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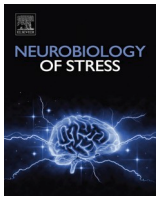

Effects of chronic stress on cognitive function – From neurobiology to intervention

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ABSTRACT

Exposure to chronic stress contributes considerably to the development of cognitive impairments in psychiatric disorders such as depression, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and addictive behavior. Unfortunately, unlike mood-related symptoms, cognitive impairments are not effectively treated by available therapies, a situation in part resulting from a still incomplete knowledge of the neurobiological substrates that underly cognitive domains and the difficulty in generating interventions that are both efficacious and safe.

In this review, we will present an overview of the cognitive domains affected by stress with a specific focus on cognitive flexibility, behavioral inhibition, and working memory. We will then consider the effects of stress on neuronal correlates of cognitive function and the factors which may modulate the interaction of stress and cognition. Finally, we will discuss intervention strategies for treatment of stress-related disorders and gaps in knowledge with emerging new treatments under development.

Understanding how cognitive impairment occurs during exposure to chronic stress is crucial to make progress towards the development of new and effective therapeutic approaches.

1. Introduction

Stress is a prominent part of modern life. Humans, like other species, have evolved adaptive mechanisms to limit the physiological or psychological impact of stress. However, exposure to traumatic or cumulative stressors can considerably contribute to the development of psychiatric disorders such as, depression, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and addictive behavior (Adams et al., 2018; Maeng and Milad 2017; Patriquin and Mathew 2017; Siegrist 2008; Sinha 2008). Indeed, a recent article reported that cases of depression alone were 3-fold higher during the COVID-19 pandemic compared to pre-pandemic data (Ettman et al., 2020).

Cognitive impairment is a transdiagnostic domain shared by multiple psychiatric disorders, including stress-related disorders (Millan et al., 2012); for example, abnormalities in various cognitive functions such as cognitive flexibility, working memory and behavioral inhibition have been documented in depression, PTSD and substance use disorder (Dossi et al., 2020; Ramey and Regier 2019; Snyder 2013), and a large body of evidence suggests that stress exacerbates cognitive impairments (Lupien et al., 2009). Unfortunately, unlike mood-related symptoms, cognitive impairments are not effectively treated by currently available therapies, and large gaps still exist in both identifying the neurobiological substrates that underly cognitive domains and in developing effective interventions.

In this review, we will present an overview of the cognitive domains affected by stress with a specific focus on cognitive flexibility, behavioral inhibition, and working memory. We will then specify how these cognitive domains are affected by acute and chronic stress (see Table 1 for a summary of relevant literature). Sex differences will be discussed if reported in the original paper, however, for an in-depth analysis of the interaction of sex and stress on cognitive function we refer the reader to recent focused reviews (Bangasser and Kawasumi 2015; Orsini et al., 2022; Swaab and Bao 2020; Wellman et al., 2020). Finally, we will discuss intervention strategies for treatment of stress-related disorders and gaps in knowledge with emerging new treatments under development.

Overall, it is vital to understand the relationship between the effects of stress on the brain and how cognitive impairment occurs during exposure to chronic stress. Through better understanding of mechanisms underlying the relationship between stress and cognition, new avenues

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List of abbreviations

HPA axis	hypothalamic-pituitary-adrenal axis
GCs	Glucocorticoids
CORT	corticosterone, cortisol
CRH/CRF	corticotropin-releasing hormone/factor
ACTH	adrenocorticotropic hormone
GR	glucocorticoid receptor
MR	mineralocorticoid receptor
E	epinephrine
NE	norepinephrine
CNTF	ciliary neurotrophic factor
JAK	Janus kinase
SSRIs	elective serotonin reuptake inhibitors
PCP	phencyclidine
MDMA	3,4-methylenedioxymethamphetamine
ACC	anterior cingulate cortex
PVN	paraventricular nucleus of the hypothalamus
LC	locus coeruleus
RVLM	rostral ventrolateral medulla
NTS	nucleus of the solitary tract
IML	dorsal intermediolateral cellular column
mPFC	medial prefrontal cortex
DLPFC	dorsolateral prefrontal cortex
OFC	orbitofrontal cortex
NAC	nucleus accumbens
BLA	basolateral amygdala
PH	posterior hypothalamus
STN	subthalamic nucleus
MDT	mediodorsal thalamus
CIC stress	chronic intermittent cold stress
CMS	chronic mild stress
CUS	chronic unpredictable stress
PTSD	post-traumatic stress disorder
AST	attentional set-shifting test
ED	extra-dimensional
SSRTT	stop signal reaction time test
5-CSRTT	5-choice serial reaction time test
CANTAB	Cambridge Neuropsychological Test Automated Battery
WCST	Wisconsin Card test
CBT	Cognitive Behavior Therapy
TMS	Transcranial Magnetic Stimulation
rTMS	repetitive TMS
tDCS	Transcranial Direct Current Stimulation
TRD	Treatment Resistant Depression
DREADD	designer receptor exclusively activated by designer drugs
SERT	serotonin transporter
LTP	long-term potentiation
LTD	long-term depression
NF1	neurofibromatosis 1
OCD	obsessive-compulsive disorder
PTSD	post-traumatic stress disorder
GAD	generalized anxiety disorder

may appear towards the development of new therapeutic approaches.

2. A brief overview of stress neurobiology

The neuroendocrine stress response is a remarkably well-conserved homeostatic process from amphibians to mammals, a fact that underscores its essential role in species survival and adaptation (Sapolsky 2021). Indeed, the response to stress is fundamentally an adaptive phenomenon directed toward the reallocation of physiological resources in response to an external or internal stimulus that has threatened homeostasis. This process of active adaptation through mobilization of neuroendocrine and immune mechanisms has been called allostasis (Sterling and Eyer, 1988. Allostatic load refers to the cost of this rebalancing process for the organism. In situations of acute or sporadic stress exposure, the cost is low and transient. However, in situations where either the stressor is persistent or the organism is debilitated, the prolonged engagement or overstimulation of allostatic systems causes a physiological burden that may lead to disease (McEwen 1998).

As an example, in socially complex species such as humans and non-human primates, the stress response can be activated and sustained in the absence of an "actual" contingent stressor, in part as a reaction to negative past experiences or in anticipation of negative future events. Such chronic engagement of the stress response system has been associated with an array of health disturbances, including cardiovascular, immunological, and reproductive dysfunction and increased incidence of stress-related psychiatric disorders (Sapolsky 2021). Thus, the current view is that stress-related pathologies develop from the unnecessary, excessive, or over-lasting activation of the stress response system that takes a toll on organism physiology. Fortunately, given the conservation of the stress response across species, it is possible to investigate the mechanisms of adaptive and maladaptive stress response, including effects on cognitive function, in animal models designed for high translational validity.

2.1. Physiological response to stress

For reasons of space, we will only briefly introduce the basic concepts of autonomic and neuroendocrine responses to stress. We refer the interested reader to comprehensive reviews on the subject (Carrier et al., 2021; Godoy et al., 2018; Gray et al., 2017; Hassamal 2023; McEwen and Akil 2020).

Acute stress can be defined as a real or perceived temporary challenge to the organism ability to maintain homeostasis and can be either physiological or psychological in nature. The organism responds to acute stress by rapidly mobilizing the autonomic and neuroendocrine systems, producing physiological changes that facilitate the response to the threat and the return to homeostasis. Autonomic system activation releases epinephrine (E, secreted by the adrenal medulla) and norepinephrine (NE, from the adrenal medulla and sympathetic nerves) that act on peripheral adrenergic receptors. Additionally, catecholamines are released within the brain where they activate central nervous system receptors. Acute catecholamine effects are short-lived, disappearing within 1 h (Tank and Lee Wong 2015), and include cardiovascular actions, metabolic resource allocation and sustained alertness.

The neuroendocrine response is under the control of the hypothalamic-pituitary-adrenal axis (HPA axis). Within this system, glucocorticoids (cortisol in humans and corticosterone in rodents, CORT) are released by the adrenal cortex in response to circulating adrenocorticotropic hormone (ACTH), released by the anterior pituitary. Release of ACTH is in turn elicited by corticotropin-releasing hormone (CRH or CRF) produced by parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN). In contrast to catecholamine-driven responses, glucocorticoid effects can be both rapid (within minutes after the stimulus) and long-lasting. The long-term effects develop over several hours and include transcriptional effects of activated glucocorticoid receptors (GRs) and epigenetic effects, such as methylation changes in target genes (Gray et al., 2017; Thomassin et al., 2001). Glucocorticoids can also bind to and exert activities through the mineralocorticoid receptors (MRs) (de Kloet 2013).

Table 1
List of studies describing effects of stress on cognitive domains examined in this review.

Rodent studies

Cognitive domain	Stress type	Stress paradigm	Sex/species	Stress effect	Sex difference	References
Reversal learning	Acute	30 min restraint	Male rats	Facilitation		Bryce and Howland, 2015
	Acute	10 min swim, 3d	Male mice	Facilitation		Graybeal et al., 2011
	Acute	30 min restraint	Male rats	Facilitation		Thai et al., 2013
	Early life	Fragmented maternal care	Male and female rats	No effect in males, deficit in females	Y	Goodwill et al., 2018
	Chronic	6h/14d cold stress	Male rats	Deficit		Danet et al., 2010, Donegan et al., 2014, Furr et al., 2012, Lapiz-Bluhm et al., 2009, Patton et al., 2017, Wallace et al., 2014
	Chronic	14-21d unpredictable mild stress	Male rats	Deficit		Bondi et al., 2007, Bondi et al., 2010, Jett et al., 2013, Jett et al., 2015, Hill et al., 2005 Quan et al., 2011, Yu et al., 2016
Set-shifting	Acute	15 min tail pinch	Male rats	Deficit		Butts et al., 2013
	Acute	30 min restraint	Male rats	No effect		Thai et al., 2013
	Acute	Single prolonged stress	Male rats	Deficit		George et al., 2015
	Chronic	6h/14d cold stress	Male rats	No effect		Lapiz-Bluhm et al., 2009
	Chronic	21d repeated restraint	Male rats	Deficit		Liston et al., 2006
	Chronic	14d unpredictable mild stress	Male rats	Deficit		Bondi et al., 2008, Fucich et al., 2016, Jett et al., 2013, Morilak et al., 2005,
Behavioral inhibition	Acute	Footshock on 2 consecutive days	Male rats	No effect on impulsive action		Girotti et al., 2022
	Early life	5d variable stress	Male and female rats	Increased cocaine-induced impulsive action in females	Y	Paine et al., 2021
	CORT exposure in early life	20 d corticosterone administration	Male rats	Reduced impulsive action but increased impulsive choice		Torregrossa et al., 2012
	Chronic	6h/14d cold stress	Male rats	Increase impulsive action in well trained task		Girotti et al., 2022
	Chronic	14d unpredictable mild stress	Male rats	Increase impulsive action in well trained and novel tasks		Girotti et al., 2022
Working memory	Acute	60 min restraint	Male and female rats	Deficit in females	Y	Shansky et al., 2006
	Acute	20 min swim stress	Male rats	Enhancement		Yuen et al., 2009, Yuen et al., 2011
	Acute	40 min intermittent footshock	Male rats	Enhancement soon after stress, deficit at later times		Musazzi et al., 2019
	Early life	Maternal separation	Male rats	Deficit in adults		Banqueri et al., 2021
	Early life	Maternal separation	Male rats	Deficit in adolescence		Brenhouse and Andersen, 2011
	Early life	Maternal separation	Male rats	Deficit in adults		Sanchez et al., 2021
	Early life	Maternal separation	Male mice	Deficit in adults		Viola et al., 2019
	Early life	Maternal separation	Male and female rats	No effect in males, slight deficit in females	Y	Sun et al., 2020
	Chronic	4 weeks unpredictable mild stress	Male rats	Deficit		Cerqueira et al., 2007a
	Chronic	21d repeated restraint	Male rats	Deficit		Wright and Conrad, 2008
	Chronic	28d repeated restraint	Male rats	Deficit		Mika et al., 2012
	Chronic	7d repeated restraint	Male and female rats	Deficits in males, no effect in females	Y	Wei et al., 2014

