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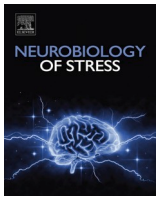

Heightened SAM- and HPA-axis activity during acute stress impairs decision-making: A systematic review on underlying neuropharmacological mechanisms

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ABSTRACT

Individuals might be exposed to intense acute stress while having to make decisions with far-reaching consequences. Acute stress impairs processes required for decision-making by activating different biological stress cascades that in turn affect the brain. By knowing which stress system, brain areas, and receptors are responsible for compromised decision-making processes, we can effectively find potential pharmaceutics that can prevent the deteriorating effects of acute stress. We used a systematic review procedure and found 44 articles providing information on this topic. Decision-making processes could be subdivided into 4 domains (cognitive, motivational, affective, and predictability) and could be referenced to specific brain areas, while mostly being impaired by molecules associated with the sympathetic-adrenal-medullar and hypothalamic-pituitary-adrenal axes. Potential drugs to alleviate these effects included α_1 and β adrenoceptor antagonists, α_2 adrenoceptor agonists, and corticotropin releasing factor receptor$_{1/2}$ antagonists, while consistent stress-like effects were found with yohimbine, an α_2 adrenoceptor antagonist. We suggest possible avenues for future research.

1. Introduction

In daily life, we are confronted with everyday choices that force use to choose between several options. For many, the majority of decisions are relatively simple under relaxing conditions. However, in some circumstances, choices have to be made while experiencing stress. In some occupations in particular, such as healthcare workers, and uniformed professions, the outcome of decisions could have great (moral) repercussions, while potentially being impaired by the effects of stress (Richardson et al., 2020; Stephenson et al., 2022). Indeed, in a laboratory setting, military personnel mistook friends more often as foes and wrongfully pulled the trigger when exposed to moderate stress (Gamble et al., 2018), proving that acute stress impacts the brain and the decision-making process profoundly (Hermans et al., 2014). Additionally, paramedics and police communicators showed more errors during medical tasks and a complex cognitive task, respectively, after a high-stress event (LeBlanc et al., 2012; Regehr et al., 2013; Regehr and LeBlanc, 2017). Brain areas responsible for cognitive capabilities associated with decision-making, such as the prefrontal cortex (PFC), reduce activity in response to high levels of stress hormones (Yan and Rein, 2021), while connections in limbic areas are heightened (Arnsten, 2009, 2015; Yu, 2016). These findings are in accordance with proposed decision-making models, in which the brain either utilizes a slow, effortful and elaborate system, or a fast, intuitive and automatic system, in which stress could "flip the switch" to the latter (Evans, 2003, 2008; Yu, 2016). When exposed to various levels of stress, people's decision-making behaviour changes, and, considering the situation at hand, potentially for the worse (Gamble et al., 2018; Starcke and Brand, 2012; Wemm and Wulfert, 2017).

When an individual experiences a potentially threatening situation, the stress systems become active. The rapid sympathetic-adrenomedullar (SAM) and slower hypothalamic-pituitary-adrenal (HPA) axis are both heavily implicated in the stress response, and release catecholamines and glucocorticoids accordingly (Arnsten, 2009; Joëls and Baram, 2009). The SAM-axis has particularly been involved in impaired cognition. There is an inverted U-shaped relationship between catecholamine levels and higher cognitive functions, as both extremely low and high levels of either dopamine and/or noradrenaline result in

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impaired working memory capacities (Arnsten, 2009). Thus, large catecholaminergic increases as a result of acute stress might surpass their ideal levels in the PFC, effectively disrupting higher cognitive behaviour. Glucocorticoids on the other hand, can further strengthen catecholaminergic activity by blocking glial removal of catecholamines in the extracellular space, thus augmenting their potentially disruptive effects at higher levels (Arnsten, 2015). Besides catecholamines and glucocorticoids, other molecules are associated with the stress response, such as corticotropin-releasing factor (CRF) and neuropeptide Y (NPY) and have differential effects on behaviour (Joëls and Baram, 2009; Stephenson et al., 2022). This plethora of stress associated molecules, that are mostly part of either SAM or HPA axes, have one way or another been connected to specific brain areas and decision-making behaviour, but their exact mechanisms remain unidentified (Sarmiento Rivera and Gouveia, 2021; von Dawans et al., 2021).

Stress molecules affect brain areas that are of particular importance regarding decision-making processes (Sarmiento Rivera and Gouveia, 2021). The frontal cortices, specifically the ventromedial prefrontal (vmPFC) (Hiser and Koenigs, 2018), anterior cingulate (ACC) and orbitofrontal (OFC) cortices (Klein-Flügge et al., 2022), are brain areas that have been strongly associated with cognitive processes such as decision-making (Datta and Arnsten, 2019). In addition, limbic areas such as the amygdala, striatum, and ventral tegmental area (VTA) (Starcke and Brand, 2012), all seem to have differential roles in decision-making behaviour, while activity in these regions and cortical areas seem to change when exposed to the effects of acute stress (Datta and Arnsten, 2019; Yan and Rein, 2021). Indeed, increases in catecholamine and glucocorticoid levels as a consequence of stress, eventually impair working memory in humans as PFC activity is reduced. In contrast, amygdala and striatal neurons increase in firing when exposed to stress molecules, resulting in stronger affective and habitual behaviour, effectively switching the brain from thoughtful, goal-directed behaviour to habitual responding (Arnsten, 2015; Yu, 2016).

By preventing the potentially deleterious effects of acute stress on decision-making in the military, disastrous short- and long-term outcomes may be prevented. Many studies have tried to identify how a wide array of stress molecules affect certain brain areas of interest associated with decision-making. In turn, psychoactive compounds may provide an opportunity to counteract these effects. Considering the complexity of both the human stress response, as well as brain activity and behaviour associated with decision-making, it is difficult to select an appropriate drug candidate that would selectively and accurately enhance decision-making capabilities in situations of acute stress. A multitude of psychoactive compounds have been examined that could influence these processes, yet a clear overview is lacking.

Our goal was to (1) provide an overview of the decision-making framework; (2) examine how the SAM and HPA axes affect decision-making; (3) find out which brain areas are implicated in specific decision-making processes and how they are affected by acute stress; and (4) investigate which pharmacological agents modulate the effects of acute stress on decision-making.

2. Methods

The study protocol was pre-registered and uploaded in PROSPERO International Prospective Register of Systematic Reviews (CRD42022331492). In addition, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.1. Literature search strategy and inclusion criteria

We selected Medline (PubMed), Embase and APA PsychINFO (OVID) as databases for the systematic literature search. A publication period interval of 2010 to current (2022, April 20th) was indicated while review type publications were excluded. We selected specific indexing terms available in each database and search terms relating to our key elements to capture articles that were not categorized in our chosen database index terms (see Supplementary Material for the full search query). Articles would be included if they (1) were randomized controlled trials (RCTs), controlled before-after (CBA) studies, and animal intervention studies published in peer-reviewed journals; (2) used healthy subjects, either human or animal, of adult age; (3) investigated phenomena associated with an acute stress response in relation to decision-making associated processes; and (4) utilized a control group or condition in their experimental design. We only included articles that were written in the English language and did not include any grey literature.

2.2. Study selection and data extraction

We first deduplicated the gathered references by using EndNote X9 software (The EndNote Team, 2013) built-in automatic deduplication feature, followed by a manual check. The remaining articles were first screened for relevancy (see Supplementary Material for inclusion and exclusion criteria) based on article titles, abstracts and key words by two investigators (LvH and FS), using ASReview Lab software (van de Schoot et al., 2021). Discrepancies were resolved by including other group members as arbitrators (AdW and BB). Following the first selection step, the complete text of the remaining articles was then screened for relevancy by one investigator (LvH), while two random sample selections of 10% of the remaining articles were screened by two other investigators (AdW and BB). Again, any discrepancies were resolved and a final selection of articles was made.

Using a standardized template created prior to data extraction, the first author (LvH) extracted the data from each remaining article. The template included bibliography, aim, takeaway, study design, sample characteristics, intervention(s) of interest, approach, primary and secondary outcomes of each study (see Supplementary Material). Considering the scope of this review and preliminary reading, we expected the data of the included articles to display low homogeneity in terms of outcome measures. Thus, we opted to extract a broad amount of data that could be utilized to construct a narrative synthesis.

2.3. Quality assessment

To assess the quality of each study, the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019) was used in studies including human subjects, while the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) RoB tool (Hooijmans et al., 2014) was utilized in studies containing laboratory animals. Using both tools, studies were assessed on their quality by the first author (LvH), in which data extracted from studies displaying risks of bias were perceived with caution in the following narrative synthesis.

2.4. Data analysis

We constructed a narrative synthesis as the collected data proved to be too heterogeneous to perform a meta-analysis.

3. Results

A total of 1306 potential articles were found using our literature search strategy. After deduplication and screening, 44 articles were included in the narrative synthesis. An overview of the selection process can be seen in Fig. 1. Out of the included articles, a majority utilized animals as test subjects ($n = 24$), with studies involving humans as a close second ($n = 18$), and only rarely using *in silico* models ($n = 2$).

