs adult cognitive performance in BALB/cJ mice. *Psychopharmacology (Berl)*. 2011

- Watanabe Y, Gould E, Cameron HA, Daniels DC, McEwen BS. Phenytoin prevents stress- and corticosterone-induced atrophy of CA3 pyramidal neurons. *Hippocampus*. 1992; 2:431–435. [PubMed: 1308199]
- Watson DJ, Stanton ME. Intrahippocampal administration of an NMDA-receptor antagonist impairs spatial discrimination reversal learning in weanling rats. *Neurobiol Learn Mem*. 2009a; 92:89–98. [PubMed: 19248837]
- Watson DJ, Stanton ME. Medial prefrontal administration of MK-801 impairs T-maze discrimination reversal learning in weanling rats. *Behav Brain Res*. 2009b; 205:57–66. [PubMed: 19643149]
- Watson DJ, Stanton ME. Spatial discrimination reversal learning in weanling rats is impaired by striatal administration of an NMDA-receptor antagonist. *Learn Mem*. 2009c; 16:564–572. [PubMed: 19713355]
- Wilber AA, Southwood CJ, Wellman CL. Brief neonatal maternal separation alters extinction of conditioned fear and corticolimbic glucocorticoid and NMDA receptor expression in adult rats. *Dev Neurobiol*. 2009; 69:73–87. [PubMed: 19025931]
- Wilber AA, Walker AG, Southwood CJ, Farrell MR, Lin GL, Rebec GV, Wellman CL. Chronic stress alters neural activity in medial prefrontal cortex during retrieval of extinction. *Neuroscience*. 2011; 174:115–131. [PubMed: 21044660]
- Willmore CB, Krall DM, Spears FM, Makriyannis A, Elmer GI. Cognitive effects of psychotomimetic drugs in rats discriminating number cues. *Psychopharmacology (Berl)*. 2009; 206:653–664. [PubMed: 18843483]
- Woodson JC, Macintosh D, Fleshner M, Diamond DM. Emotion-induced amnesia in rats: working memory-specific impairment, corticosterone-memory correlation, and fear versus arousal effects on memory. *Learn Mem*. 2003; 10:326–336. [PubMed: 14557605]
- Yamada D, Wada K, Sekiguchi M. Facilitating actions of an AMPA receptor potentiator upon extinction of contextually conditioned fear response in stressed mice. *Neurosci Lett*. 2011; 488:242–246. [PubMed: 21094221]
- Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, Yan Z. Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc Natl Acad Sci U S A*. 2009; 106:14075–14079. [PubMed: 19666502]
- Yuen EY, Liu W, Karatsoreos IN, Ren Y, Feng J, McEwen BS, Yan Z. Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. *Mol Psychiatry*. 2011; 16:156–170. [PubMed: 20458323]
- Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; 63:856–864. [PubMed: 16894061]
- Zhao MG, Toyoda H, Lee YS, Wu LJ, Ko SW, Zhang XH, Jia Y, Shum F, Xu H, Li BM, Kaang BK, Zhuo M. Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory. *Neuron*. 2005; 47:859–872. [PubMed: 16157280]

Table 1

Studies of stress effects of stress on measures of cognitive and executive functions