Human studies

Cognitive domain	Stress type	Stress paradigm	Sex examined	Stress effect	Sex difference	References
Reversal learning	Acute	TSST	Males	Facilitation		Wieland et al., 2023
	Acute	CPT	Males and females	Impairment	Not reported	Raio et al., 2017
	Early + Acute	Early life stress + TSST	Males and females	Increased perseveration	Not reported	Franco and Knowlton, 2023
	Early life	History of medical and mental problems	Males and females adolescents	Deficit	Not reported	Harms et al., 2018
	Chronic	Perceived chronic stress	Females	Deficit		Monni et al., 2023
Set-shifting	Acute	TSST	Males	No effect		Hendrawan et al., 2012
	Acute	"Virtual" TSST	Males and females	Improved flexibility	Not reported	Delahaye et al., 2015
	Acute	TSST	Males and females	Deficit in males, no effect in females	Y	Shields et al., 2016
	Acute	CPT	Males and females	Deficit in males, no effect in females	Y	Kalia et al., 2018
	Acute	TSST	Males and females	Deficit	Not reported	Alexander et al., 2007
	Acute	Noise stress	Males and females	Deficit	Not reported	Hillier et al., 2006
	Chronic	Perceived chronic stress	Males and females	Deficit	Not reported	Orem et al., 2008

(*continued on next page*)

Glucocorticoids participate in the termination of the stress response through a negative feedback process mediated by GRs that reduces the secretion of CRH in the PVN and ACTH in the pituitary to limit the effects of these hormones (Keller-Wood and Dallman 1984). Negative feedback mechanisms include transcriptional effects that are both ligand-dependent (Lachize et al., 2009; McKay and Cidlowski 1998) and ligand-independent (Rainville et al., 2019), as well as signaling effects via membrane-bound GRs (Di et al., 2003). Finally, the HPA axis has a prominent circadian and ultradian rhythms that play an important role in the organism's health (Lightman et al., 2020; Yao and Silver 2022).

With prolonged and/or intense stress exposure (chronic stress), the physiological burden to reinstate allostasis may produce detrimental consequences for the organism. Chronic secretion of glucocorticoids decreases GR expression in the brain which results in reduced negative feedback and dysregulation of the HPA axis (for review see (Herman et al., 2016; Tsigos et al., 2000)).

Because of lowered GR levels, CRH levels increase and the balance between MR and GR expression is changed; these alterations affect the function of other brain areas, notably the prefrontal cortex and hippocampus, and may underlie the emotional and cognitive impairments produced by chronic stress.

2.2. Impact of stress hormones on cognitive function

Indeed, persistent elevation of CORT or CRF has been associated with cognitive impairment especially in hippocampal dependent memory tasks (De Alcubierre et al., 2023; Henckens et al., 2016; Spannenburg and Reed 2023). For example, exposure to elevated glucocorticoids, in healthy humans produces reversible impairments in verbal declarative memory (Newcomer et al., 1999). In patients with Cushing Syndrome, a disorder characterized by hypercortisolemia, the most frequent cognitive symptoms reported are impaired memory (83%) and shortened attention span (66%) (Starkman 2013). Possible mechanisms leading to these impairments were suggested by early animal studies showing that chronic stress or chronic glucocorticoid exposure produced hippocampal and cortical atrophy, shorter dendritic branches and alterations in neurotransmitter levels (Cerqueira et al. 2005a, 2005b; Liston and Gan 2011; Magarinos et al., 1996; Radley et al., 2006; Wellman 2001). Measures of hippocampal volume in humans receiving high doses of glucocorticoids have yielded mixed results with some studies showing decreases in volume (Bermond et al., 2005; Brown et al., 2004; Wilner et al., 2002) and others finding no change (Coluccia et al., 2008; Hajek et al., 2006). In Cushing's patients smaller hippocampal and cortical volumes were found to correlate with longer disease duration (Bauduin et al., 2020; Bourdeau et al., 2002; Starkman et al., 1992). Low glucocorticoids levels also produce impaired cognition, especially in visual memory and attention, as it has been shown in individuals with adrenal insufficiency and with Addison's disease (Klement et al., 2009; Tiemensma et al., 2016). In rodents, adrenalectomy casues dendritic retraction in the mPFC (Cerqueira et al., 2007b). Thus, glucocorticoids effects on brain function follow an inverted-U relationship (Joels 2006), where both low and high levels of glucocorticoids produce deficits, brought about by imbalanced signaling through MR and GR. Indeed, several pharmacological studies with agonists and antagonists of GR and MR have revealed the importance of each receptor in cognitive function (Otte et al., 2007; Piber et al., 2016; Vogel et al., 2016; Wingenfeld and Otte 2019; Yalin et al., 2021; Young et al., 2004). For a recent review see (de Kloet and Joels 2023).

Elevated CRH following chronic stress also has negative effects on cognition that are mainly mediated by CRFR1 receptors (Henckens et al., 2016; Maras and Baram 2012; Uribe-Marino et al., 2016). Similar to glucocorticoids, elevated CRH produces cortical and hippocampal plasticity changes, spine actin depolarization, selective loss of spines, and detrimental effects on learning and memory (Chen et al., 2013; Wang et al., 2011).

2.3. Rodent models of chronic stress

Various rodent models of chronic stress have been developed and shown to produce behavioral and neuronal changes recapitulating elements of core symptoms of mood and anxiety disorders, or other stress-dependent psychophysiological disorders (for comprehensive reviews,

Table 1 (*continued*)

Human studies						
Cognitive domain	Stress type	Stress paradigm	Sex examined	Stress effect	Sex difference	References
	Early life + Chronic	Perceived chronic stress	Males and females	Deficit	Not reported	Kalia and Knauft, 2020
	Early life + Chronic	Perceived chronic stress	Males and females	Deficit	Not reported	Kalia et al., 2021
Behavioral inhibition	Acute	CPT	Males and females	Increase gambling as a function of trait impulsivity	Not reported	Canale et al., 2017
	Acute	CPT	Males and females	Increase decision speed	Not reported	Raio et al., 2020
	Acute	Anticipate a videotape speech	Males	Increase choice for later, larger rewards		Lempert et al., 2012
	Chronic	Lifetime stress exposure questionnaire	Males and females	Higher stress correlated with higher implsivity and food addiction	Not reported	McMullin et al., 2021
	Chronic	Lifetime stress exposure questionnaire	Males and females	Higher impulsivity and lifetime stress in metamphetamine users	Not reported	Mahoney et al., 2015
Working memory	Acute	TSST	Males	Deficit		Luethi et al., 2008
	Acute	TSST	Males	Deficit		Schoofs et al., 2008
	Acute	CPT	Males	Deficit		Schoofs et al., 2009
	Acute	Hydrocortisone administration	Males	Deficit		Lupien et al., 1999
	Acute	CPT	Males and females	No effect	Not reported	Porcelli et al., 2008
	Acute	TSST	Males	Slight improvement		Weerda et al., 2010
	Acute	TSST	Males and females	Enhanced working memory in males	Y	Cornelisse et al., 2011b
	Acute	Video of aversive images	Females	No effect		Qin et al., 2009
	Acute	TSST	Males and females	Enhanced working memory in males, impairment in females	Y	Scoriels et al., 2013

Abbreviations: CPT, cold pressor test; TSST, Trier Social Stress Test.

see (Buynitsky and Mostofsky 2009; Qiao et al., 2016). As prenatal and early life stress are addressed elsewhere in this issue, here we will focus on adult stress.

Adult life stress is a well-recognized risk factor for psychopathology, and several rodent models have been developed to study this. Here, we will focus on 3 types of adult chronic stress: repeated restraint, chronic intermittent cold stress and chronic unpredictable stress.

Repeated restraint stress has been used as a model of chronic stress since the early 1980s, initially to examine homotypic stress habituation of the adrenergic system, HPA axis, and c-Fos activation in the brain, phenomena that arise within 4–6 days of exposure (Cole et al., 2000; Girotti et al., 2006; Stone and Platt 1982; Watanabe et al., 1994). Studies investigating the duration of stress protocols as a variable revealed that distinct brain regions exhibit differential responses to varying lengths of stress exposure. Daily sessions of restraint stress as short as one week (Brown et al., 2005; Garrett and Wellman 2009) caused dendritic remodeling in the mPFC, whereas a longer duration of the same stress procedure was necessary to observe morphological changes in the hippocampus. For example, Qiao et al., (2014) demonstrated a reduction in apical spine density in hippocampal CA1 and CA3 only when employing daily restraint stress for at least 3 weeks. Similarly, Watanabe and collegues (1992) reported apical dendritic retraction in CA3 after 3 weeks, the only time point they examined. McLaughlin and collegues (2007) found that 6 h of restraint for 21 days caused dendritic retraction in CA3, whereas 2 h of restraint stress for 21 days, 2 h for 10 days, and 6 h for 10 days did not. In conclusion, morphology in the PFC appears to be more sensitive to stress than morphology in the hippocampus.

Additionally, repeated restraint has been shown to decrease sucrose preference (Mao et al., 2022), and increase aggression, allodynia, and inflammatory pain (Bardin et al., 2009; Wood et al., 2003).

Chronic intermittent cold stress (CIC stress) is a homotypic chronic metabolic stressor that reproduces behavioral and functional changes paralleling those found in psychiatric disorders. For example, CIC stress has been shown to sensitize the HPA axis response (Ma and Morilak 2005), sensitize noradrenergic reactivity (Pardon et al., 2003), alter prefrontal and hypothalamic neuronal activity (Acosta et al., 1993; Correll et al., 2005; Moore et al., 2001), change spine and dendritic morphology in the orbitofrontal cortex (Adler et al., 2020), sensitize neuroimmune activity in the prefrontal cortex and hypothalamus (Girotti et al., 2011) and increase microglia-induced neuroinflammation in the hippocampus (Lang et al., 2020).

Another widely used chronic stress paradigm is chronic unpredictable stress. First developed by Katz and colleagues (Katz et al., 1981) as a 3 week variable stress paradigm that included severe stressors such as footshock, cold swimming, and immobilization, this paradigm was subsequently modified by Willner and coworkers (Willner et al., 1987) who substituted the severe stressors with milder ones, to better reproduce the human experience of daily, light but persistent stress exposure. Other variants of the CUS/CMS paradigm have also been developed (Banasr et al., 2007; Li et al., 2011). CUS/CMS induces a spectrum of behavioral abnormalities in rodents that parallel depressive symptoms including changes in reward sensitivity, decreased motivation, reduced grooming, and sleep changes. For a comprehensive review, see (Willner 2005). Along with behavioral effects, chronic unpredictable stress also causes structural changes, such as dendritic morphology and spine changes (Dias-Ferreira et al., 2009; Li et al., 2011).

3. Effects of stress on executive function

3.1. Cognitive flexibility

Cognitive flexibility can be defined as the ability of an individual to adapt their behavior to a changing environment or the ability to suppress old information in order to learn new information. Indeed, a lack of cognitive flexibility often leads to perseverance of behaviors that are no longer beneficial, or the inability to learn a new set of "rules." Cognitive flexibility is often dysfunctional in patients with stress-related disorders, including depression and PTSD, where biased attention to perceived threats, ruminative focus on negative outcomes and perseverative behaviors are often a main symptom of the disorder (Clancy et al., 2016; Disner et al., 2011). For example, reduced cognitive flexibility shortly after a stressful or traumatic event is predictive of PSTD symptom severity a full year later (Ben-Zion et al., 2018). Two examples of cognitive flexibility that have been studied in relation to stress will be discussed in this review: reversal learning and extradimensional set shifting.