3.1. Types of decision-making

After carefully reviewing every included article, we concluded that

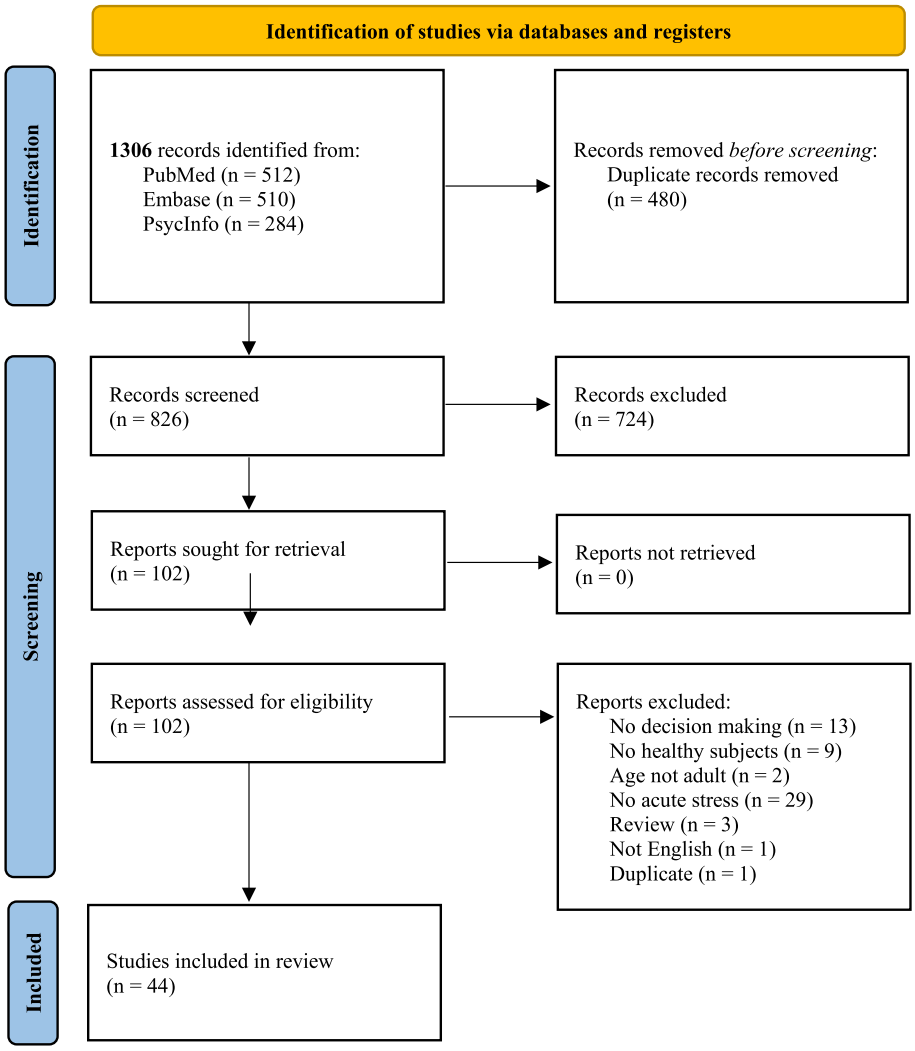

Fig. 1. The PRISMA flowchart of the research article selection process.

although the decision-making paradigm is inherently complex, 4 different subtypes could be constructed, based on the type of decision-making process that was examined (see Table 1 and Fig. 2). One of the more prevalent subtypes (n = 17), the cognitive domain, entails processes like working memory, several forms of learning, selective attention, discrimination of stimuli, cognitive flexibility, and to some extent impulse control. These processes all relate to executive functioning (Plieger and Reuter, 2020) and, not surprisingly, were often investigated alongside frontal brain area activity. On the other hand, the motivational domain (n = 20) contains exploration, place preference, discounting processes, risk-taking, reward processing, and impulse control to some extent as well. Impulse control was deemed to entail both cognitive and motivational aspects, since the ability to suppress impulses has been associated with frontal activity and executive functioning (Plieger and Reuter, 2020), while the impulse itself elicits motivation to action (Cools et al., 2019).

Quite less prevalent compared to the first two subtypes, the affective domain (n = 4) consists of innate preference, trust, and empathy, and are all related to more instinctual, emotional processes. To strengthen this distinction, we found that the amygdala was predominantly associated with this domain as one would expect. Lastly, in some studies, the emphasis was put on entropy (Muller et al., 2019; Ohira et al., 2013, 2014) and a concept called "vicarious trial and error", in which animals would look back and forth, possibly contemplating between possible options (Amemiya et al., 2014, 2016, 2020; Amemiya and Redish, 2016). After carefully reading the objectives and outcomes of these studies, we decided to categorize them into the predictability domain (n = 7). To face the differing entropic states of the environment, observers construct internal models to make predictions that in turn affect decisions (Muller et al., 2019). Likewise, vicarious trial and error behaviour seen in rats should be indicative of rats contemplating several predictions (Redish, 2016). Although making predictions is fundamental to any form of decision-making, these studies aimed to elucidate these processes.

3.2. Stress-response systems

We further determined which of the two stress-response systems were investigated in each study (see Table 1) by examining which stress molecules and brain areas were of primary interest. Accordingly, studies focussing on brain catecholamines, locus coeruleus activity, and concepts like arousal were categorized as having a focus on the SAM axis, while studies that examined the involvement of the endocrine system in acute stress were sorted to the HPA axis. Notably, a minority of studies elicited acute stress without differentiation between the SAM and HPA axis, while consecutively only measuring outcome parameters relating to either the SAM or HPA axis alone (e.g. taking only cortisol measurements) (Amemiya et al., 2020; Bellebaum et al., 2017; Bryce and Floresco, 2016; Carvalheiro et al., 2021; Karakilic et al., 2018; Kimura et al., 2013; Otto et al., 2013; Salam et al., 2017; Smith et al., 2014;

Table 1
Table summarizing all included studies.

Study	N[a]	Species	Stress System Investigated	Type of Stress Induced	Decision-Making Domain	Decision-Making Process	Effect of Stress on Decisions[b]	Brain Areas Investigated	Drug Intervention	Robust Against Bias[c]
Sun et al. (2010)	1.16 ♂ 2.12 ♂ 3.35 ♂	Rat	SAM	Pharmacological	Cognitive, Motivational	Impulse Control, Attention	↓	OFC, mPFC, NAcc	Yohimbine	–
Jepma and Nieuwenhuis (2011)	52 (26 ♂)	Human	SAM	n/a	Motivational	Exploration-Exploitation	n/a	n/a	Reboxetine, Citalopram	+
Dent and Neill (2012)	1.12 ♂ 2.15 ♂ 3.43 ♂ 4.15 ♂ 5.24 ♂ 6.24 ♂	Rat	SAM	n/a	Cognitive, Motivational	Working Memory, Place Preference	n/a	mPFC	Dopamine	–
Kim et al. (2012)	2 ♂	Rhesus Monkey	SAM	n/a	Motivational	Delay Discounting, Risk-Taking	n/a	n/a	Guanfacine	+/−
Avery et al. (2013)	10,053	Synthetic, Neuron	SAM	n/a	Cognitive	Working Memory	n/a	dlPFC	n/a	n/a
Garrido et al. (2013)	1.32 ♂ 2.23 ♂ 3.24 ♂	Rat	SAM, HPA	Affective	Cognitive	Working Memory	↓	n/a	n/a	− −
Kahnt and Tobler (2013)	21 (9 ♂)	Human	SAM	n/a	Cognitive	Associative Learning	n/a	Ventral Striatum, LC, TPJ	n/a	+ +
Kimura et al. (2013)	39 (30 ♂)	Human	HPA	Social	Motivational	Delay Discounting	↓	n/a	n/a	+
Ohira et al. (2013)	23 ♂	Human	SAM	n/a	Predictability	Entropy	n/a	Somatosensory Cortex, Insula, ACC, Pons	n/a	+ +
Otto et al. (2013)	48 ♂/♀	Human	HPA	Nociceptive	Cognitive	Reinforcement Learning, Working Memory	↓	n/a	n/a	+/−
Pabst et al. (2013)	40 ♂	Human	SAM, HPA	Social	Motivational	Risk-Taking	↓	n/a	n/a	+
Pardey et al. (2013)	43 ♂	Rat	SAM	n/a	Motivational	Delay Discounting	n/a	mPFC, OFC	SCH23390, Raclopride, Phenylephrine, Guanfacine	+/−
Abela and Chudasama (2014)	19 ♂	Rat	SAM	n/a	Motivational	Delay Discounting	n/a	vHC	Muscimol/Baclofen, Guanfacine, SCH23390	–
Amemiya et al. (2014)	1.27 ♂ 2.11 ♂	Rat	SAM	n/a	Predictability	Vicarious Trial and Error	n/a	LC	Clonidine	+
Montoya et al. (2014)	19 ♂	Human	HPA	Pharmacological	Motivational	Reward Processing	↕	NAcc, CN, BLA, CMA, SFA	Hydrocortisone	+
Ohira et al. (2014)	16 ♂	Human	SAM	n/a	Predictability	Entropy	n/a	Insula, dlPFC, IPL	n/a	+ +
Smith et al. (2014)	1.62 ♂ 2.43 ♂	Mouse	HPA	Social	Affective	Innate Preference	↓	BLA, CeA	n/a	+/−
Tervo et al. (2014)	1.38 ♂ 2.24 ♂ 3.20 ♂ 4.31 ♂ 5.8 ♂	Rat	SAM	Pharmacological	Cognitive	Reinforcement Learning	↓	ACC	DREADDs rM3D and hM4D, Muscimol, Channelrhodopsin	–
Varazzani et al. (2015)	1.3 ♂ 2.93 ♂ 3.90 ♂	Rhesus Monkey, Neuron	SAM	n/a	Motivational	Effort Discounting	n/a	SNc, LC	n/a	+
Amemiya et al. (2016)	28 ♂	Rat	SAM	n/a	Predictability	Vicarious Trial and Error	n/a	mPFC, Amygdala	Clonidine	+

(*continued on next page*)

Table 1 (*continued*)