Species	Assay	Stressor	Effect	Reference
Rat	Attentional set-shifting task	2wk unpredictable stress	Impaired reversal, extra-dimensional shifts	(Bondi et al., 2008, 2010)
Rat	Attentional set-shifting task	2wk, 5wk intermittent cold	Impaired reversal	(Danet et al., 2010)
Rat	Attentional set-shifting task	5wk intermittent cold	Impaired reversal	(Furr et al., 2011)
Rat	Attentional set-shifting task	2wk intermittent cold	Impaired reversal	(Lapiz-Bluhm et al., 2009)
Rat	Attentional set-shifting task	3wk restraint stress	Impaired extra-dimensional shifts	(Liston et al., 2006)
Mouse	Attentional set-shifting task	2wk neonatal maternal separation	Impaired extra-dimensional shifts	(Mehta and Schmauss, 2011)
Rat	Attentional set-shifting task	1wk restraint stress	Impaired extra-dimensional shifts	(Nikiforuk and Popik, 2011, 2012)
Rat	Attentional set-shifting task	Acute intracerebroventricular corticotrophin-releasing factor	Impaired reversal, intra-dimensional shifts, extra-dimensional shifts	(Snyder et al., 2011)
Mouse	T-maze (spatial)	2wk neonatal maternal separation	Impaired reversal	(Wang et al., 2011)
Rat	Morris water maze	4wk dexamethasone injections 6d or 4wk unpredictable stress	Impaired reversal, working memory	(Cerqueira et al., 2005, 2007)
Mouse	Morris water maze	Acute footshock stress	Impaired reversal	(Francis et al., 1995)
Rat	Morris water maze	3wk unpredictable stress	Impaired reversal	(Hill et al., 2004)
Rat	Morris water maze	40d unpredictable stress	Impaired working memory	(Tagliari et al., 2011)
Rat	Morris water maze Barnes radial maze	3wk restraint stress or 3wk corticosterone injection	Impaired working memory	(Trofimiuk and Braszko, 2008)
Rat	Radial arm maze	Acute (2hr) restraint stress	Facilitated working memory	(Barha et al., 2007)
Rat	Radial arm maze	2wk neonatal maternal separation	Impaired working memory	(Brenhouse and Andersen, 2011)
Rat	Radial arm maze	Acute (15 min) tail-pinch stress	Impaired working memory	(Butts et al., 2011)
Rat	Radial arm maze	Daily predatory stress (prior to each WM test)	Impaired working memory	(Diamond et al., 1999)
Mice	Radial arm maze	6wk unpredictable stress	Impaired working memory	(Mineur et al., 2007)
Rat	Radial arm maze	1wk postnatal social isolation	Impaired working memory	(Sandstrom, 2005, Sandstrom and Hart, 2005)
Rat	Radial arm maze	Acute (30 min) predatory stress	Impaired working memory	(Woodson et al., 2003)
Rat	Delayed alternation T-maze	Acute (1 d) neonatal maternal separation and 2wk corticosterone pellet implants	No effect on working memory	(Choy et al., 2008)
Rat	Delayed alternation T-maze	Acute (10 min in open field) stress	Impaired working memory	(Del Arco et al., 2007, 2011)
Rat	Delayed alternation T-maze	3wk restraint stress	Impaired working memory	(Hains et al., 2009)
Mouse	Delayed alternation T-maze	4wk cold water immersion	Impaired working memory	(Mizoguchi et al., 2000)
Mouse	Delayed alternation T-maze	2wk neonatal maternal separation	Impaired working memory	(Mehta and Schmauss, 2011)
Rat	Delayed alternation T-maze	Acute (15 min) predator odor	Impaired working memory	(Morrow et al., 2000)

Species	Assay	Stressor	Effect	Reference
Rat	Delayed alternation T-maze	Acute (20 min) forced swim stress	Facilitated working memory	(Yuen et al., 2009, 2011)
Rat	5-choice serial reaction time task	Acute intracerebroventricular infusion of corticotrophin-releasing factor	Increased accuracy	(Ohmura et al., 2009)
Rat	Fear conditioning and extinction	3wk restraint stress	Males: impaired extinction Females: enhanced extinction	(Baran et al., 2009)
Rat	Fear conditioning and extinction	7d escapable stress	Reduced fear conditioning, facilitated fear extinction	(Baratta et al., 2007, Baratta et al., 2008)
Mouse	Fear conditioning and extinction	Acute corticosterone injections post extinction	Impaired extinction	(Blundell et al., 2011)
Mouse	Fear conditioning and extinction	Acute corticosterone injection pre or post acquisition	Pre: impaired fear extinction (C57BL/6J) Post: facilitated fear extinction (BALB/c)	(Brinks et al., 2009)
Rat	Fear conditioning and extinction	2wk neonatal maternal separation	Enhanced fear relapse	(Callaghan and Richardson, 2011)
Rat	Fear conditioning and extinction	1wk restraint stress	Impaired fear extinction	(Farrell et al., 2010)
Rat	Fear conditioning and extinction	2wk oral corticosterone	Impaired fear extinction	(Gourley et al., 2009)
Rat	Fear conditioning and extinction	Prenatal stress and chronic stress	Impaired fear extinction	(Green et al., 2011)
Rat	Fear conditioning and extinction	Acute predatory stress pre/post extinction	Impaired fear extinction	(Goswami et al., 2010)
Mouse	Fear conditioning and extinction	3d forced swim stress	Impaired fear extinction	(Izquierdo et al., 2006)
Rat	Fear conditioning and extinction	5d postnatal footshock stress	Impaired fear extinction	(Judo et al., 2010)
Rat	Fear conditioning and extinction	5d postnatal footshock stress	Impaired fear extinction	(Matsumoto et al., 2008)
Rat	Fear conditioning and extinction	1wk restraint stress	Impaired fear extinction	(Miracle et al., 2006)
Rat	Fear conditioning and extinction	2wk neonatal maternal separation	Impaired fear extinction	(Stevenson et al., 2009a, 2009b)
Rat	Fear conditioning and extinction	1wk restraint stress 2 wk neonatal maternal separation	Impaired fear extinction	(Wilber et al., 2009, 2011)
Mouse	Fear conditioning and extinction	One day (restraint, forced swim, ether inhale)	Impaired fear extinction	(Yamada et al., 2011)