3.1.1. Rodent models of cognitive flexibility

Several rodent models of cognitive flexibility exist, many of which were originally based on human tests, such as the Wisconsin Card Sorting Test (Merriam et al., 1999) or the Cambridge Neuropsychological Test Automated Battery (CANTAB). One example is the attentional set-shifting task (AST) developed by Birrel and Brown (Birrell and Brown 2000) as a rodent analogue of the ID/ED sub-test of the CANTAB cognitive test battery developed by Sahakian and Robbins for human and non-human primates (Robbins et al., 1998). Both reversal learning and set shifting are evaluated in this test. Briefly, in the AST, rats dig for a food reward in small pots defined by cues along two stimulus dimensions: the material with which they are filled (sawdust, beads, etc) and an odor with which they are scented. The rats must learn which of these dimensions is relevant for locating the reward, and then which cue within that dimension is associated with the reward. After mastering a given contingency, the rules are changed, and the rat must learn a new association. For instance, the odor clove signals reward at first and the odor nutmeg does not; after mastering this discrimination, the rule is switched, whereby nutmeg is now associated with the reward, and clove is not (a Reversal). Subjects are then required to learn this new rule until they meet a predefined criterion. During this phase, subjects will produce errors that can be broadly classified as "perseverative," i.e., persistent responses according to the obsolete rule, or "regressive," i.e., relapses back to the old contingency after a series of correct responses. After a series of such tests in which the same stimulus dimension is informative regardless of how the rules are changed, the animals form a cognitive set, or a strategy that guides them in adapting to subsequent changes. Then, in the extra-dimensional (ED) cognitive set-shift portion of the test, odor is no longer the relevant dimension, but becomes the distractor, and the digging medium becomes the cue that signals reward. Thus, the animal must abandon the strategy of using odor as a guide and pay attention to tactile information instead. Cognitive flexibility in both reversal and set-shifting is measured by how readily the animal is able to suppress the old information and learn the new rule. More recently, operant-based systems to measure reversal learning and set shifiting have been developend for rats and mice, using operant boxes with retractable levers (Brady and Floresco 2015; Floresco et al., 2008) or touchscreen pads (Turner et al., 2017).

3.1.2. Brain areas and circuits in reversal learning

Human imaging studies show increased activity in medial prefrontal areas (Boehme et al., 2017; Cools et al., 2002), orbitofrontal areas (Ghahremani et al., 2010; Remijnse et al., 2006), parietal cortex, insula and cingulate cortex during reversal tasks (Yaple and Yu 2019). The orbitofrontal cortex is especially important for reversal learning, as evidenced in human studies (Hampshire et al., 2012), and in a large body of animal lesion studies, including monkeys (Dias et al., 1996), mice (Bissonette et al., 2008) and rats (McAlonan and Brown 2003). Other brain regions important for reversal learning are the striatum (Cools et al., 2002; Rogers et al., 2000b), amygdala (Izquierdo et al., 2013; Schoenbaum et al., 2003), and the hippocampus (Mala et al., 2015). Lesions in the ventral mid-thalamus (rhomboid and reuniens nuclei) and mediodorsal thalamus have also been shown to impair reversal learning (Chudasama et al., 2001; Linley et al., 2016). Recently, efforts have been directed at defining specific connectivity between the

areas that functionally mediate reversal. Studies in humans and rodents show that major projection pathways involved in reversal include corticostriatal, thalamocortical, and cortico-amygdalar pathways. Thus, in human MRI studies, probabilistic reversal learning was associated with functional connectivity between the lateral orbitofrontal cortex and ventral striatum (Morris et al., 2016b). In rats, optogenetically inducing long-term potentiation (opto-LTP) in a MDT to orbitofrontal projection produces deficits in reversal learning (Adler et al., 2020). In an elegant study using selective viral ablation, Groman and colleagues showed that OFC-amygdala-striatal pathways mediate different aspects of value-reward encoding during a probabilistic reversal test. Rats with ablation of an OFC to nucleus accumbens projection showed deficits in reversal due to the inability to use negative outcomes to guide subsequent behaviors. By contrast, the ablation of an amygdala projection to OFC created deficits by not allowing rats to learn from positive outcomes. Interestingly, ablation of the reciprocal projection (OFC to amygdala) enhanced reversal (Groman et al., 2019). These nuanced outcomes may explain the inconsistencies in early reports of the effects of amygdala lesions on reversal learning (Izquierdo et al., 2013; Schoenbaum et al., 2003; Stalnaker et al., 2007), and indicate the necessity of circuit-level analyses to precisely dissect the anatomical correlates of reversal.

3.1.3. Neurochemical modulation of reversal learning

Glucocorticoids and CRH. Few studies have addressed the effects of elevated stress hormones on reversal learning; however, available evidence suggests that altered stress hormone signaling can negatively impact reversal learning. Thus, mice in which the MR/GR balance is altered by overexpression of MR and underexpression of GR show deficits in reversal tasks and increased perseveration (Harris et al., 2013). In rats, blockade of CRFR1 in the prefrontal cortex prevents stress-induced deficits in temporal order memory and reversal learning (Uribe-Marino et al., 2016).

Serotonin. Ample evidence points to the involvement of serotonergic signaling in the OFC in reversal. Depletion of serotonin either by removal of dietary tryptophan, 5-7-DHT lesions or use of the tryptophan hydroxylase depleting agent PCPA impairs reversal in humans, non-human primates, and rats (Clarke et al., 2007; Lapiz-Bluhm et al., 2009; Rogers et al., 1999). Receptor-specific manipulations with serotonin receptor antagonists or serotonin reuptake inhibitors suggest a complex picture of regulation. Antagonism of 5HT2A receptors impairs performance (Furr et al., 2012; Hervig et al., 2020), whereas antagonism of 5HT2C receptor facilitates reversal (Boulougouris et al., 2008; Nilsson et al., 2012), indicating a specificity in serotonergic modulation of reversal. In general, however, reduced serotonergic signaling in the OFC seems to be associated with increased perseveration (Clarke et al., 2004).

Dopamine. The importance of dopaminergic transmission in reversal behavior has been well documented, especially after extensive training on reversal learning, when the likelihood of reversal is "expected" (Costa et al., 2015; Klanker et al., 2015). There seems to be regional specificity to the effects of dopamine on reversal learning. Unlike serotonin, depleting dopamine in the OFC does not affect reversal learning (Clarke et al., 2007), whereas depletion in the striatum impairs reversal learning (Clarke et al., 2011). In human studies, increased dopaminergic activity in the striatum correlated with optimal reversal learning (Clatworthy et al., 2009). Both D1 and D2 receptor subtypes are involved in modulating reversal learning in humans, non-human primates, and rodents (Boulougouris et al., 2009; Izquierdo et al., 2006; Lee et al., 2007; Marino et al., 2022; Mehta et al., 2001; Smith et al., 1999; van der Schaaf et al., 2014). Recent evidence supports the notion that the differential role of D1 or D2 receptors in reversal may be region-specific (Sala-Bayo et al., 2020; Verharen et al., 2019).

Glutamate. Glutamate transmission in specific areas of the OFC is also implicated in visual reversal learning (Hervig et al., 2020), but little is known regarding the specific receptors involved. Subchronic administration of the NMDAR antagonist phencyclidine (PCP) produces impairments in reversal learning (Abdul-Monim et al., 2007), but subsequent analyses reported no stable effect of PCP on reversal (but reproducible negative effects on set-shifting) (Janhunen et al., 2015). Given the diversity of glutamate receptors and signaling modes, it is likely that more selective targeting of receptors or receptor subunits is required to clarify the involvement of glutamatergic transmission in reversal. In this vein, a role for the metabotropic receptor mGluR5 seems indicated by the fact that mGluR5 knockout mice display impaired visual reversal (Lim et al., 2019). Additionally, multiple studies have reported that antagonism or gene deletion of NMDA receptor subunit 2B (GluN2B) in OFC and dorsal striatum impairs reversal learning (Brigman et al., 2013; Dalton et al., 2011; Thompson et al., 2015a). Further investigation is necessary to better understand the role of glutamate signaling in reversal.

3.1.4. Stress effects on reversal learning

Human studies. Acute stress has been associated with both better performance in reversal learning (Wieland et al., 2023), as well as impairments (Raio et al., 2017) Conversely, early life stress and chronic adult stress impair reversal learning. For example, in healthy young adults, early life stress correlates with increased perseveration on a reversal task and increased propensity for increased alcohol use (Franco and Knowlton 2023). In an adolescent cohort with a history of early life stress, individuals with higher life stress scores had more difficulty in updating contingencies during reversal learning tasks (Harms et al., 2018). In a study that used a modified reversal learing task to assess sensitivity to punishement and reward, adult females with high self-reported chronic stress showed increased perseverative errors in the punishment condition and reduced punishment sensitivity in the reward condition (Monni et al., 2023). Moreover, reversal learning deficits have been documented in several stress-related psychiatric disorders such as major depressive disorder (where it was accompanied by abnormalities in the OFC) obsessive compulsive disorder, and generalized anxiety disorder (Drevets 2007; Szabo et al., 2013), and in individuals repeatedly exposed to traumatic events (Levy-Gigi and Richter-Levin 2014).

Rodent studies. In rats, acute stress is generally associated with better performance in reversal learning (Bryce and Howland 2015; Graybeal et al., 2011; Thai et al., 2013). In contrast, early life stress impaired reversal learning in female mice, and this was associated with increased expression and density of parvalbumin expressing neurons in OFC (Goodwill et al., 2018). Chronic intermittent cold stress in adult rats results in robust deficits in olfactory reversal learning task (Danet et al., 2010; Donegan et al., 2014; Furr et al., 2012; Lapiz-Bluhm et al., 2009; Patton et al., 2017; Wallace et al., 2014). Reversal impairments are also observed after two weeks of chronic unpredictable stress in both olfactory and spatial reversal tasks (Bondi et al. 2007, 2010; Hill et al., 2005; Jett et al., 2015; Jett and Morilak 2013; Quan et al., 2011; Yu et al., 2016). Mechanistically, chronic stress has been shown to decrease the levels of ciliary neurotrophic factor (CNTF) and reduce activation of its downstream effector JAK2 in the OFC. Restoration of CNTF levels within this brain region was sufficient to correct the effects of stress on reversal learning (Girotti et al., 2019). Functionally, chronic stress effects on reversal learning can be recapitulated by optogenetically inducing long term-potentiation (opto-LTP) in the OFC; conversely, chronic stress deficits are ameliorated by optogenetic long term depression (opto-LTD) in the OFC (Adler et al., 2020). Interestingly, JAK signaling is involved in hippocampal LTD (McGregor et al., 2017; Nicolas et al., 2012), and it is possible that this signaling pathway is also implicated in establishing LTD in the OFC. Taken together, these data support the notion that optimal reversal learning is associated with long-term depression in the OFC, in part mediated by CNTF/JAK signaling, that enables flexible behavior. In support of this idea, it is worth noting that depotentiation is associated with other forms of reversal; for example, temporary depotentiation in the hippocampus accompanies spatial reversal learning (Dong et al., 2013; Duffy et al., 2008; Mills et al., 2014; Morice et al.,

2007). Conversely, stress may produce reversal deficits by inducing a state of increased excitability and hyperactivity in the OFC that precludes the depotentiation necessary for optimal reversal. Indeed, this possibility is supported by morphological evidence that chronic stress associated with behavioral inflexibility produces hyper-elaboration and increased dendritic length and spine numbers in the OFC (Adler et al., 2020; Liston et al., 2006).