Study	N[a]	Species	Stress System Investigated	Type of Stress Induced	Decision-Making Domain	Decision-Making Process	Effect of Stress on Decisions[b]	Brain Areas Investigated	Drug Intervention	Robust Against Bias[c]
Amemiya and Redish (2016)	1.6 ♂ 2.27 ♂	Rat	SAM	n/a	Predictability	Vicarious Trial and Error	n/a	dHC	Clonidine	+
Bryce and Floresco (2016)	1.17 ♂ 2.13 ♂ 3.9 ♂ 4.8 ♂ 5.9 ♂	Rat	HPA	Pharmacological	Motivational	Effort Discounting	↓	VTA	Alpha-helical CRF, CRF	+/−
Park et al. (2016)	1.11 ♂ 2.8 ♂	Rat	SAM	Pharmacological	Cognitive	Set-Shifting	↕	dmPFC, OFC	FG7142	+/−
Adams et al. (2017)	26 ♂	Rat	SAM	Pharmacological	Cognitive, Motivational	Impulse Control	↓	OFC	Yohimbine, Prazosin, Propranolol	+
Bellebaum et al. (2017)	36 ♂	Human	SAM	Auditory	Cognitive	Feedback Learning	≠	n/a	Modafinil	+ +
Cieślak et al. (2017)	1.19 ♂ 2.21 ♂ 3.26 ♂ 4.40 ♂ 5.136 ♂	Mouse, Neuron	SAM	n/a	Cognitive, Motivational	Set-Shifting, Attention, Impulse Control, Feedback Learning	n/a	LC	n/a	+/−
Kane et al. (2017)	1.8 ♂ 2.9 ♂ 3.15 ♂	Rat	SAM	Pharmacological	Motivational	Exploration-Exploitation	↓	LC	DREADD hM3Dq-HA	− −
Kluen et al. (2017a)	103 (51 ♂)	Human	SAM, HPA	Pharmacological	Cognitive	Associative Learning	↓	n/a	Hydrocortisone, Yohimbine	+ +
Kluen et al. (2017b)	103 (51 ♂)	Human	SAM, HPA	Pharmacological	Motivational	Risk-Taking	↕	n/a	Hydrocortisone, Yohimbine	+ +
Salam et al. (2017)	38 ♂	Human	HPA	Social, Nociceptive	Affective	Trust	↓	n/a	n/a	+
Warren et al. (2017)	22 (9 ♂)	Human	SAM	n/a	Motivational, Predictability	Exploration-Exploitation, Entropy	n/a	n/a	Atomoxetine	+
Georgiou et al. (2018)	17 (8 ♂)	Rat	SAM, HPA	Pharmacological	Motivational	Risk-Taking	↕	ACC, OFC, NAcc, Amygdala	Eticlopride, Quinpirole, Yohimbine, Antalarmin	–
Karakilic et al. (2018)	30 ♂	Rat	HPA	Nociceptive	Affective	Empathy	↑	PFC, Amygdala	n/a	–
Staton et al. (2018)	56 ♂	Mouse	HPA	Social	Affective	Innate Preference	↕	BLA, ITC	MK-1064, [Ala11, D-Leu15]-OrxB	− −
Bryce and Floresco (2019)	1.19 ♂ 2.10 ♂ 3.10 ♂ 4.9 ♂ 5.7 ♂ 6.12 ♂ 7.11 ♂ 8.15 ♂ 9.15 ♂	Rat	SAM, HPA	Pharmacological	Motivational	Effort Discounting	↕	NAcc	SKF81297, Quinpirole, PD-128,907, CRF	+
Loughnane et al. (2019)	33 ♂	Human	SAM	n/a	Cognitive	Discrimination	n/a	Parietal Cortex	Methylphenidate, Atomoxetine, Citalopram	+
Muller et al. (2019)	16 ♂/♀	Human	SAM	n/a	Predictability	Entropy	n/a	mOFC, ACC, preSMA	n/a	+
Tu et al. (2019)	1.12 ♂ 2.18 ♂ 3.18 ♂ 4.18 ♂ 5.18 ♂	Rat	SAM, HPA	Affective	Motivational	Food Foraging	↓	ACC	n/a	–

(*continued on next page*)

Table 1 (*continued*)

Study	N[a]	Species	Stress System Investigated	Type of Stress Induced	Decision-Making Domain	Decision-Making Process	Effect of Stress on Decisions[b]	Brain Areas Investigated	Drug Intervention	Robust Against Bias[c]
	6.16 ♂ 7.16 ♂									
Xiang et al. (2019)	4 ♂	Rat	SAM	n/a	Cognitive	Set-Shifting	n/a	LC	n/a	–
Amemiya et al. (2020)	20 ♂	Rat	SAM	Affective	Predictability	Vicarious Trial and Error	↓	LC, DRN, VTA	n/a	+/−
Grueschow et al. (2020)	48 (20 ♂)	Human	SAM	n/a	Cognitive	Working Memory	n/a	dlPFC, dmPFC, ACC, LC	n/a	+
Carvalheiro et al. (2021)	37 ♂	Human	SAM	Audiovisual	Cognitive	Reinforcement Learning	↓	Dorsal Striatum, NAcc, Insula	n/a	+
Sullivan et al. (2021)	39 (19 ♂), young adults	Human	SAM	n/a	Motivational	Risk-Taking	n/a	n/a	n/a	+
Sörensen et al. (2022)	1.10 2.20	Synthetic	SAM	n/a	Cognitive	Discrimination	n/a	n/a	n/a	n/a

SAM – sympathetic-adrenal-medullary; HPA – hypothalamic-pituitary-adrenal; OFC – orbitofrontal cortex; mOFC – medial orbitofrontal cortex; PFC – prefrontal cortex; mPFC – medial prefrontal cortex; dlPFC – dorsolateral prefrontal cortex; dmPFC – dorsomedial prefrontal cortex; vHC – ventral hippocampus; dHC – dorsal hippocampus; NAcc – nucleus accumbens; CN – caudate nucleus; ACC – anterior cingulate cortex; TPJ – temporoparietal junction; IPL – inferior parietal lobule; preSMA – pre-supplementary motor area; BLA – basolateral amygdala; CMA – central medial amygdala; SFA – superficial amygdala; CeA – central amygdala; ITC – intercalated cells; VTA – ventral tegmental area; SNc – substantia nigra pars compacta; LC – locus coeruleus; DRN – dorsal raphe nucleus; DREADD – designer receptors exclusively activated by designer drug; CRF – corticotropin-releasing factor; n/a – not available.

[a] Total sample sizes after exclusions. Multiple numbers in one study indicate multiple experiments carried out with different cohorts.

[b] Stress could affect decisions by enhancing (↑) or impairing (↓) decisions, while simultaneous effects (↕) or no effects (≠) were also possible.

[c] Risk of Bias was assessed using the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) for studies that included human subjects, while the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) RoB tool was used for animal studies. A score of (++) indicates a high robustness, while a score of (−−) indicates a low robustness.

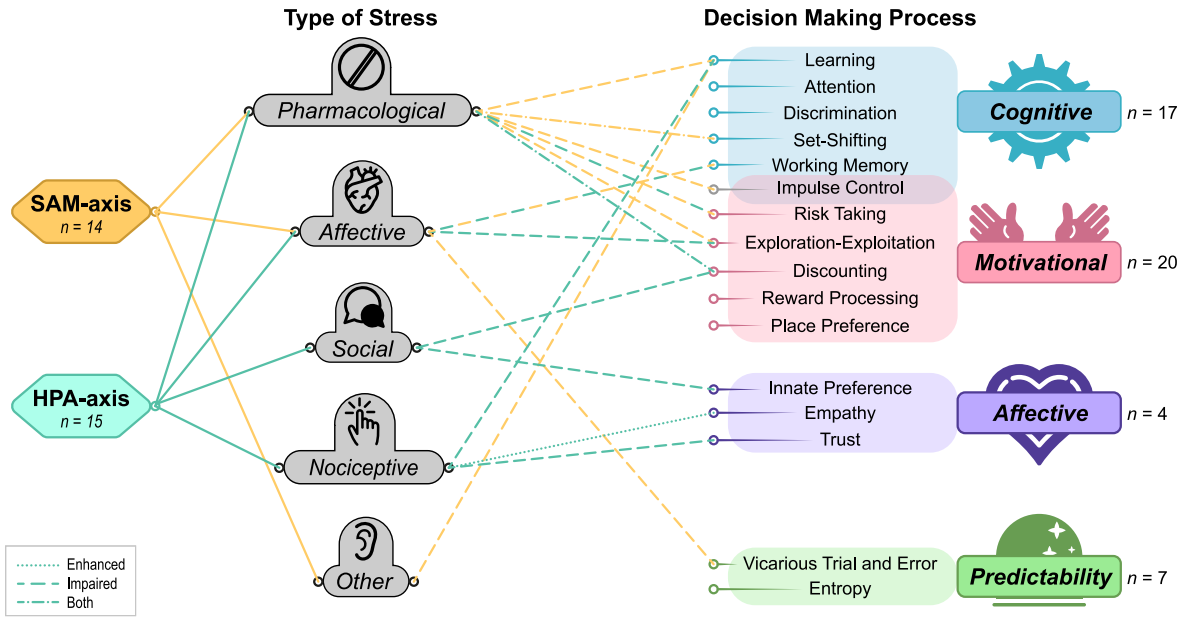

Fig. 2. An overview of all articles that utilized an acute stressor in their experimental design. A distinction was made between studies that investigated SAM axis (orange) or HPA axis (cyan) related phenomena. Effects of acute stress could either enhance, impair or do both on decision-making related processes. Decision-making processes are further categorized in four domains: cognitive (blue; $n = 17$), motivational (red; $n = 20$), affective (purple; $n = 4$), and predictability (green; $n = 7$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Staton et al., 2018). These studies were categorized to either the SAM or HPA axis, based on the outcome parameters provided, although the effects of acute stress on brain and behaviour are indistinguishable and are likely to encompass activation of both axes.

Following these criteria, the SAM axis was predominantly investigated ($n = 36$), followed by the HPA axis ($n = 15$). It should be noted that within these distinctions, a selection of studies examined outcomes relating to both axes ($n = 7$). In addition, we further categorized how stress was induced in their sample when applicable and, most importantly, what the effects of acute stress were with regard to decision-making processes.