3.1.5. Brain areas and circuits in set-shifting

Human and animal studies have long suggested that the thalamo-fronto-striatal circuit is vital in set-shifting behavior. Prefrontal activity is associated with set-shifting performance in human subjects (Manes et al., 2002; Miller and Cohen 2001; Owen et al., 1991; Rogers et al., 2000a; Stuss et al., 2000). Animal lesion studies indicate that mPFC damage results in deficits specifically in set-shifting while reversal learning remains unaffected (Birrell and Brown 2000; Bissonette et al., 2008). Lesions of mediodorsal thalamus (Ouhaz et al., 2022) or ventral hippocampus (Mala et al., 2015; Placek et al., 2013) also produce deficits in set-shifting. Optogenetically inducing long-term depression specifically within MDT terminals in the mPFC impairs set-shifting (Bulin et al., 2020).

Recent chemogenic manipulation using designer receptors exclusively activated by designer drugs (DREADDs) implicated the LC in modulating the mPFC during set-shifting. Elevated activity in LC neurons projecting specifically to mPFC was improved set-shifting and reduced regressive errors (Cope et al., 2019). Further studies suggest that the LC may be important in "rule switching", allowing the animals to acquire the new rule easier during set shifting (McBurney-Lin et al., 2022).

3.1.6. Neurochemical modulation of set-shifting

Glucocorticoids and CRH. Few studies have addressed the role of stress hormones in set-shifting. In humans, pharmacological stimulation of GR or MR does not have any effect on flexibility tasks (Deuter et al., 2019; Wingenfeld et al., 2011). However, antagonizing MR with spironolactone diminished set shifting performance in humans, suggesting a potential role for this receptor in cognitive flexibility (Otte et al., 2007). CRH effects on set-shifting may be region-specific and dose-dependent. In one study in rodents, intracerebral administration of CRH impaired set-shifting with an inverted-U dose relationship. Conversely, microinjection into the locus coeruleus improved performance, (Snyder et al., 2012), consistent with evidence that CRH stimulates NE release from the LC (Curtis et al., 1997) and that NE in the mPFC is required for optimal set-shifting (Lapiz and Morilak 2006).

Serotonin. Evidence suggests that, besides reversal, serotonin is also involved in set-shifting. Serotonin transporter (SERT) knockout rats, which have increased extracellular serotonin, perform better than intact controls on set-shifting (Nonkes et al., 2012). However, in the opposite direction, serotonin depletion often has no effect on set-shifting (Clarke et al., 2005; Gallagher et al., 2003; Hughes et al., 2003). Serotonin receptor antagonists often ameliorate stress effects. For example, in rats, the negative effects of chronic restraint stress on set-shifting were ameliorated by the 5-HT_7 receptor antagonist amisulpride (Hedlund 2009; Hedlund et al., 2005; Leopoldo et al., 2011; Nikiforuk and Popik 2013). The 5-HT_6 receptor antagonists SB 271046 and sertindole were also shown to reduce deficits in set-shifting produced by PCP (Idris et al., 2010; Rodefer et al., 2008).

Dopamine and Norepinephrine. Dopamine activity in the mPFC is required for optimal performance in set-shifting tasks. Thus, in monkeys, depletion of dopamine in the mPFC using 6-OHDA produced deficits in set-shifting (Crofts et al., 2001; Robbins and Roberts 2007) and in humans increasing dopamine activity in the mPFC improved set-shifting (Apud et al., 2007). The role played by different dopamine receptors in this behavior is complex (Floresco 2013). For example, the D_1 receptor antagonist SCH23390 infused within the mPFC impaired set-shifting in rats (Haluk and Floresco 2009; Ragozzino 2002), while mPFC infusions of the D_4 antagonist L-745,870 improved set-shifting (McQuail et al., 2021). Norepinephrine also contributes to attentional set-shifting. Deafferentiation of noradrenergic input into the mPFC results in set-shifting deficits (McGaughy et al., 2008; Tait et al., 2007). In humans, tonic activity of noradrenergic neurons in the LC (assessed by pupillary dilation) facilitated set-shifting (Pajkossy et al., 2017). In animals, acute activation of noradrenergic signaling in the mPFC by administration of atomoxetine, a serotonin and norepinephrine uptake inhibitor (Newman et al., 2008), or atipamezole, an α_2-adrenergic autoreceptor antagonist (Bondi et al., 2010; Lapiz and Morilak 2006), both improved set-shifting.

Glutamate. Glutamate transmission is also implicated in set-shifting. Direct antagonism of AMPA or NMDA receptors, but not mGluR5, in the mPFC produced set-shifting deficits (Jett et al., 2017). By contrast, systemic administration of the partial NMDA receptor agonist D-cycloserine rescued set-shifting impairments induced by scopolamine (Siddik and Fendt 2022). Expression of the GluA1 AMPA receptor subunit decreased within the mPFC of stressed animals that exhibited set-shifting deficits (Sun et al., 2022). Cortical expression of the NMDAR NR1 subunit is decreased in aged rats with set-shifting deficits (McQuail et al., 2021). Electrophysiological experiments have also revealed increased AMPA/NMDA ratios on fast-spiking interneurons in the mPFC of aged rats with set-shifting deficits (McQuail et al., 2021).

3.1.7. Stress effects on set-shifting

Human studies. In humans, not many studies have addressed the effect of stress on set-shifting using the Wisconsin Card test (WCST) or CANTAB tests and the results seem variable. For example, in one study using the WCST, acute stress did not impact cognitive flexibility (Hendrawan et al., 2012), whereas in another study using a virtual TSST and a variant of the WCST, investigators reported improved cognitive flexibility (Delahaye et al., 2015). In work comparing sexes, it was found that acute stress reduced cognitive flexibility measured with the WCST in males but not in females (Kalia et al., 2018; Shields et al., 2016). In other studies using tests of cognitive flexibility other than the WCST, some investigators have reported a negative impact of acute stress on this cognitive domain and no difference between males and females (Alexander et al., 2007; Hillier et al., 2006). In the few studies evaluating chronic stress, the data collected with tests other than the WCST suggest that high perceived stress correlates with set-shifting deficits (Orem et al., 2008). Early life stress stress also correlated with decreased cognitive flexibility in adulthood, especially in individuals with a high degree of self-reported ongoing stress (Kalia and Knauft 2020; Kalia et al., 2021).

Rodent studies. In rodent studies, the effects of acute stress on set-shifting are dependent on the type of stress the subject is exposed to prior to the set-shifting test. For example, a 15-min tail pinch is sufficient to produce deficits in set-shifting, but not reversal learning (Butts et al., 2013), while a 30-min acute restraint stress does not alter set-shifting (Thai et al., 2013). Additionally, a single prolonged stress paradigm (SPS) in which rats are acutely exposed to multiple stressors within a short time (a common model for PTSD), also resulted in set-shifting deficits (George et al., 2015). This suggests there may be a "threshold" above which acute stress produces set-shifting deficits. Subjects exposed to chronic restraint stress or CUS consistently exhibit deficits in set-shifting (Bondi et al., 2008; Fucich et al., 2016; Jett et al., 2013; Liston et al., 2006; Morilak et al., 2005). Interestingly, CIC stress that impaired reversal learning had no effect on set-shifting (Lapiz-Bluhm et al., 2009). Chronic stress can lead to decreased activity in the mPFC in both humans and animal models (Liston et al., 2009), and reduces responsivity of the mPFC to afferent stimulation as measured by local field potentials (Jett et al., 2017). Reduced response to afferent input was unique to the MDT pathway to mPFC, as the response to stimulation from the ventral hippocampus remained intact after CUS (Jett et al., 2017). Using optogenetics to induce long-term depression specifically within the MDT-mPFC pathway mimicked the effects of chronic stress on

set-shifting. By contrast, long-term potentiation induced optogenetically within the MDT-mPFC pathway of stressed rats ameliorated the stress-induced deficits in set-shifting (Bulin et al., 2020). Decreased mPFC activity and responsiveness also correlate with stress-induced morphological changes, as subjects exposed to chronic stress exhibit reduced length of the apical dendrite and reduced dendritic branching in glutamatergic pyramidal neurons, and an overall loss of dendritic spines (Anderson et al., 2020; Cerqueira et al. 2005a, 2005b, 2007a, 2007b; Cook and Wellman 2004; Dias-Ferreira et al., 2009; Liston et al., 2006; Radley et al. 2004, 2006; Silva-Gomez et al., 2003).

3.2. Attention and behavioral inhibition

Broadly speaking, attention is the ability to actively process specific information in the environment while ignoring irrelevant information, whereas behavioral inhibition is characterized by the ability to restrain a response. Even within these general definitions, it is apparent that the two constructs are inter-related, in that a degree of inhibitory control is exerted during tasks of attention (when responses to extraneous stimuli need to be restrained) and vice versa, attention to environmental change is a prerequisite for inhibition of a response that has become ineffective (Bari and Robbins 2013). Indeed, as we will discuss later, behavioral tasks measuring deficits in attention also report on behavioral disinhibition.

Impulsivity is a component of normal behavior that manifests as loss of behavioral inhibition, including intolerance for delayed rewards, and actions performed hastily and without due consideration of the consequences. High levels of impulsivity are associated with psychiatric disorders such as attention-deficit disorder, bipolar disorder, substance use disorder, and other addictive disorders (Winstanley et al., 2006). Impulsivity manifests in both the innate tendency of the subject to express behavioral disinhibition (trait impulsivity) and in the response to environmental pressures that may produce disinhibited behavior (state impulsivity). Impulsivity can be conceptualized behaviorally and neurobiologically under two broad categories: motor impulsivity, or the inability to inhibit a prepotent motor response, and choice impulsivity, or the selection of a small, immediate reward in favor of a larger, delayed reward (Bari and Robbins 2013; Dalley and Robbins 2017; Evenden 1999b; Winstanley et al., 2006).

3.2.1. Rodent models for attention and behavioral inhibition

3.2.1.1. Motor impulsivity. The 5-choice serial reaction time test (5-CSRTT) is used to measure both attention and response inhibition in rodents (Bari et al., 2008; Carli et al., 1983). Modified versions of this test, e.g., the 4-choice serial reaction test and the Sussex5CSRTT, are used in humans (Sanchez-Roige et al., 2016; Voon et al., 2014). In the rodent task, subjects are trained to detect brief flashes of light presented randomly in 1 of 5 holes and make a nose-poke response in the correct location to receive a food reward. Responses made before presentation of the stimulus (premature responses) are considered an index of motor impulsivity, whereas responses in one of the unlit holes (incorrect responses) indicate deficits in attention (Eagle and Baunez 2010; Sosa et al., 2021). The Go No-Go test is another motor inhibition test in which separate signals (different tones) are associated with "go" and "no-go" trials; the subject must respond in go trials but inhibit responding in no-go trials. Motor impulsivity can also be evaluated by considering "speed" of inhibitory control, measured with the Stop-Signal-Reaction-Time Test (SSRTT). In this task, rats are presented with two levers. The animal is required to press in quick succession first the left then the right lever to receive a food pellet. On 20% of trials a stop signal (a tone, for example) is played after the left lever press signaling that the subject must withhold responding on the right lever to receive the reward (Eagle and Baunez 2010; Eagle et al., 2008). The critical measure in SSRTT is the time taken to stop the response. Thus, SSRTT specifically measures inhibition of actions that have been started and engage "stopping" processes, whereas Go No-Go and 5-CSRT tests measure the ability to inhibit the initiation of the response and engage "wait" processes during inhibitory responses. Interestingly, several studies have highlighted neuroanatomical and pharmacological differences between "waiting" and "stopping" impulsivity that provide useful frameworks for further mechanistic analysis in rodent models of impulsivity (Dalley et al., 2011; Dalley and Robbins 2017).