3.2.1. SAM axis

Out of all the SAM axis oriented studies, only 14 studies utilized an actual established acute stress paradigm in which the effects of an acute stressor on decision-making processes were investigated. Specifically, pharmacological stressors were mainly used to assess the effects of SAM axis heightened activity on cognitive and motivational associated processes, all seen in Fig. 2. Using yohimbine, an α_2-adrenergic receptor antagonist, mimicking the SAM axis acute stress response, it was found that premature responding in the five-choice serial reaction time task (5CSRT) and Rat Gambling Task significantly increased in rats compared to vehicle, while attention remained unaffected (Adams et al., 2017; Georgiou et al., 2018; Sun et al., 2010). In addition, when administering yohimbine to human participants, memory generalization in an associative learning task was significantly impaired in women, but not in men (Kluen et al., 2017a), while the tendency to take risks in the balloon analogue risk task (BART) was decreased for both sexes (Kluen et al., 2017b). This cautionary effect of yohimbine on risk-taking was found in both sexes of rats as well, suggesting a translational effect (Georgiou et al., 2018). Moreover, using designer receptors exclusively activated by designer drugs (DREADDs), pharmacological control was taken over noradrenergic terminals in the anterior cingulate cortex (ACC) of rats and reinforcement learning processes were effectively blocked by heightened noradrenergic activity (Tervo et al., 2014). Similarly, DREADDs were used to stimulate locus coeruleus (LC) activity in rats, resulting in increased exploratory behaviour and reduced performance in a foraging task (Kane et al., 2017). Lastly, using FG7142, an inverse agonist of allosteric benzodiazepine binding sites in $GABA_A$ receptors that has been associated with increased dopaminergic (D_1) or noradrenergic (α_1) receptor activity, rats were able to perform better and worse on set-shifting between two rulesets, depending on which rule started first (Park et al., 2016). The ability to set-shift between sets of rules is taken as an indicator of cognitive flexibility.

Other acute stressors that were utilized included affective stressors, in which acute restraint stress increased contemplation of decisions in rats via noradrenergic mechanisms (Amemiya et al., 2020). In addition, following acute restraint stress in rats, increases in dopamine in the PFC were associated with working memory errors in a radial arm water-maze task (Garrido et al., 2013), confirming excessive levels of catecholamines to impair decision-making across multiple domains. This dopaminergic effect was also shown in a human study, in which audiovisual stress reduced the reinforcement learning capabilities in the dopaminergic striatum using fMRI (Carvalheiro et al., 2021). However, one study reported no effect of auditory stress on feedback learning processes in humans (Bellebaum et al., 2017). Based on these aforementioned experiments in which the effects of acute stress on decision-making processes are actively induced, evidence suggests that processes associated with decision-making in the cognitive domain (i.e. impulse control, learning, set-shifting, working memory), motivational domain (i.e. impulse control, risk-taking, exploration-exploitation) and predictability domain (i.e. vicarious trial and error) all deteriorate in response to acute stress. Additionally, considering the outcome parameters of these studies, increased activity of the SAM axis seems to be responsible for these impairments in behaviour.

The remaining studies that focused on decision-making phenomena associated with the SAM axis did not actively induce acute stress, but rather examined either more fundamental mechanisms behind the SAM stress response, functionally located important brain areas, or modulated molecules involved in the axis using pharmaceutics. These findings will be mentioned in other sections of this review.

3.2.2. HPA axis

All 15 studies that focused on the HPA axis in their experimental design effectively induced acute stress using various means while investigating its effect on decision-making processes as indicated in

Fig. 2. Looking at the pharmacological stress designs, hydrocortisone was utilized to investigate phenomena associated with cognitive and motivational decision-making in human subjects, while CRF was used to examine motivational decision-making in rats. Following administration of hydrocortisone, associative learning in humans was not altered compared to placebo (Kluen et al., 2017a). On the contrary, hydrocortisone administration resulted in an increase in risk-taking behaviour specifically in men, but not in women (Kluen et al., 2017b). Continuing in the motivational decision-making domain, using the Monetary Incentive Delay (MID) task in humans which is indicative of reward processing, hydrocortisone seems to decrease motivation for reward and overall motor behaviour, while also having time specific bidirectional effects on reward learning (Montoya et al., 2014). Similarly, by using effort discounting tasks in rats, CRF administration reduced overall motivation for reward while also reducing preference for putting more effort into obtaining a larger reward instead of an immediate smaller reward for less effort (Bryce and Floresco, 2016, 2019).

When observing other methods to induce acute stress, both affective and nociceptive stress were found to affect processes associated with the cognitive decision-making domain, as seen in Fig. 2. Second, affective stress was found to influence motivational decision-making. Third, the effects of nociceptive stress were investigated in relation to affective decision-making. Using a food foraging test, rats exposed to affective acute restraint stress showed higher corticosterone levels and a decreased tendency to exploit food when a social competitor was present compared to non-stressed rats (Tu et al., 2019), showing how glucocorticoids might affect social aspects of decision-making. Again, using acute restraint stress, the number of errors in a radial arm water-maze task increased, indicative of impaired spatial working memory in rats (Garrido et al., 2013). Furthermore, in a different cohort of the same study, an increase of corticosterone after the same stress procedure was found, suggesting an involvement of corticosterone in working memory impairment, although no direct relationship was measured. Interestingly, working memory capacity seems to be protective of the detrimental effects of cortisol in acute nociceptive stress on reinforcement learning in humans, as subjects scoring higher on a measurement of working memory capacity were still able to utilize model-based learning strategies when exposed to nociceptive stress (Otto et al., 2013). In contrast, subjects scoring low on working memory capacity used a model-free strategy more often, indicative of decreased executive control. Nociceptive stress was also used to investigate processes in the affective decision-making domain, as trust and empathy were impaired and enhanced, respectively. Although the enhanced display of empathy in rats was associated with increased corticosterone levels following acute foot-shock stress (Karakilic et al., 2018), the detrimental effects of both nociceptive and social stress on trust in humans seem to be unrelated to cortisol (Salam et al., 2017).

Continuing with socially induced acute stress and motivational decision-making, innate preferential decision behaviour in mice to either stay or escape from a socially aggressive competitor seems to be associated with corticosterone levels. Mice that innately choose to stay instead of escape display significant higher levels of this hormone (Smith et al., 2014; Staton et al., 2018). However, this is likely because the continuation of the presence of the stressor is heightening HPA axis activity, while the stressor is removed for mice who chose to escape. Looking at humans, using the well-established Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), a distinction was made between cortisol and non-cortisol responders, since it is suggested that a specific single nucleotide polymorphism (SNP) in FK506 binding protein 5 might inherently lower or raise plasma levels of cortisol (Kimura et al., 2013). Following this distinction, cortisol responders showed a tendency to favour a lower immediate reward compared to a higher delayed reward. Lastly, using the same TSST but not making a distinction in cortisol responsivity, risky decisions were measured using the Game of Dice Task (GDT) after various amounts of time had passed. It is suggested that, following acute stress, cortisol alone did not affect risky decisions, as risk-taking only seems to be decreased after a short amount of time, indicative of early SAM axis activity instead of slightly slower HPA axis activity (Pabst et al., 2013).

In summary, glucocorticoid activity after an acute stressor seems to decrease overall decision-making capabilities in multiple domains, similarly to studies investigating the SAM axis, with some exceptions as visualized in Fig. 2. Glucocorticoids could actually enhance reward learning processes, when considering the timing of the stress molecule (Montoya et al., 2014), and mild levels of glucocorticoids might even strengthen empathetic decisions (Karakilic et al., 2018). However, considering the complex intertwined feedback between the SAM and HPA axes during an actual acute stress response, it would be preeminent to analyse processes associated with both systems, simultaneously, in one experimental design as some studies have done (Garrido et al., 2013; Georgiou et al., 2018; Kluen et al., 2017a, 2017b; Pabst et al., 2013; Tu et al., 2019), so that the role of the key players of each axis (i.e. noradrenaline, CRF, cortisol) on decision-making processes can be fully comprehended.

3.3. Brain areas

In addition to identifying different types of decision-making and observe whether the SAM- and/or HPA-axis can affect these types of decision-making, we aimed to locate brain areas involved in specific decision-making processes, while additionally discerning whether these areas are affected by acute stress. Specifically, major areas of interest included the frontal cortex ($n = 22$), amygdala ($n = 10$), striatum ($n = 8$), brainstem ($n = 10$), and midbrain ($n = 3$), while areas like the hippocampus and parietal cortex were less commonly examined, as seen in Table 2.

3.3.1. Frontal cortex

Taking a closer look at the frontal cortex, the PFC ($n = 20$) was examined most frequently. Out of these 20 investigations, 15 were found to be involved in decision-making as seen in Fig. 3. One study found that low intensity acute stress improved affective decision-making behaviour (i.e. empathy) in rats, with increased levels of vasopressin and oxytocin observed in the PFC (no further specification was given), while this effect was not found with high intensity acute stress (Karakilic et al., 2018).

When looking specifically at the rodent medial PFC (mPFC) and the cognitive decision-making domain, local dopamine injections of 5 μg into the mPFC of rats improved choice performance on a T-maze choice task indicative of working memory, while a higher dose of 20 μg impaired choice performance (Dent and Neill, 2012). In contrast, using yohimbine as a noradrenergic pharmacological stressor in rats, deterioration in attention and impulse control, were found to be unrelated to changes in phosphorylated cAMP response element-binding protein (pCREB) and phosphorylated extracellular signal-regulated kinase 42 (pERK42) in the mPFC (Sun et al., 2010). Both these proteins are known to be affected by the effects of stress and thus it is concluded that the impulsive effects of yohimbine could not be attributed to stress-related changes in mPFC activity. Continuing in the motivational domain, local injections of dopamine in the mPFC did not change place preference behaviour in rats (Dent and Neill, 2012), while local antagonism of both the D_1 and D_2 receptors in the mPFC of rats alters sensitivity to delay, increasing impulsive choice and confirming that a minimal level of catecholamines is necessary for normal decision-making behaviour (Pardey et al., 2013). Lastly, specifically in the mPFC, direct injection of an α_2 adrenoceptor agonist in the mPFC of rats prevented an increase in deliberation behaviour during a T-maze task, resulting in a decreased capacity to learn in a contemplative situation (Amemiya et al., 2016).