3.2.1.2. Choice impulsivity. Impulsive choice is exhibited by subjects who choose an immediately available small reward in preference to a larger but delayed reward. This type of decisional impulsivity is heavily shaped by reward valuation and the loss in perceived reward value when its delivery is delayed. In rodents, impulsive choice is often measured with delay-discounting tests (Evenden 1999a). Briefly, animals choose between two levers, one of which provides a reward of one pellet, the other a reward of 4 pellets. Over the period of the test the delay to the large reward increases from 0 s to 10, 20, 40, and finally 60 s and a delay-discounting curve can be obtained. Animals typically show a strong preference for the larger reward early in the session when the delay is short or absent but shift their preference to the smaller reward as delay to the larger reward increases. Individuals who generate steeper discounting curves, such that each unit of time-delay has a greater negative effect on the valuation of the reward, are described as exhibiting more decisional impulsivity.

3.2.2. Brain regions and circuits involved in attention and behavioral inhibition

3.2.2.1. Motor impulsivity. Many of the neuroanatomical substrates of behavioral inhibition have been identified from rodent brain lesion studies (for review see (Eagle and Baunez 2010)). To summarize, lesions in the OFC, dorsal medial striatum and subthalamic nucleus (STN) affect stopping processes measured on SSRT as well as premature responding on the 5-CSRTT. Additionally, lesions in the infralimbic cortex (Chudasama et al., 2003b), insular cortex (Dambacher et al., 2015), ventral hippocampus (Abela et al., 2013), and cingulate cortex (Muir et al., 1996) all increase premature responding in the 5-CSRTT. The role of the nucleus accumbens may be more nuanced with differential effects mediated by the shell and the core (Besson et al., 2010; Sesia et al., 2008). Recently, using a cued sensory association task, the secondary motor cortex was implicated in coding and controlling premature motor output (Guzulaitis et al., 2022). In humans, motor impulsivity is also associated with corticostriatal and corticosubthalamic connectivity (Aron et al., 2003; Hannah and Aron 2021). Specifically, the STN is well recognized as an inhibitory modulator of cortico-striatal motor outputs (Morris et al., 2016a). Recent evidence from human studies of Parkinson disease (Mosley et al., 2020) confirms previous work that connectivity of premotor areas to the STN signal motor stopping (Aron et al., 2016) but also show a role of STN in facilitating disinhibitory control, possibly via connectivity of STN with prefrontal and orbitofrontal cortices (Dagher 2020; Mosley et al., 2020). In rodents, several lines of evidence, including lesion studies (Baunez and Robbins 1997, Phillips and Brown 2000) and disconnect studies (Chudasama et al., 2003a) have supported the notion of the STN as an "action stop" center. More recently, mapping of the underlying circuitry has confirmed the role of secondary motor cortex to STN connections (Adam et al., 2022) and mPFC to STN connections (Li et al., 2020) in motor inhibition.

3.2.2.2. Choice impulsivity. Lesion studies in rodents and functional imaging studies in humans implicate the nucleus accumbens (NAC) core, basolateral amygdala (BLA), hippocampus, insula, lateral prefrontal cortex (PFC), posterior cingulate cortex, parietal cortex, and medial and lateral orbitofrontal OFC in delay discounting impulsivity (Cardinal et al., 2001; Kable and Glimcher 2007; Tanaka et al., 2004; Winstanley

et al., 2004b). With respect to corticosubthalamic circuitry, lesions of the STN actually reduce impulsive choice (Winstanley et al., 2005a). However, there is also evidence for a role of STN to mediate some aspects of cognitive or choice impulsivity, both in rodents and humans, with a putative regulation by associative and limbic cortices (mPFC and OFC) (Heston et al., 2020; Mosley et al., 2020). Indeed, a recent report showed that activity levels in the pre-supplementary motor area were shown to predict impulsive choice in a gambling test in humans (Lohse et al., 2023).

3.2.3. Neurochemical modulation of attention and behavioral inhibition

3.2.3.1. Motor impulsivity. Glucocorticoids and CRH. Studies that have investigated the role of stress hormones in impulsive responding did not report significant effects (Kentrop et al., 2016). Instead, stress hormones seem to affect attention. In particular, MR blockade impairs selective attention in healthy humans (Cornelisse et al., 2011a; Otte et al., 2007) and polymorphisms within the MR gene are associated with increased hyperactivity and decreased attention in ADHD cohorts (Kortmann et al., 2013).

Serotonin. Serotonin neurotransmission plays an important role in both reward evaluation and inhibitory responses (Desrochers et al., 2022). Several lines of evidence, not all in concordance, have shown the importance of serotonin in motor inhibition. Thus, in some studies, increased tonic extracellular serotonin levels in mPFC correlated with impulsive action in the 5-CSRTT (Dalley et al., 2002; Puumala and Sirvio 1998). However, there is also evidence that depleting serotonin in the frontal cortex increases motor impulsivity in rodents (Harrison et al., 1997; Winstanley et al., 2004a) and humans (Worbe et al., 2014) and that increasing serotonin in the cortex improves wait impulsivity. (Fonseca et al., 2015; Miyazaki et al. 2014, 2020). Thus, to fully characterize serotonergic involvement in impulsivity a more nuanced approach that considers receptor-, region- or circuit-specific effects may be necessary. With respect to receptor subtypes, 5-HT2A and 5-HT2C receptors seem to have opposite effects on motor impulsivity; 5-HT2C receptor antagonism (in prefrontal cortex and accumbens) is associated with greater premature responding, and activation of these receptors lowers premature responding in 5-CSRTT. Conversely, 5-HT2A receptor antagonism is associated with decreased premature responding and activation is associated with increased premature responding in 5-CSRTT (Fletcher et al., 2007; Koskinen et al., 2000; Robinson et al., 2008a; Silveira et al., 2020; Winstanley et al., 2004c).

Dopamine and norepinephrine. The dopaminergic and noradrenergic systems are also implicated in the modulation of impulsive responding in the 5-CSRTT, perhaps through cross-signaling. In particular, D2 receptor availability has been associated with high trait impulsivity in humans (Volkow et al. 1993, 2001) and in rodents performing tests of motor impulsivity (Caprioli et al., 2013; Dalley et al., 2007; Pattij et al., 2007). Increasing norepinephrine (and dopamine) levels with NE reuptake inhibitors such as atomoxetine and desipramine decreases impulsive responding in the 5-CSRTT (Navarra et al., 2008; Paine et al., 2007; Paterson et al., 2011; Robinson et al., 2008b). Finally, interactions between the noradrenergic and dopaminergic systems were reported in a study where the beneficial effects of atomoxetine and duloxetine (a serotonin and norepinephrine reuptake inhibitor) on decreasing motor impulsivity were blocked by a D1-like receptor antagonist (Sasamori et al., 2019).

Glutamate and GABA. Other neurotransmitter systems that have a role in impulsive action include the ionotropic and metabotropic glutamate receptors (Higgins et al., 2016; Isherwood et al., 2017). In particular, metabotropic glutamate receptor 5 (mGluR5) is differentially involved in impulsive action and impulsive choice, as positive allosteric modulation of this receptor reduces impulsive action but does not affect impulsive choice (Isherwood et al., 2015). GABAergic transmission also plays a role in motor impulsivity. Thus, high trait impulsivity in rats is associated with reduced GABA levels in the ventral striatum and decreasing glutamate decarboxylase (GAD65/67) expression in the nucleus accumbens increased impulsivity in low impulsivity rats (Caprioli et al., 2014; Sawiak et al., 2016).

3.2.3.2. Choice impulsivity. Serotonin. Serotonin's role in behavioral inhibition is not restricted to motor impulsivity but extends to choice impulsivity, although in this instance again, pharmacological effects are complex and outcomes have varied across studies. Some studies indicated that depleting central serotonin in rodents does not produce effects on a delay discounting task (Winstanley et al., 2004a), in concordance with human studies. (Crean et al., 2002; Dougherty et al., 2015; Worbe et al., 2014). In other work, however, central 5-HT depletion did increase impulsive choice in rodents (Mobini et al., 2000) and serotonin efflux in the dorsal raphe nucleus is higher while waiting for delayed rewards (Miyazaki et al., 2011). Moreover, in rodents, selective serotonin reuptake inhibitors (SSRIs) increase selection of larger, delayed rewards (Bizot et al., 1999). Thus, serotonin effects appear to be complex and may depend on interplay with other neurotransmitter systems (Winstanley et al., 2005b).

Dopamine and norepinephrine. Depletion of dopamine in the striatum increases discounting rates in delay discounting tests (Tedford et al., 2015), and rats with higher discounting rates have a blunted cue dopamine response (Moschak and Carelli 2017). Accordingly, optogenetic stimulation that induces dopamine release within the nucleus accumbens produces a shift toward waiting for delayed larger rewards in rats (Saddoris et al., 2015). Expression of D2 receptors is important for choice impulsivity as knock-down of these receptors in the ventral tegmental area shifted preference for the smaller, immediate reward in rats (Bernosky-Smith et al., 2018). As with other neurotransmitters, however, the effects of dopamine on delay discounting seems to be region-dependent. Thus, discounting rates are increased by infusions of D2, but not D1, receptor antagonists in nucleus accumbens (Yates and Bardo 2017). Conversely, discounting rates are increased when D1, but not D2, antagonists are infused in the prefrontal cortex (Loos et al., 2010). These functional differences may be linked to the heterogeneity of dopamine receptor expression in cortical compared to subcortical regions.

A large volume of work with norepinephrine reuptake inhibitors suggests an important role for norepinephrine not only in impulsive action but also in impulsive choice. Pharmacological increases in extracellular norepinephrine levels by norepinephrine transporter (NET) blockers, such as atomoxetine, consistently increase preference for larger delayed rewards in delay discounting tasks (Robinson et al., 2008b; Sun et al., 2012). These effects appear to be mediated by the α_2 adrenergic receptor, as administration of α_2 agonists decrease impulsive choice (Nishitomi et al., 2018) and α_2 antagonists increase impulsive choice (Schippers et al., 2016). Despite the clear role of norepinephrine in impulsivity it is important to note the possibility that some of the behavioral effects described above may be in part due to changes in dopaminergic tone, as atomoxetine also increases cortical dopamine levels (Bymaster et al., 2002) and α_2 agonists have been found to decrease dopamine release (Ihalainen and Tanila 2002).

Glutamate and GABA. Like motor impulsivity, choice impulsivity is also regulated by excitatory and inhibitory neurotransmitters. Thus, levels of cortical glutamate-glutamine and GABA predict impulsive decision making and gambling severity in humans (Weidacker et al., 2020). In rodents, ionotropic glutamate receptors have been shown to be implicated in delay discounting (Yates and Bardo 2017; Yates et al., 2015).

3.2.4. Stress effects on behavioral inhibition

Human studies. In humans there is evidence that both acute and chronic stress affect behavioral inhibition. A meta-analysis of interactions of acute stress and risky behaviors revealed that overall, stress

exposure led to more disadvantageous and risky decisions than nonstress conditions (Starcke and Brand 2016). Interestingly, stress does not uniformly increase impulsive responding, rather it interacts with trait impulsivity as a factor to reveal preexisting biases in goal-directed behavior. Thus, in healthy adults acute stress impaired decision making and speed of choice in both non-gambling and gambling settings, and these effects were more pronounced in individuals with higher impulsivity (Canale et al., 2017; Raio et al., 2020). However, in humans other complicating factors, such as Individual perception of stress, may also affect choice behavior. In one study, researchers found that in the presence of an acute stressor individuals who are more likely to perceive stressful situations as such show a preference for larger, delayed rewards, while those with low perceived stress prefer short, immediate rewards (Lempert et al., 2012). The authors suggest that individuals with high perceived stress may interpret the acute stress as more threatening and this reduces their reward response in the short term. Indeed, a correlation between acute stress, decreased reward sensitivity and increased choice for later reward have been documented in previous work (Bogdan and Pizzagalli 2006). More prolonged stress has been linked to increased impulsivity and increased risk of developing specific addictive behaviors. In one study, greater lifetime stress exposure was significantly correlated with a greater tendency to make impulsive decisions under negative emotionality and was predictive of developing food addiction but not alcohol addiction (McMullin et al., 2021). In another study, stress significantly correlated with higher impulsivity in methamphetamine users but not in cocaine users (Mahoney et al., 2015).