Studies that mention the dorsomedial PFC (dmPFC) investigate processes relating to the cognitive domain. Set-shifting, or in other words cognitive flexibility, deteriorated in response to a pharmacological stressor, which was found to be related to decreased neuronal firing

Table 2
Table summarizing all studies that investigated specific brain areas.

Study	Global Brain Area	Specific Brain Area	Brain Area Affected by Stress[a]	Involved in Decision-Making[b]	Decision-Making Domain	Decision-Making Process
Sun et al. (2010)	Frontal	OFC mPFC	↓	✓ x	Cognitive,	Impulse Control, Attention
	Frontal	NAcc	≠	x	Motivational	
	Striatum		≠			
Dent and Neill (2012)	Frontal	mPFC	n/a	✓	Cognitive, Motivational	Working Memory, Place Preference
Avery et al. (2013)	Frontal	dlPFC	n/a	✓	Cognitive	Working Memory
Kahnt and Tobler (2013)	Striatum	Ventral Striatum	n/a	✓	Cognitive	Associative Learning
	Brainstem	LC	n/a	✓		
	Other	TPJ	n/a	✓		
Ohira et al. (2013)	Parietal	Somatosensory	n/a	x	Predictability	Entropy
	Other	Cortex	n/a	✓ x		
	Frontal	Insula	n/a	x		
	Brainstem	ACC	n/a			
		Pons				
Pardey et al. (2013)	Frontal	mPFC	n/a	✓	Motivational	Delay Discounting
	Frontal	OFC	n/a	✓		
Abela and Chudasama (2014)	Hippocampus	vHC	n/a	✓	Motivational	Delay Discounting
Amemiya et al. (2014)	Brainstem	LC	n/a	✓	Predictability	Vicarious Trial and Error
Montoya et al. (2014)	Striatum	NAcc	↓	✓	Motivational	Reward Processing
	Striatum	CN	↓	✓ x		
	Amygdala	BLA	↓	x		
	Amygdala	CMA	≠	✓		
	Amygdala	SFA	≠			
Ohira et al. (2014)	Other	Insula dlPFC	n/a	✓	Predictability	Entropy
	Frontal	IPL	n/a	✓		
	Parietal		n/a	✓		
Smith et al. (2014)	Amygdala	BLA	↕	✓	Affective	Innate Preference
	Amygdala	CeA	↕	✓		
Tervo et al. (2014)	Frontal	ACC	↓	✓	Cognitive	Reinforcement Learning
Varazzani et al. (2015)	Midbrain	SNc	n/a	✓	Motivational	Effort Discounting
	Brainstem	LC	n/a	✓		
Amemiya et al. (2016)	Frontal	mPFC	n/a	✓	Predictability	Vicarious Trial and Error
	Amygdala	Amygdala	n/a	✓		
Amemiya and Redish (2016)	Hippocampus	dHC	n/a	✓	Predictability	Vicarious Trial and Error
Bryce and Floresco (2016)	Midbrain	VTA	↓	✓	Motivational	Effort Discounting
Park et al. (2016)	Frontal	dmPFC	↓	✓ n/a	Cognitive	Set-Shifting
	Frontal	OFC	↓			
Adams et al. (2017)	Frontal	OFC	↓	✓	Cognitive, Motivational	Impulse Control
Cieślak et al. (2017)	Brainstem	LC	n/a	✓	Cognitive, Motivational	Set-Shifting, Attention, Impulse Control, Feedback Learning
Kane et al. (2017)	Brainstem	LC	↑	✓	Motivational	Exploration-Exploitation
Georgiou et al. (2018)	Frontal	OFC	≠	x	Motivational	Risk-Taking
	Striatum	NAcc	≠	✓		
	Amygdala	Amygdala	↑	✓		
Karakilic et al. (2018)	Frontal	PFC	↑	✓	Affective	Empathy
	Amygdala	Amygdala	↑	✓		
Staton et al. (2018)	Amygdala	BLA	n/a	n/a	Affective	Innate Preference
	Amygdala	ITC	n/a	n/a		
Bryce and Floresco (2019)	Striatum	NAcc	↕	✓	Motivational	Effort Discounting
Loughnane et al. (2019)	Parietal	Parietal Cortex	n/a	✓	Cognitive	Discrimination
Muller et al. (2019)	Frontal	mOFC	n/a	✓	Predictability	Entropy
	Frontal	ACC preSMA	n/a	✓ x		
	Frontal		n/a			
Tu et al. (2019)	Frontal	ACC	↓	✓	Motivational	Exploration-Exploitation
Xiang et al. (2019)	Brainstem	LC	n/a	✓	Cognitive	Set-Shifting
Amemiya et al. (2020)	Brainstem	LC	↑	✓	Predictability	Vicarious Trial and Error
	Brainstem	DRN	↑	✓ x		
	Midbrain	VTA	≠			
Grueschow et al. (2020)	Frontal	dlPFC	n/a	✓	Cognitive	Working Memory
	Frontal	dmPFC	n/a	✓		
	Frontal	ACC	n/a	✓		
	Brainstem	LC	n/a	✓		
Carvalheiro et al. (2021)	Striatum	Dorsal Striatum	↓	✓	Cognitive	Reinforcement Learning
	Striatum	NAcc	≠	✓		
	Other	Insula	↓	✓		

OFC – orbitofrontal cortex; mOFC – medial orbitofrontal cortex; PFC – prefrontal cortex; mPFC – medial prefrontal cortex; dlPFC – dorsolateral prefrontal cortex; dmPFC – dorsomedial prefrontal cortex; vHC – ventral hippocampus; dHC – dorsal hippocampus; NAcc – nucleus accumbens; CN – caudate nucleus; ACC – anterior cingulate cortex; TPJ – temporoparietal junction; IPL – inferior parietal lobule; preSMA – pre-supplementary motor area; BLA – basolateral amygdala; CMA – central medial amygdala; SFA – superficial amygdala; CeA – central amygdala; ITC – intercalated cells; VTA – ventral tegmental area; SNc – substantia nigra pars compacta; LC – locus coeruleus; DRN – dorsal raphe nucleus; n/a – not available.

[a] Stress could affect brain areas by enhancing (↑) or impairing (↓) them, while simultaneous effects (↕) or no effects (≠) of stress were also possible.

[b] Brain areas could be either involved (✓) or not involved (x) in decision-making processes.

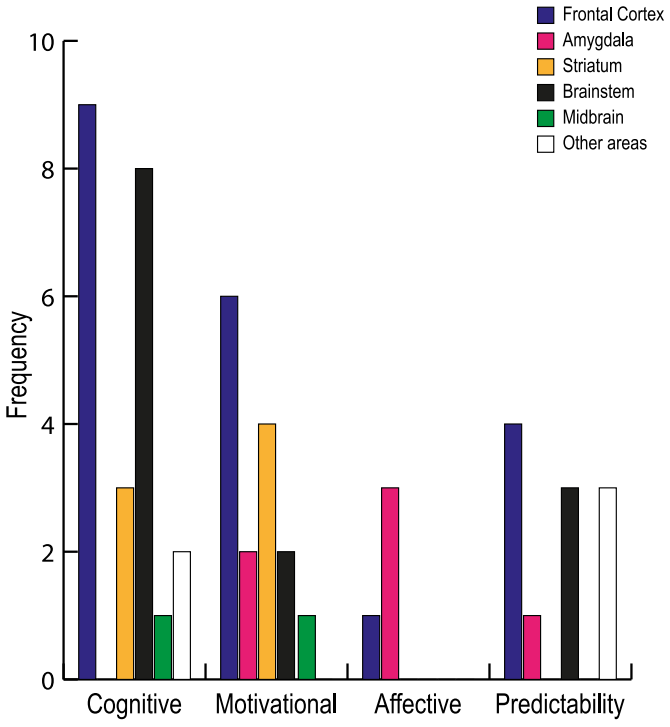

Fig. 3. Frequencies of brain areas that were involved in decision-making processes, subdivided into the 4 decision-making domains. Frontal cortex ($n = 20$), amygdala ($n = 6$), striatum ($n = 7$), brainstem ($n = 13$), midbrain ($n = 2$), and other brain areas ($n = 5$).

in the dmPFC of rats (Park et al., 2016). In a similar vein, a functional coupling was found between the dmPFC and the LC noradrenergic arousal system during an emotional Stroop task testing working memory in humans, in which the heightened reaction time in conflict trials compared to non-conflict trials was strongly related to brain activity in these regions (Grueschow et al., 2020). Again, it seems that catecholaminergic activity which is heightened in stressful situations, has the ability to deteriorate functioning in specific frontal areas, effectively disrupting cognitive processes involved in decision-making.

Three studies examined the dorsolateral PFC (dlPFC), of which two investigated the cognitive decision-making domain. Confirming what was found *in vivo* in the dmPFC and using a computational model based on actual dlPFC neurons, the inverted U-curve of catecholaminergic activity on working memory was confirmed *in silico* (Avery et al., 2013), suggesting that both these brain areas are similarly susceptible to catecholaminergic levels, even across methodological domains. In addition, the functional coupling between the LC noradrenergic system and the dmPFC was also confirmed for the dlPFC, effectively suggesting that both the dmPFC and dlPFC are similarly affected by acute stress and receive similar input (Grueschow et al., 2020). Lastly, it was found that the more unpredictable a choice was, the more activity was found in the dlPFC during exploration, while the effects of catecholaminergic activity on decision-making might also be affected by the degree of entropy in the environment (Ohira et al., 2014).