Rodent studies. Fewer studies have addressed the role of stress on impulsivity in rodents. Perinatal stress has been shown to increase impulsive action but reduce impulsive choice in adulthood (reviewed in (Sanchez and Bangasser 2022)). Moreover, sex difference may be at play, as the type of perinatal stress applied elicits different effects on impulsivity (especially impulsive choice) in males versus females (Paine et al., 2021; Sanchez and Bangasser 2022). Conversely, administration of corticosterone to adolescent rats decreased premature responding at longer intertrial intervals on the 5-CSRTT but increased delay discounting (Torregrossa et al., 2012). Thus, with the caveat that corticosterone administration does not fully recapitulate the effects of natural stress, it appears that stress experienced before adulthood may have differential effects on impulsive action and impulsive choice. Stress applied in adulthood is also capable of altering impulse control in rodents. Accordingly, the response of rats in a motor impulsivity test analogous to the 5-CSRTT varies in a manner that is dependent on the type of stress used: while an acute stressor did not change performance, CIC stress lowered premature responses while CUS increased premature responses at longer intertrial interval times (Girotti et al., 2022). CUS also increased impulsive choice in a genetic mouse model of schizophrenia (Buhusi et al., 2017). Taken together, a large body of evidence suggests that stress has a nuanced effect on impulsive responding that depends on individual baseline setpoints of goal-directed behavior.

3.3. Working memory

Working memory is defined as the temporary storage and manipulation of content used to perform cognitive tasks such as language comprehension, learning, and reasoning (Baddeley 1992). This also requires attentional processes, in particular focused or selective attention (Diamond 2013). In humans working memory can directly be assessed with simple ordering tasks (presenting subjects with random numbers and asking them to reorder them in ascending or descending order). The N-back task, in which the subject is presented with a series of stimuli and is asked to indicate when a current stimulus matches one from n steps earlier, is also a widely used task to assess working memory, although selective and sustained attention are also heavily employed in this task (Owen et al., 2005; Pelegrina et al., 2015).

3.3.1. Rodent models for working memory

In rodents, T-maze alternation tasks, the 8-arm radial maze, and object recognition tasks with variable lengths of delay are some of the most used tests of spatial and non-spatial working memory (Kinnavane et al., 2015; Lalonde 2002; Olton 1987; Warburton and Brown 2015). These tasks rely on the intrinsic propensity of the animal to explore novel locations or objects when given a choice between a previously experienced situation and a novel one. Deficits in working memory will diminish preference for the novel location/object, as the animal does not retain information about previously encountered situations.

3.3.2. Brains areas and circuits of working memory

Human and non-human primate studies have revealed a central role of the frontal cortex in the regulation of working memory. Early studies in monkeys identified neurons in the PFC that maintain robust activity during cue presentation and during the delay period while the subjects keep stimulus information in working memory. This sustained activity is correlated with the ability to remember the information and is susceptible to distractions (Fuster & Alexander 1971, 1973). Human neuroimaging studies also found sustained activation in the lateral PFC while the subjects kept visual items in working memory (Courtney et al., 1998; Sakai et al., 2002). Moreover, specific involvement of parietal, sensory and premotor cortices has been shown in both human and primate studies of working memory (Khan and Muly 2011; Klingberg et al., 1997).

Rodent lesion studies have shown the importance of perirhinal, entorhinal cortex, hippocampus, prefrontal cortex and insular cortex for recognition memory (Albasser et al., 2012; Barker and Warburton 2011; Bermudez-Rattoni 2014; Ennaceur and Aggleton 1997; Tuscher et al., 2018; Warburton and Brown 2015). Subcortical areas involved in recognition memory include thalamus, hypothalamus, striatum, septum, amygdala and cerebellum (for a comprehensive review see (Chao et al., 2022)). At the circuit level, electrophysiology studies implicated connectivity between PFC-thalamus (reuniens nucleus) and hippocampus as mediating behavior in a T-maze test (Hallock et al., 2016; Ito et al., 2015). Moreover, chemogenic inhibition showed that reciprocal PFC-mediodorsal thalamus (MDT) projections mediate different phases of working memory processing, and that MDT input is necessary in sustaining prefrontal activity during working memory maintenance (Bolkan et al., 2017).

3.3.3. Neurochemical modulation of working memory

Glucocorticoids and CRH. Several reports indicate that alteration of stress hormone signaling negatively impacts working memory. MR seems to be particularly important for working memory. For example, individuals with Addison's disease performed better in working memory tasks when both receptors were activated compared to when only GRs were activated (Tytherleigh et al., 2004). In another study, mifepristone, a GR antagonist that shifts the MR/GR balance towards MR, improved spatial working memory and recognition memory in individuals with bipolar disorder (Young et al., 2004). CRHR1 signaling is also implicated in working memory. In humans CRHR1 polymorphisms interact with early life stress to produce deficits in working memory (Fuge et al., 2014). Administration of a selective CRFR1 antagonist prevented cognitive impairments in recognition memory in stressed mice (Philbert et al., 2013).

Dopamine and Norepinephrine. The importance of dopamine in working memory was established from observations that monkeys with dopamine depletion in the PFC showed profound deficits in working memory (Brozoski et al., 1979). Early studies aimed at defining receptor subtypes unveiled a critical role for D1 receptors in the effect of dopamine on working memory. Interestingly, optimal outcomes follow an inverted-U-shaped dose-response curve where both insufficient and excessive D1 activation result in impairments (Williams and Castner 2006; Williams and Goldman-Rakic 1995). Since D1 receptors are more abundant than D2 receptors in the prefrontal cortex they have been the

focus of much early research; however, more recent studies have also highlighted a potential role for D2 receptor signaling in working memory. For example, bromocriptine, a D2 receptor agonist, improved working memory in a variety of rodent maze tests (Onaolapo and Onaolapo 2013; Phelps et al., 2015; Tarantino et al., 2011), and treatment with a D2 receptor antagonist (haloperidol) produced deficits in spatial working memory and object recognition (Terry et al. 2007a, 2007b).

Noradrenergic receptor signaling is also important for working memory, in particular α_2 adrenoreceptors. Prefrontal cortex infusion of yohimbine, a noradrenergic α_2 receptor antagonist, impairs performance on working memory tasks (Li et al., 1999), whereas, administration of the α_2-adrenoceptors agonist guanfacine improves working memory functions in humans (Jakala et al., 1999; Swartz et al., 2008), monkeys (Arnsten et al., 1988) and rats (Hains et al., 2015).

Other neurotransmitter systems. In addition to catecholamines, there is evidence for an involvement of cholinergic receptors, with differential roles of nicotinic and muscarinic receptors in different aspects of the working memory processing (Granon et al., 1995). The glutamate system is also important for working memory function. For example, in rodents, infusion of NMDA within the septum improves consolidation in a working memory task (Puma et al., 1998). Administration of NMDA receptor antagonists either systemically or locally within the dorsomedial PFC impairs spatial working memory in rats (Aura and Riekkinen 1999; Gutnikov and Rawlins 1996). Interestingly, the NMDA antagonist AP5 infused within the septum, showed dose-dependent effects, with improved performance in a recognition task at low doses (Puma and Bizot 1998) and impairment at high doses (Puma et al., 1998), underscoring the potential subtleties of pharmacological manipulation on this behavioral measure. Beside excitatory transmission, evidence shows that inhibitory transmission also modulates working memory. For example, levels of GABA in the prefrontal cortex change during working memory tasks in humans (Michels et al., 2012; Yoon et al., 2016) and blockade of GABAA receptors in the prefrontal cortex of monkeys and rats reduces working memory capacity (Auger and Floresco 2014; Rao et al., 2000).

Finally, the role of serotonin in working memory is not well defined. Work in non-human primates suggests that 5-HT2A receptor stimulation facilitates spatial working memory (Williams et al., 2002), and studies in rodents indicate that prefrontal serotonin depletion may exert negative effects on select aspects of working memory (Gonzalez-Burgos et al., 2012). However, many outstanding questions remain, in part because serotonergic influence on working memory may, in fact, not be direct but derive from interplay with other neurotransmitter systems (such as the cholinergic system) (Ohno and Watanabe 1997).

3.3.4. Stress effects on working memory

Human studies. Stress has been reported to have mixed effects on working memory in healthy humans. Thus, some studies reported impairments in working memory after acute stress (Luethi et al., 2008; Schoofs et al. 2008, 2009) or after acute administration of corticosteroids (Lupien et al., 1999). But other studies found no effect of stress (Porcelli et al., 2008) or even enhancement of working memory (Cornelisse et al., 2011b; Weerda et al., 2010). Some studies showed enhancement of working memory in males but no effect or impairments in females (Cornelisse et al., 2011b; Qin et al., 2009; Schoofs et al., 2013). One issue may be the use of widely different tasks to measure working memory, some relying on visual imagery, others on letter recognition or digit-based n-back tasks that may differentially recruit other executive functions such as sustained attention.

Another important factor influencing stress outcomes on working memory may be related to the timing of behavioral testing with respect to stress exposure. In a recent metanalysis of existing literature by (Geissler et al., 2023) the authors found that negative effects of stress on working memory are clustered within two timeframes of 0–9 min and 25–50 min post-stressor. The authors suggest these timeframes represent effects mediated by sympathetic nervous system activation (early phase) and cortisol effects (late phase).

Rodent studies. In rodents, stress has also been shown to produce different effects depending on the timing and stressor type (for a metanalysis see (Moreira et al., 2016) Acute stress was shown to improve working memory with a mechanism attributed to glucocorticoid receptor-dependent regulation of glutamate receptors in the prefrontal cortex in male rats (Yuen et al. 2009, 2011). Another group reported improved performance in male rats in the T-maze soon after application of acute footshock, but worse performance at later times of testing (Musazzi et al., 2019). In a study comparing male and female rats it was shown that 60 min restraint produced impairments in proestrus female rats but not male rats, whereas 2h restraint produced deficits in both sexes, leading the authors to conclude that high estrogen levels may render females more sensitive to the effects of stress on working memory (Shansky et al., 2006). With respect to chronic stress, some models have been shown to improve working memory, particularly in spatial working memory tests (see (Conrad 2010). However, chronic stress is also reported to impair working memory in male rats (Cerqueira et al., 2007a; Mika et al., 2012; Wright and Conrad 2008). In one study, one week of repeated restraint impaired working memory in male rats but not female rats (Wei et al., 2014). Early life stress has generally produced deficits in working memory in the male offspring (Banqueri et al., 2021; Brenhouse and Andersen 2011), and can exacerbate outcomes after additional insults (Sanchez et al., 2021; Viola et al., 2019). Some studies, however, did not observe the negative impacts of early stress on working memory in males but did observe slight deficits in females, again highlighting that stress outcomes are greatly nuanced and variable depending on protocols, sex, and age of testing (Sun et al., 2020).

4. Treatment strategies for cognitive impairment in stress-related psychiatric illness

This section will delve into current clinical interventions and novel therapeutic targets identified either preclinically or clinically for treatment to mitigate stress-induced cognitive dysfunctions. When appropriate, we discuss key preclinical mechanistic studies with translational potential. In other instances, such as the case concerning device-based neuromodulation approaches (section 4.2), we focus primarily on clinical studies.

4.1. Pharmacological treatments

4.1.1. Monoamine neurotransmission targeting drugs

As discussed in the previous sections, monoaminergic neurotransmission involving serotonin, norepinephrine and dopamine exert a critical role in brain circuits associated with cognitive functions.

Pehrson and colleagues (Pehrson et al., 2015) conducted an in-depth review of preclinical studies in rodents on monoamine neurotransmission-targeting drugs and their impact on cognition. Monoamine-targeting drugs, often referred to as conventional antidepressants, are the leading prescribed drugs to treat stress-related psychiatric disorders. While conventional antidepressants have shown varying degrees of clinical efficacy regarding mood improvement, their impact on cognitive symptoms remains negligible (Rosenblat et al., 2015; Shilyansky et al., 2016), except for vortioxetine (Bennabi et al., 2019), a multi-modal drug that is the only FDA-approved antidepressant for which the prescribing information mentions enhancements in cognitive domains.

4.1.1.1. Serotonergic system targeting drugs. As previously noted, the serotonergic system has crucial regulatory effects on different domains of cognitive function. Not surprisingly then, several preclinical studies have supported the use of serotonergic modulators to improve cognitive deficits. For example, CIC-induced deficits in reversal learning in male

rats were rescued by acute and chronic treatment with the selective serotonin reuptake inhibitor (SSRI), citalopram (Danet et al., 2010). This effect was specific to the serotonin system because desipramine treatment (a norepinephrine reuptake blocker) did not rescue the CIC stress-induced reversal learning deficit (Danet et al., 2010). SSRIs such as citalopram, escitalopram and fluoxetine have also shown to be effective in ameliorating CUS-induced set-shifting deficits in male rats (Bondi et al., 2008; Minchew et al., 2021; Nikiforuk and Popik 2011).

Vortioxetine, an N-arylpiperazine derivative, is a potent selective inhibitor of the SERT, similar in this respect to other SSRIs. However, it also has potent actions at multiple 5-HT receptors (partial 5-HT_{1B} agonism, 5-HT_{1A} agonism, and 5-HT_{1D}, 5-HT_3, 5-HT_7 antagonism), a property not shared by other SSRIs. In addition, vortioxetine can modulate the dopaminergic, noradrenergic, histaminergic, cholinergic, GABAergic, and glutamatergic systems (Pehrson et al., 2016). An in-depth review of preclinical and clinical findings implicating the antidepressant effects of vortioxetine was published by Sanchez and colleagues (Sanchez et al., 2015). Preclinical studies carried out in male rats have also shown that vortioxetine efficacy in rescuing 5-HT depletion-induced deficits in reversal learning is likely due to its action at postsynaptic 5-HT receptors, as PCPA-induced blockade of serotonin reuptake did not prevent the beneficial effects of vortioxetine (Wallace et al., 2014). In the same study, the authors also showed that chronic vortioxetine treatment rescued CIC-induced deficits in reversal learning. Vortioxetine has recently been shown to recover set-shifting deficits in male rats. (Vaiana et al., 2023). In a preclinical study relevant to the study of depression and anxiety-related disorders, vortioxetine mitigated the excessive display of conditioned fear and rescued adaptive coping behaviors compromised by chronic stress in male rats (Hatherall et al., 2017).

It is worth noting that, more recently, a promising target that has garnered attention in the realm of therapeutics for stress-related psychiatric disorders is the 5-HT4 receptors. As such, an extensive review of the role of 5-HT4 receptor pharmacology, its role in cognition, and its potential as therapeutics for stress-related psychiatric disorders has been published (Murphy et al., 2021).

4.1.1.2. Noradrenergic system targeting drugs. Lapiz and colleagues demonstrated that naïve male rats treated subchronically with the NE-reuptake blocker desipramine showed improvement in set-shifting correlated with upregulation of mPFC NE (Lapiz et al., 2007). Chronic treatment with milnacipran, a serotonin-norepinephrine uptake inhibitor, can also restore set-shifting compromised by stress (Craine et al., 2023; Naegeli et al., 2013). In male rats subject to CUS, chronic treatments with either the norepinephrine reuptake blocker desipramine or the SSRI escitalopram prevented the deficit in set-shifting induced by stress (Bondi et al. 2008, 2010). In male rats. acute postsynaptic α_1 adrenergic receptor antagonism with benoxathian administration into the mPFC before testing prevented the beneficial effects of desipramine (Bondi et al., 2010), whereas infusions of β_1 or β_2 adrenergic receptor antagonists into the mPFC do not have a similar blocking effect (Lapiz and Morilak 2006). Furthermore, the same authors demonstrated that the systemic administration of atipamezole, an α_{2A}-adrenergic receptor antagonist, enhances set-shifting in male rats. However, while the faciliatory effects of norepinephrine persisted during chronic stress, they became detrimental to reversal learning in male rats (Jett et al., 2013).

These data show that while antagonism of α_{2A}-adrenergic receptor is associated with cognitive improvement (Bondi et al., 2007), it is essential to recognize that treatments targeting the modulatory role of α_{2A}-adrenergic receptors in rescuing stress-induced cognitive deficits will vary as a function of the inverted-U shaped noradrenergic-mediated response to stress (Arnsten 2011, 2015; Berridge and Arnsten 2013).

4.1.1.2.1. The α_{2A}-adrenergic receptor agonist guanfacine. Guanfacine is a selective and potent agonist of postsynaptic α_{2A}-adrenergic receptors, capable of strengthening PFC network connections (Arnsten and Jin 2012; Arnsten 2020). Moreover, guanfacine treatment exhibits pro-cognitive effects across species (Arnsten 2020). In 2009, the FDA approved a long-acting formulation of the drug (Intuniv™) for the treatment of ADHD in children.

Mice with a single copy deletion of the neurofibromatosis 1 (NF1) gene, namely, NF1 (±) mice, are useful for the study of ADHD and associated deficits in inhibitory control, as NF1 mutations in humans are associated with ADHD in clinical populations (Hyman et al., 2005; Hyman et al., 2005) Using the delay discounting test as a proxy for choice impulsivity, NF1 (±) male mice displayed greater impulsivity when compared to the wild-type male mice. Treatment with guanfacine (0.3 mg/kg, *i.p.*) was effective in rescuing NF1 (±) mice deficits in choice impulsivity (Lukkes et al., 2020).

The repurposing of guanfacine for various indications linked to neurological and psychiatric disorders has increased significantly (Woolley 2023), bearing profound implications for the amelioration of cognitive deficits associated with cognitive dysfunction in a clinical population characterized as biotype 6 described in section 4.4.

4.1.2. Multiple neurotransmitter system targeting drug: modafinil success in the clinic

Modafinil is a prescription medication used to promote wakefulness and enhance cognitive function with a complex pharmacological profile, including the blockade of monoamines (noradrenaline, dopamine, and serotonin) as well as modulation of the glutamatergic and GABAergic system (Mereu et al., 2013). Modafinil is FDA-approved for use in individuals with multiple sleep-associated disorders, effectively aiding them in maintaining alertness during waking hours. In preclinical studies, acute but not chronic modafinil treatment promotes neurogenesis by increasing precursor cell proliferation and survival (Brandt et al., 2014). Modafinil treatment reversed stress-induced spatial memory deficits in rats (Alam and Choudhary 2023).In healthy individuals, short-term modafinil treatment improves cognition and attentional set-shifting (Turner et al., 2004). Schizophrenia-related cognitive impairments were also improved with acute modafinil treatment (Scoriels et al., 2013; Turner et al., 2004) but not with chronic administration (Sinkeviciute et al., 2018).

In remitted depressed patients with persistent cognitive symptoms, modafinil treatment significantly improved episodic and working memory, but no beneficial effects were detected on attention and planning strategies (Kaser et al., 2017). Furthermore, although systematic reviews and meta-analyses of the clinical use of augmentation drugs for depression show favorable results for modafinil (Goss et al., 2013; Nunez et al., 2022), clinical trials evaluating its effects on various cognitive domains are lacking.

4.1.3. Ketamine as a breakthrough leading to novel therapeutic modalities: glutamatergic and GABAergic system-targeting drugs

Ketamine, an NMDA receptor channel blocker, is a rapidly acting antidepressant with its (S)-isomer, (S)-ketamine (intranasal Spravato), approved by the FDA in 2019 for Treatment Resistant Depression (TRD). The fact that ketamine is mechanistically distinct from conventional monoamine-based antidepressants has stimulated research for drugs that would reproduce its rapid therapeutic effects associated with the improvement of depressive symptomatology without the confounds of its psychotomimetic and abuse-related properties.

The disinhibition hypothesis posits that ketamine initially blocks NMDA receptors on fast-spiking GABAergic neurons, thus promoting local inhibition of interneuron (Zanos and Gould 2018). Consequently, transient disinhibition of glutamatergic pyramidal cells occurs and rapidly induces AMPA receptor-mediated synaptic plasticity in relevant corticolimbic circuits. Furthermore, the disinhibition-induced plasticity of excitatory synapses weakened by chronic stress has become a therapeutic principle for achieving rapid (24 h after treatment) restoration of stress-induced deficits in reward sensitivity related to mood disorders (Thompson et al., 2015b).

In preclinical studies, ketamine has shown promising effects in correcting the effects of stress on executive functions. Ketamine administered 24 h before testing rescued deficits in set-shifting and reversal learning in stressed male rats (Jett et al., 2015). When ketamine was administered daily before stress, it prevented stress-induced deficits in set-shifting (Nikiforuk and Popik 2014). The prophylactic effects of ketamine have been reviewed recently (Evers et al., 2022). Moreover, a subanesthetic dose of ketamine in combination with an AMPAkine reduces premature responses in a motor impulsivity test in non-stressed rats (Davis-Reyes et al., 2021). Ketamine administration to TRD patients has been linked to improvements in executive function, visual memory, and working memory (Gill et al., 2021; Shiroma et al. 2014, 2022; Stippl et al., 2021). In addition, ketamine is associated with a reduction in suicidal ideation, with indications associating this effect to enhanced inhibitory control (Lee et al., 2016; Zhang and Ho 2016). It is worth noting that acute ketamine has been reported to also induce cognitive impairments (likely due to its psychotomimetic-inducing properties) in healthy but not in TRD patients. Specifically, in healthy volunteers, but not in TRD patients, ketamine administration was correlated with transient decreases in working memory, attention, and long-term memory measured up to 1 h post treatment (Harborne et al., 1996; Hetem et al., 2000; Morgan et al., 2004). Measures of functional connectivity in these cohorts revealed increases and decreases in frontostriatal functional connectivity in TRD and healthy individuals, respectively (Mkrtchian et al., 2021), reflecting the contrasting impacts of ketamine on executive function.

Given the side effects associated with the use of ketamine (Short et al., 2018), an alternative approach to promoting disinhibition of pyramidal neurons is to use subtype-selective modulation of benzodiazepine (BZ) site–containing GABAA receptors (GABAARs). Although α5-containing GABAARs (α5-GABAARs) comprise only 10% of total brain GABAARs, the expression of α5-GABAARs is enriched in the hippocampus and the prefrontal cortex. Selective a5-GABAAR negative allosteric modulators (a5-GABAAR-NAMs) such as L-655,708, aIA, and MRK-016 are being developed as potential cognitive enhancers with the idea of selectively targeting hippocampus and cortex (Atack 2011). Although selective a5-GABAAR-NAMs have been shown preclinically to improve memory in naïve rodents (Chambers et al., 2002; Street et al., 2004), they have not been extensively tested preclinically in stress-induced cognitive dysfunctions. Moreover, poor pharmacokinetics, toxicity issues, and low tolerance in older adults prevented further testing in humans (Atack 2010, 2011; Atack et al., 2009).