Looking at the most frontal part of the PFC, the OFC was examined numerous times, with the cognitive and motivational domains taking precedence. Unlike the effects related to CREB being absent in the mPFC, increases in pCREB and pERK42 in the OFC of rats following yohimbine administration were found to be related to decreased capabilities in attention and impulse control (Sun et al., 2010). Additionally, direct infusion of yohimbine into the OFC of rats resulted in similar deficits in impulse control, showing that this particular subregion might specifically be involved in inhibition and is susceptible to the effects of acute stress (Adams et al., 2017). On the other hand, although a different pharmacological stressor did show decreased firing patterns in OFC neurons, this change was not found to be related to cognitive flexibility, unlike the inhibited neuronal firing in the dmPFC (Park et al., 2016). When examining processes limited to motivation, antagonism of the D_2 receptors in the OFC of rats increased impulsive choice in a delay discounting framework, as was found in the mPFC (Pardey et al., 2013). Considering risk-taking behaviour however, the expression of the D_2 and the CRF receptors did not change in the OFC following pharmacological manipulations in rats, but did so in the prelimbic cortex and the amygdala (Georgiou et al., 2018). To conclude, mOFC fMRI activity was indicative of a probabilistic model of the environment in a 4-arm bandit task, while changes in pupil dilation represented these changes in mOFC activity (Muller et al., 2019).

As the final frontal brain area associated with decision-making, the ACC appears to be involved in determining whether decisions should be made based on or independently of prior experience (Tervo et al., 2014). Rats facing simulated competitors in a reinforcement learning decision-making task show that when LC input in the ACC is enhanced, rats abandon an internal decision model for stochastic decision-making, while this internal model can be restored when noradrenergic input is reduced (Tervo et al., 2014). Furthermore, a plethora of brain areas involved in a conflict resolution task were found to extend projections to the ACC using fMRI in human participants (Grueschow et al., 2020), indicating the role of the ACC as a gateway of information. Moreover, the ACC was directionally sensitive to changes in predictability: the greater the increase in entropy from a previous trial of a 4-arm bandit task, the greater the activity in the ACC, again showing how the ACC might act as a feedback area leading to changes of belief (Muller et al., 2019). Lastly, acute stress appears to decrease activity in the ACC in rats as indicated by reduced expression of c-Fos, pCREB and pERK 1/2, while exploration-exploitation behaviour seems to depend on ACC activity as well, although these effects do not seem to interact (Tu et al., 2019).

To summarize, the PFC and its subregions were of primary interest across species, while the ACC was additionally examined. Looking at the mPFC, dmPFC, dlPFC, OFC, and ACC, cognitive (i.e. working memory, set-shifting, attention, impulse control, learning), motivational (delay discounting, impulse control), and predictability (vicarious trial-and-error, entropy) decision-making either deteriorated in response to catecholaminergic modulation or were related to SAM axis activity, as visualized in Fig. 4. No relation was found or reported between these areas and HPA axis activity.

3.3.2. *Amygdala*

Out of the 10 studies that examined decision processes in the amygdala, only 6 found the region or its subregions to be involved in decision-making, as indicated in Table 2 and Fig. 3. In general, the amygdala appears to have more CRF_1 receptors in female rats compared to male rats, while a higher expression of the receptor's gene *Crhr1* in the amygdala was found to be correlated with a suboptimal performance on a motivational decision-making task following a pharmacological

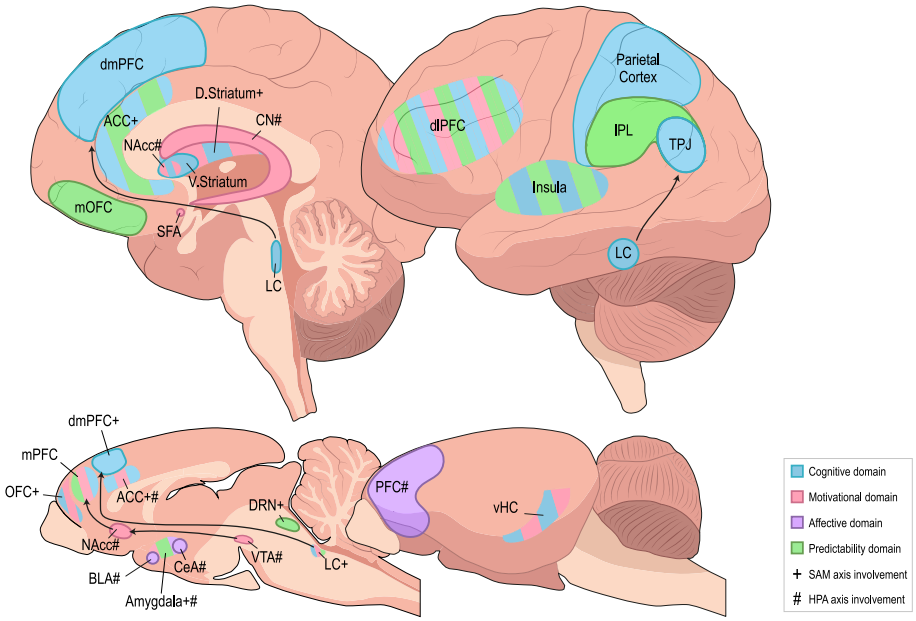

Fig. 4. Brain areas in the human (top) and rodent (bottom) brain that appear to be involved in decision-making processes and may be affected by the effects of acute stress. Brains are sliced on the midsagittal axis, displaying inner and outer areas. As colour coded in Fig. 2, four domains of decision-making were associated with different brain areas: OFC (rodent $n = 3$); mOFC (human $n = 1$); PFC (rodent $n = 1$); mPFC (rodent $n = 3$); dlPFC (human $n = 3$); dmPFC (human $n = 1$, rodent $n = 1$); vHC (rodent $n = 1$); ventral striatum (human $n = 1$); NAcc (human $n = 2$, rodent $n = 2$); dorsal striatum (human $n = 2$); CN (human $n = 1$); ACC (human $n = 2$, rodent $n = 2$); parietal cortex (human $n = 1$); TPJ (human $n = 1$); IPL (human $n = 1$); insula (human $n = 2$); amygdala (rodent $n = 3$); BLA (rodent $n = 1$); SFA (human $n = 1$); CeA (rodent $n = 1$); VTA (rodent $n = 1$); LC (human $n = 2$, rodent $n = 4$); DRN (rodent $n = 1$). Involvement of SAM and/or HPA activity during acute stress is indicated in respective brain areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

stressor (Georgiou et al., 2018). Furthermore, direct injection of an α_2 adrenoceptor agonist into the amygdala resulted into a constant state of contemplation in rats in later phases of a decision-making task, while under normal circumstances vicarious trial and error would decrease as the task progressed (Amemiya et al., 2016). These studies show that mechanisms from both the SAM and HPA axis seemingly affect amygdala structures, while decision-making is affected for the worse. Even so, acute stressors not only seem to deteriorate decision-making processes, as low acute stress actually improved empathic decisions in a novel test in which rats were trained to open a gate and save a congener faster compared to the no stress group (Karakilic et al., 2018).

Studies mentioning specific subregions of the amygdala indicate that the basolateral (BLA) and central nuclei (CeA) appear to be primarily involved in decision-making processes associated with the affective domain, as mice that chose to submit instead of escape of an aggressor displayed lower levels of brain-derived neurotropic factor (BDNF) and higher neuropeptide S gene expression, both indicative of stress related neuronal activity (Smith et al., 2014). Additionally, the reduction in anxiety that mice experienced after choosing to escape was associated with parvalbumin expressing GABAergic neurons in both the BLA and the intercalated cells (ITC), but it is not known if this effect is directly related to decision-making, or just an effect of being separated from the stressor (Staton et al., 2018). Looking at the motivational domain, administration of hydrocortisone in humans decreased activity in the BLA, although this effect did not seem to influence reward processing during a decision-making task (Montoya et al., 2014). In contrast, although the superficial amygdala (SFA) does seem to be involved in reward processing, as the SFA responded differently to reward- and non-reward trials, it was not affected by HPA axis pharmacological modulation (Montoya et al., 2014). All in all, motivational (i.e. risk-taking, reward processing) and contemplative (i.e. vicarious trial and error) decision-making seem to be affected by SAM and HPA axis activity for the worse, while affective (i.e. empathy) decision-making seems to be positively modulated by HPA axis activity, as indicated in Fig. 4.

3.3.3. *Striatum*

Out of the 8 studies that investigated the striatum, 7 found the brain region to be involved with decision-making processes, as seen in Table 2. Regarding the ventral striatum and its subregions, the expected value of stimuli guided choices during a learning decision-making task and was associated with activity in the ventral striatum of humans, using fMRI (Kahnt and Tobler, 2013). Focussing on the nucleus accumbens (NAcc) specifically, prediction errors during a learning decision-making task were shown to be related to NAcc neuronal activity, albeit not affected by acute stress (Carvalheiro et al., 2021). Moreover, the pro-impulsive effects of yohimbine in rats did not seem to be related to NAcc activity (Sun et al., 2010). In contrast, activation of D_2 receptors and direct infusion of CRF into the NAcc altered effort discounting motivational behaviour in rats, with the former resulting in an overall shift to low effort and low reward options, while the latter resulted in a shift from low effort and high reward to high effort and high reward choices (Bryce and Floresco, 2019). These disturbances of CRF on reward processing seem similar to how hydrocortisone decreased preference ratings for cues signalling reward in humans, with fMRI correlating this behaviour to decreased activity in the NAcc (Montoya et al., 2014). It seems that the NAcc is involved primarily in motivational decision-making, while mostly being affected by HPA axis stress mechanisms in addition to dopaminergic modulation. Indeed, during a risk-taking task, sex specific effects in rats were found when dopaminergic receptors were either blocked or activated, with lower expression levels of D_2 and D_3 receptors in the NAcc potentially exacerbating impulsivity in males (Georgiou et al., 2018).