A more recently screened selective α5-GABAAR-NAM, Basmisanil, mitigated diazepam-induced hippocampal-dependent spatial learning impairment in male rats (assessed using the Morris water maze), and improved prefrontal cortex-mediated executive function in male non-human primates (evaluated using the object retrieval task in cynomolgus macaques) (Hipp et al., 2021). In addition, Basmisanil did not demonstrate anxiogenic or proconvulsant effects in male rats and Phase I clinical studies (Hipp et al., 2021). Therefore, Basmisanil possesses a favorable profile for exploring the potential therapeutic advantages of α5-GABAAR modulation.

In contrast to selective NAMs acting through the a5-GABAAR benzodiazepine binding site, S44819 is a recently identified GABA competitive antagonist at a5-GABAAR. It shares pro-cognitive effects with NAMs in preclinical studies, including inhibiting a5-GABAAR tonic current, enhancing LTP, reversing scopolamine-induced spatial working memory impairment, and improving object recognition memory (Etherington et al., 2017; Ling et al., 2015). Additional research is needed to explore its potential impact on stress-induced executive function deficits.

In addition to the beneficial effects of a5-GABAAR-NAMs discussed thus far, there is a body of work showing that selective positive allosteric modulators of the a5-GABAAR (a5-GABAAR-PAMs) have potential for the treatment of mood disorders as well as cognitive dysfunctions (Luscher et al., 2023; Prevot et al., 2019). Chronic treatment with the selective a5-GABAAR-PAM GL-II-73 rescued stress-induced and age-related working memory deficits in mice (Prevot et al., 2019). A putative reconciliation and working hypothesis explaining how a5-GABAAR-NAMs and a5-GABAAR-PAMs might exert similar outcomes has been proposed by Prevot and Sibille (Prevot and Sibille 2021) and is that both treatments increase signal-to-noise ratio of hippocampal and cortical transmission, although via distinct mechanism.

Many other compounds targeting the GABAergic system, collectively known as GABAkines, are currently being tested for the treatment of neurological and stress-induced psychiatric disorders (Cerne et al., 2022; Witkin et al., 2022; Zou et al., 2023).

4.2. Non-pharmacological treatments

4.2.1. Device-based neuromodulation

In contrast to pharmacological interventions, which predominantly target neurochemical communication between cells, device-based neuromodulation offers a distinct approach by selectively targeting specific components of neural cell activity, namely the membrane potentials in axons and dendrites. Device-based neuromodulation holds the potential to serve a dual role: first, as a valuable research tool, enabling the selective and non-invasive alteration of neural excitability to explore its effects on brain circuits and behavior; second, as an effective non-invasive therapeutic approach for stress-induced cognitive dysfunctions (Begemann et al., 2020). In this section, we describe clinical studies.

4.2.1.1. Transcranial magnetic stimulation (TMS). During TMS, an alternating magnetic field produces weak electrical currents in the brain. The precise control of the magnetic field allows for non-invasive targeted stimulation, making it a valuable tool in neuroscience research and clinical practice. In 2008, TMS became FDA-approved for TRD. In 2017, deep TMS was approved as an adjunct treatment for OCD, and in 2020, for smoking cessation. The disadvantage of TMS is that it must be applied in a specialized clinical facility, as the equipment is large and expensive.

To test the hypothesis that impulsivity could be associated with poor weight management in obese patients, one group received deep TMS with active stimulation in the PFC and insula for 5 weeks, while the other received sham stimulation. The results showed a reduction of impulsivity in patients receiving deep TMS accompanied by significant improvement in body mass index, illustrating the effectiveness of deep TMS therapy in restoring the top-down inhibitory control of the PFC (Luzi et al., 2021).

A recent review evaluating the effectiveness of repetitive TMS (rTMS) to the PFC for TRD concludes that rTMS is reliable, well-tolerated, and efficacious (Adu et al., 2022). Nonetheless, although emerging evidence substantiates its short-term effectiveness in improving depressive symptomatology, there is a scarcity of literature supporting its long-term effects in cognitive symptom domains in TRD patients. Furthermore, to establish a standardized approach to rTMS implementation, further research is essential to explore variables such as frequency, intensity, pulse quantities, site of application, and inclusion of cognitive tests.

Regarding treatment for trauma-related disorders, a meta-analysis performed by Cirillo and colleagues (Cirillo et al., 2019) evaluating the effects of rTMS (ranging from 1 to 20 Hz) with traditional figure-of-eight coils to DLPFC indicates that rTMS is effective for PTSD and generalized anxiety disorders.

4.2.1.2. Transcranial direct current stimulation (tDCS). tDCS is a safe way to non-invasively manipulate brain activity using weak electrical currents between two electrodes, one acting as a positive pole (anode) and the other as a negative pole (cathode) over the targeted cortical regions. The effects of tDCS will vary based on the polarity

configuration, such that anodal stimulation promotes cell membrane depolarization, consequently increasing brain excitability. Cathodal stimulation has the opposite effect. The advantages of tDCS are portability and relatively low cost.

Evidence-based reviews of tDCS effectiveness in neurological and psychiatric disorders have been published (Fregni et al., 2021). Additionally, although the tDCS-induced current density is restricted primarily to the brain region surrounding the electrodes, the effects can be extended to distant neural networks, promoting broader connectivity-related effects (Ardolino et al., 2005; Cambiaghi et al., 2020). Researchers have increasingly used tDCS to investigate how cognitive and behavioral functions are linked to specific brain circuits. For example, applying anodal tDCS to the dorsolateral prefrontal cortex (DLPFC) in healthy individuals has been shown to improve planning (Dockery et al., 2009), working memory (Zaehle et al., 2011), attention (Stone and Tesche 2009), and reduced risk-taking behavior (Fecteau et al., 2007; Pripfl et al., 2013). Moreover, in patients with gambling disorder, anodal tDCS over the DLPFC improved decision-making and impulse control (Salatino et al., 2022). Another critical brain region with an established role in decision-making and impulse control is the OFC, and a small study in healthy individuals whereby anodal tDCS targeted the OFC showed improvement in decision-making and impulse control (Ouellet et al., 2015). A recent pilot study has established the feasibility of the use of tDCS over the OFC as a neuromodulatory non-invasive treatment of OCD (Fineberg et al., 2023).

In summary, non-invasive brain neuromodulation holds great promise regarding treatment options for cognitive dysfunctions. Recent research, with its emphasis on customizing brain stimulation to individual requirements, is pivotal in enhancing the effectiveness and safety of these techniques for all individuals. This personalized approach seeks to extend the advantages of brain stimulation to a broader spectrum of patients. A limited preliminary study suggested that anodal tDCS may improve extinction consolidation in patients with PTSD (Van't Wout et al., 2017).

4.2.2. Cognitive behavior therapy (CBT)

CBT encompasses a variety of techniques and strategies, including exposure therapy, aimed at identifying and modifying negative thought patterns and behaviors. Negatively biased cognitive inflexibility is present in both PTSD and depression, and it manifests as the automatic generation of thoughts, reactions, and interpretations consistently reinforced by avoidance behaviors.

Evidence-based exposure therapy treatments for PTSD revolve around reducing avoidance behaviors and actively engaging with traumatic memories. The cognitive element in the case of exposure therapy, where extinction plays a crucial role, is new learning-induced circuit-level plasticity, enabling cognitive flexibility and transitioning towards more adaptive and suitable behavioral responses. In a preclinical model of prolonged exposure therapy, one session of cue-conditioned fear extinction learning 24 h before testing rescued CUS-induced set-shifting impairments. Inhibition of protein synthesis within the IL mPFC during extinction prevented these behavioral effects, and the activity of IL mPFC glutamatergic neurons was necessary and sufficient for the therapeutic effects of extinction (Fucich et al. 2016, 2018; Paredes and Morilak 2019). At the circuit level, extinction reversed the CUS-induced attenuation of medial dorsal thalamus glutamatergic afferent-evoked electrical responses in IL mPFC (Fucich et al., 2018). While the ventral hippocampal afferent-evoked electrical responses in the IL mPFC were not affected by CUS, BDNF signaling within this pathway was necessary for the therapeutic effects of extinction (Paredes and Morilak 2023).

Although exposure therapy successfully improves PTSD-related cognitive dysfunctions (Nijdam and Vermetten 2018), a significant shortcoming is the high drop-out rate. Therefore, novel therapeutic approaches to enhance the effectiveness of exposure therapy are needed, as discussed in 4.2.3.

4.2.3. Therapy enhancement by adjunct treatment

Research evaluating novel therapeutic agents given in combination with well-established standard treatments, especially when patients have only partially responded, has gained attention in clinical and preclinical settings. The goal is to identify synergistic pairings that can enhance treatment effectiveness while minimizing the time it takes to achieve a response, and to minimize potential adverse effects or issues related to tolerability, to improve treatment results.

Krystal and Neumeister (Krystal and Neumeister 2009) proposed that combined exposure therapy and pharmacotherapy for PTSD act to enhance neuroplasticity, likely by activating neurotrophic factor signaling. In preclinical studies carried out in both male and female rats, combining a sub-therapeutic dose of ketamine with an abbreviated, sub-threshold extinction learning protocol completely reversed CUS-induced set-shifting deficits (Paredes et al., 2022). These outcomes may arise from molecular mechanisms shared by extinction and ketamine, such as enhanced neuronal plasticity in relevant circuitry (e.g., hippocampus-mPFC) or increased BDNF signaling (Paredes and Morilak 2023). Other recent research combining the entactogen phenethylamine 3,4-methylenedioxymethamphetamine (MDMA) with psychotherapy has shown improvement in PTSD symptoms Such studies suggest novel drugs that may be useful in combination with behavioral interventions to shorten treatment duration and potentially enhance efficacy (Bahji et al., 2020; Mitchell et al., 2023; Sessa et al., 2019).

4.3. Future directions and conclusions

One promising approach to achieve better treatment outcomes is associated with the characterization of biotypes of stress-related psychiatric disorders, made possible by recent advances in brain imaging and computation. Six biotypes of depression have been characterized, and each one of those biotypes are clustered based on distinct dysfunctions in large-scale brain connectivity amongst patients with varying degrees of symptomatology (Drysdale et al., 2017; Williams 2016). These clusters can provide valuable insights into clinical outcomes following treatment interventions. Of relevance to this review, biotype 6 of depression, also known as the cognitive dysfunction biotype, is characterized by disruption of cognitive control circuitry connectivity (heavily linked to the DLPFC/ACC/Precentral Gyrus/Dorsal Parietal Cortex) (Hack et al., 2023; Williams 2016), and no response to SSRIs (Tozzi et al., 2020). A clinical trial-guided study is currently in Phase 4, testing the drug guanfacine, which mechanism of action was discussed in 4.1.1.2, as a novel therapy for cognitive impairment in biotype 6 of depression, targeting the DLPFC (NCT04181736).

Therefore, assessment of individual brain connectivity maps may inform predictions regarding treatment response, facilitating selection of more tailored and effective treatments for patients with varying degrees of executive function impairment.

In summary, the field is confronted with several crucial challenges.

1. Mechanistic Insights into Subtypes: There is a need to develop a deeper mechanistic understanding of various subtypes of stress-related psychiatric disorders to pave the way to develop precise individualized therapeutic strategies. Preclinically, such insights will serve as a testing ground for tailored interventions.
2. Emphasis on Prediction and Prevention: Shifting the focus toward then predicting and preventing stress-related cognitive dysfunction is a crucial challenge. Identifying subtypes and risk factors, and strategies to mitigate them, the field can lead to significant strides in reducing the overall burden of these conditions.

These challenges underscore the need for multidisciplinary complementary research combining reductionist science, personalized medicine, and validated animal models to address stress-related cognitive dysfunctions and develop strategies to manage them before they progress to clinical disorder.

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CRediT authorship contribution statement

Milena Girotti: Writing – review & editing, Writing – original draft, Conceptualization. **Sarah E. Bulin:** Writing – review & editing, Writing – original draft, Conceptualization. **Flavia R. Carreno:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors have nothing to declare.

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