With regard to the dorsal striatum, as shown in the NAcc, prediction errors during a learning decision-making task were related to activity in the dorsal striatum using fMRI. However, acute stress did seem to affect reward processing via mechanisms in the dorsal striatum unlike in the NAcc, as positive prediction errors seem to be blunted during reward learning behaviour after auditory stress, while for negative prediction errors this effect was only found in the BOLD signal (Carvalheiro et al., 2021). Specifically examining the caudate nucleus (CN), processing of

rewards appear to involve the CN besides the NAcc, with specifically reduced activity in the right caudate due to heightened levels of cortisol, following acute stress (Montoya et al., 2014). In short, cognitive (i.e. learning, impulse control) and primarily motivational (i.e. effort discounting, reward processing, risk-taking, impulse control) decision-making appears to deteriorate predominantly through heightened HPA axis activity in the ventral striatum, and its subregion the NAcc, while similarly cognitive (i.e. learning) and motivational (i.e. reward processing) in the ventral striatum, and its subregion the CN, is impaired after acute stress through both SAM and HPA axis mechanisms, seen in Fig. 4.

3.3.4. Brainstem

Within the subregions of the brainstem, the LC was investigated predominantly ($n = 8$, see Table 2) and primarily in a cognitive context, as seen in Fig. 3. After learning values associated with certain stimuli, functional connectivity was found between the LC and right temporoparietal junction (TPJ) in humans, with this connection being stronger when expected values were high (Kahnt and Tobler, 2013). On the contrary, during a value-based learning task and around the time of making a decision, activity in the LC of rhesus monkeys was correlated with pupil dilation and physical force, but not with expected rewards (Varazzani et al., 2015). Besides the coupling with the right TPJ, other functional coupling was found between the LC and the dmPFC/dlPFC, again showing a stronger connection when conflict resolution was more effective during an emotional Stroop task (Grueschow et al., 2020). This would imply that the LC system becomes more involved in decision-making when there is more at stake and decisive action needs to be taken. Regarding other cognitive processes, genetically inactivating NMDA receptors in noradrenergic neurons of mice resulted in burst activity and a decrease in a regular firing pattern in LC cells, while behaviourally mice were cognitively more flexible and had similar attention and inhibition to unaltered mice (Cieślak et al., 2017). Particularly, cognitive flexibility has been shown to be associated with the LC, as rats first exposed to a rule change showed significantly increased firing in the LC (Xiang et al., 2019). Intriguingly, this only occurs during the first rule switch, perhaps showing an effect of unpredictability about the change in environment. In addition, activity in the LC was associated with Go decisions in a go/no go paradigm in rats, as had also been found in rhesus monkeys (Varazzani et al., 2015; Xiang et al., 2019).

Examining other decision-making domains, the NMDA inactivated genetically altered mice also showed a tendency to exploit a stimulus associated with winning rewards rather than explore other options, more so than control mice (Cieślak et al., 2017). This effect was not found when tonically stimulating LC neurons, as rats disengaged more frequently and also were less able to engage in the task, as seen in reduced participation and increased omission rates (Kane et al., 2017). Studies primarily investigating predictability and decision-making show that noradrenergic neurons in the LC of rats increase their firing rate proportionally when a choice is preceded by higher contemplation, an effect which is further reinforced by acute stress (Amemiya et al., 2014, 2020). This behaviour could effectively be prevented by injecting a noradrenergic antagonist.

Besides the LC, the dorsal raphe nucleus (DRN) and pons were investigated in relation to the predictability domain. Just like the LC neurons, serotonergic DRN neuronal activity in rats increased in response to acute stress. This response appears to affect vicarious trial and error in turn, thus effectively showing that not only the catecholamines are heightened in response to an acute stressor (Amemiya et al., 2020). Finally, in humans, an increase in adrenaline in peripheral blood was associated with larger entropy, as the tendency to explore instead of exploit increased the more uncertain the choice was, but this was not related to activity in the pons (Ohira et al., 2013). To summarize, cognitive (i.e. learning, set-shifting, impulse control), motivational (i.e. exploration-exploitation), and predictive (i.e. vicarious trial and error) decision-making was associated with increased LC activity through SAM axis mechanisms, while the DRN and serotonergic system additionally seem to be implicated in heightened SAM axis impairment of predictive (i.e. vicarious trial and error) decision-making behaviour, visualized in Fig. 4.

3.3.5. Midbrain

As a last major focus, 3 studies examined subregions within the midbrain. Infusion of CRF in the ventral tegmental area (VTA) of rats appears to mimic choice behaviour as seen with central CRF infusion and acute restraint stress (Bryce and Floresco, 2016). This finding effectively pinpoints changes in effort discounting behaviour observed under conditions of acute stress to this specific area. Infusion of CRF, or acute restraint stress, reduced the preference for larger rewards requiring more effort and decreased overall motivation to work for a reward, as seen in other studies investigating HPA axis activity (Bryce and Floresco, 2016; Carvalheiro et al., 2021; Montoya et al., 2014). In contrast, the VTA does not seem to be involved in the effects of stress on predictive decision-making, as acute stress did not affect c-Fos levels, a marker for increased neuronal activity, in the dopaminergic VTA, while noradrenergic and serotonergic neurons showed elevated c-Fos levels during "vicarious trial-and-error" (Amemiya et al., 2020). However, the VTA could still be implicated in predictive or contemplative decision-making, without being affected by acute stress. Besides the VTA, the substantia nigra pars compacta (SNc) was heavily implicated in a task requiring rhesus monkeys to exert physical force in return for varying amounts of reward. The firing of SNc neurons increased with the size of the expected reward, while it decreased with the effort required to receive the reward (Varazzani et al., 2015). Behaviourally, this effect could be observed as monkeys forgo trials that required high effort costs and resulted in small rewards. Unfortunately, no stress paradigm was utilized, thus the effects of acute stress on these firing patterns and behaviour are unknown. In sum, motivational (i.e. effort discounting) decision-making seems to involve the VTA and SNc while potentially being affected by HPA axis activity (see Fig. 4).

3.3.6. Other brain areas

Other than these major focuses, some miscellaneous areas of interest were investigated. In the parietal cortex using an oddball task, the P3b component in the human event-related potential (ERP), an important marker for the later stages of information processing, was accelerated using drugs targeting the catecholamines, which also speeded reaction times in a cognitive decision-making context (Loughnane et al., 2019). The TPJ in particular seems to be functionally connected to the LC and involved in evaluating all possible options and picking the best option (Kahnt and Tobler, 2013). Adding predictability as a factor, brain activity specifically in the inferior parietal lobule (IPL) was associated with exploring different options in a decision-making task (Ohira et al., 2014). On the contrary, although the somatosensory cortex was affected by enhanced sympathetic activity, it was not related to decision-making processes (Ohira et al., 2013).

The hippocampus was examined twice: once the ventral hippocampus (vHC) and once the dorsal hippocampus (dHC). By directly activating α_2 adrenoceptors using an agonist in the vHC, rats were willing to wait longer for a larger reward instead of immediate gratification (Abela and Chudasama, 2014). In contrast, when injected locally with a $GABA_{A/B}$ receptor agonist, the opposite was found in which rats were more impulsive. Additionally, a D_1 receptor agonist was also injected in the vHC but this did not affect decision-making capabilities, confirming that dopaminergic effects on motivational decision-making do not occur in the vHC. Looking at the dorsal hippocampus (dHC), administration of a α_2 adrenoceptor agonist lowered time spent on consideration in rats; it made rats more decisive (Amemiya and Redish, 2016). However, this decisive effect was not found to be mediated by activity in the CA1 of the hippocampus, as the drug did not change firing patterns in that region compared to placebo.

Finally, the insula appears to be involved in predictive decision-making in particular, as the tendency to explore choices with uncertain odds was affected by enhanced sympathetic activity and correlated with insular activity (Ohira et al., 2013, 2014). On the other hand, the insula was found to be involved in cognitive decision-making processes as well. During a reinforcement-learning task, prediction errors that occurred during punishment learning showed a BOLD response in the insula, while also being affected by the effects of acute stress (Carvalheiro et al., 2021).

Collectively, this data provides us an overview as visualized in Fig. 4. Specific decision-making domains seem to be roughly associated with certain brain areas and well-identified pathways, e.g. the meso-corticolimbic system. As one would expect, prefrontal cortices were predominantly associated with cognitive and motivational decision-making processes, seen in Fig. 3, receiving input from catecholaminergic nuclei such as the NAcc and LC. In addition, acute stress exposure seems to affect prefrontal areas primarily by SAM axis mechanisms, while the basal ganglia were found to be predominantly affected by effects pertaining the HPA axis. Interestingly, although also observed in the PFC of rats (Karakilic et al., 2018), affective decision-making processes could effectively be pinpointed to amygdala structures, again being affected through HPA axis mechanisms (Karakilic et al., 2018; Smith et al., 2014). Furthermore, brain areas involved in predictability seem to encompass many different areas, although in human studies only the cortices seem involved (Muller et al., 2019; Ohira et al., 2013, 2014). Precisely knowing which brain area is responsible for which decision-making process and how acute stress affects these areas, could lead to new windows in effectively modulating the acute stress response using pharmaceutics.

3.4. Drug manipulations

One of the major goals of this review was to get a clear picture of how both the SAM and HPA axes and brain areas involved in decision-making could be affected via pharmacological means. As indicated in Table 3, a plethora of pharmaceutical agents has been used to either elicit effects reminiscent of acute stress, or modulate receptors involved in the acute stress response in a decision-making framework. Predominantly human ($n = 7$) and rodent ($n = 15$) subjects were implemented in study designs within a pharmacological context, while the noradrenergic ($n = 25$) and dopaminergic ($n = 10$) systems were targeted most frequently. In addition, administration techniques such as intracranial microinfusion were utilized to locally distribute a pharmaceutical agent without affecting the whole brain. This effectively allowed observation whether specific brain areas were involved in the neuromodulatory properties of a specific agent. Following these techniques, mainly the frontal cortex was locally injected.

3.4.1. Noradrenaline

Noradrenergic modulation involved adrenoceptor subtype agonists and antagonists, selective reuptake inhibitors, and designer receptors exclusively activated by designer drugs (DREADDs). Antagonizing the α_2 adrenoceptor using yohimbine, effectively increasing noradrenergic transmission by reducing clearance in the synaptic cleft, induced consistent stress-like effects across species, while decision-making processes across cognitive and motivational domains deteriorated (Adams et al., 2017; Georgiou et al., 2018; Kluen et al., 2017a; Sun et al., 2010). Specifically, local administration of yohimbine in the OFC seems to deteriorate impulse control in rats (Adams et al., 2017; Sun et al., 2010), while intraperitoneally administered yohimbine deteriorated performance in a risk-taking task by making rats more risky (Georgiou et al., 2018). Only when looking at risk-taking behaviour in human participants did yohimbine not make participants more risky, but instead made participants more careful compared to placebo (Kluen et al., 2017b), although cognitive processes such as associative learning do seem to be affected for the worse (Kluen et al., 2017a).

When agonizing the α_2 adrenoceptor using clonidine, mixed results are found. Following intraperitoneal injection or intracranial microinfusion in the mPFC of rats, clonidine seems to make rats less contemplative when exposed to novel decisions (Amemiya et al., 2014, 2016; Amemiya and Redish, 2016). However, rats exposed to placebo show persistent learning effects during the decision-making task, decreasing behaviour reminiscent of contemplation, while rats exposed to clonidine display a constant low level of this behaviour. The opposite was found when directly injecting into the amygdala, as rats showed a constant state of contemplation throughout the task (Amemiya et al., 2016), effectively showing that α_2 adrenoceptor activation has region specific effects. Specifically agonizing the α_{2A} adrenoceptor subtype using guanfacine, enhanced effects on decision-making were observed. After intramuscular injection, guanfacine effectively increased the tendency of rhesus monkeys to delay effort for higher rewards compared to instant, albeit less, gratification, only when decision-making parameters were certain (Kim et al., 2012). In accordance, locally administering guanfacine in the vHC of rats resulted in similar effects, decreasing impulsivity and increasing willingness to wait for a larger reward (Abela and Chudasama, 2014). Even so, intracranial microinfusion of guanfacine in the OFC of rats did not influence impulsivity (Pardey et al., 2013), indicating that guanfacine's effects might be due to altered hippocampal activity.

Looking at the α_1 and β adrenoceptor, intraperitoneal injection of α_1 antagonist prazosin and β antagonist propranolol, improved impulsivity in rats elicited by α_2 adrenoceptor antagonism via yohimbine, while this effect could not be replicated following local infusion in the OFC (Adams et al., 2017), suggesting that the enhancing effects on impulse control lay elsewhere in the brain. Indeed, in another study, intracranial microinfusion of prazosin in the mPFC and OFC of rats again showed no effect on impulsive choice (Pardey et al., 2013). Another enhancing target entailed the noradrenaline transporter (NAT), as inhibiting this transporter by oral administration of both methylphenidate and atomoxetine in humans showed faster decisions and earlier peak latencies of the well-known P3b peak in human ERP, compared to placebo (Loughnane et al., 2019). Additionally, atomoxetine improved exploration-exploitation behaviour in humans, by reducing random exploration of different options with high decision noise and making decisions more resolute (Warren et al., 2017). In contrast, following the oral administration of another NAT inhibitor, reboxetine, no effects were found with regard to task engagement and exploration behaviour in humans (Jepma and Nieuwenhuis, 2011).

Lastly, utilizing a relatively novel technique, DREADDs were implemented to locally mimic the effects of noradrenaline in specific brain areas. Enhancing noradrenergic input into the ACC using rM3D receptors, induced rats to switch decision-making strategies by ignoring earlier learnt rules and make completely random choices. When noradrenergic input was lowered following activation of hM4D receptors in the ACC, favourability for the earlier strategy using learnt rules was restored (Tervo et al., 2014). This would indicate that enhanced SAM activity potentially disrupts the role of higher cognition in decision-making, as proposed by earlier decision-making models (Evans, 2003, 2008; Yu, 2016). Besides cognition, directly activating hM3Dq receptors in the LC show that stimulation of LC neurons result in decreased exploitative behaviour in favour of explorative behaviour, reducing performance in the task (Kane et al., 2017), and showing that both the cognitive and motivational domains are affected by noradrenergic DREADD modulation.

Based on these findings, yohimbine, an α_2 adrenoceptor antagonist, affected cognitive (i.e. impulse control) and motivational (i.e. impulse control, risk-taking) decision-making processes in animals through SAM axis stress-like effects, while in human participants cognitive (i.e. learning) decision-making is similarly impaired. Using α_2 adrenoceptor agonists, potential beneficial effects on cognitive (i.e. impulse control), motivational (i.e. impulse control, delay discounting), and predictive (i.e. vicarious trial and error) decision-making is reported. Similarly,

Table 3
Table summarizing all studies that utilized a pharmacological agent.

Study	Species	Drug Administration	Active pharmaceutical agent	Neurotransmitter involved	Receptor Binding	Receptor	Effect Drug on Decision-Making[a]	Decision-Making Domain	Decision-Making Process
Sun et al. (2010)	Rat	Intraperitoneal injection	Yohimbine	Noradrenaline	Antagonist	α_2	↓	Cognitive, Motivational	Attention, Impulse Control
Jepma and Nieuwenhuis (2011)	Human	Oral	Reboxetine	Noradrenaline	Antagonist	NAT	≠	Motivational	Exploration-Exploitation
			Citalopram	Serotonin	Antagonist	SERT	≠		
Dent and Neill (2012)	Rat	Intracranial microinfusion	Dopamine	Dopamine	Agonist	D_1-family, D_2-family	↕	Motivational	Place Preference
Kim et al. (2012)	Rhesus Monkey	Intramuscular injection	Guanfacine	Noradrenaline	Agonist	α_{2A}	↑	Motivational	Delay Discounting, Risk-Taking
Pardey et al. (2013)	Rat	Intracranial microinfusion	SCH 23390	Dopamine	Antagonist	D_1	↓	Motivational	Delay Discounting
			Raclopride	Dopamine	Antagonist	D_2	↓		
			Phenylephrine	Noradrenaline	Agonist	α_1	≠		
			Guanfacine	Noradrenaline	Agonist	α_{2A}	≠		
Abela and Chudasama (2014)	Rat	Intracranial microinfusion	Muscimol/Baclofen	GABA	Agonist	$GABA_{A/B}$	↓	Motivational	Delay Discounting
			Guanfacine	Noradrenaline	Agonist	α_{2A}	↑		
			SCH 23390	Dopamine	Antagonist	D_1	≠		
Amemiya et al. (2014)	Rat	Intraperitoneal injection	Clonidine	Noradrenaline	Agonist	α_2	↓	Predictability	Vicarious Trial and Error
Montoya et al. (2014)	Human	Oral	Hydrocortisone	Cortisol	Agonist	MR/GR	↓	Motivational	Reward Processing
Tervo et al. (2014)	Rat	DREADD	LC-rM3D	Noradrenaline	Agonist	DREADD	↓	Cognitive	Reinforcement Learning
		Intracranial microinfusion	LC-hM4D	Noradrenaline	Antagonist	DREADD	↑		
			Muscimol	GABA	Agonist	$GABA_A$	↑		
		Optogenetics	Channelrhodopsin	Noradrenaline	Agonist	n/a	↓		
Amemiya et al. (2016)	Rat	Intracranial microinfusion	Clonidine	Noradrenaline	Agonist	α_2	↓	Predictability	Vicarious Trial and Error
Amemiya and Redish (2016)	Rat	Intraperitoneal injection	Clonidine	Noradrenaline	Agonist	α_2	↑	Predictability	Vicarious Trial and Error
Bryce and Floresco (2016)	Rat	Intracranial microinfusion	Alpha-helical CRF	CRF	Antagonist	$CRF_{1/2}$	↑	Motivational	Effort Discounting
			CRF	CRF	Agonist	$CRF_{1/2}$	↓		
Park et al. (2016)	Rat	Intraperitoneal injection	FG7142	GABA	Inverse Agonist	$GABA_A$	↕	Cognitive	Set-Shifting
Adams et al. (2017)	Rat	Intracranial microinfusion	Yohimbine	Noradrenaline	Antagonist	α_2	↓	Cognitive, Motivational	Impulse Control
			Prazosin	Noradrenaline	Antagonist	α_1	≠		
		Intraperitoneal injection	Propranolol	Noradrenaline	Antagonist	β	≠		
			Yohimbine	Noradrenaline	Antagonist	α_2	↓		
			Prazosin	Noradrenaline	Antagonist	α_1	↑		
			Propranolol	Noradrenaline	Antagonist	β	↑		
Bellebaum et al. (2017)	Human	Oral	Modafinil	n/a	n/a	n/a	↓	Cognitive	Feedback Learning
Kane et al. (2017)	Rat	DREADD	LC-hM3Dq-HA	Noradrenaline	Agonist	DREADD	↓	Motivational	Exploration-Exploitation
Kluen et al. (2017a)	Human	Oral	Yohimbine	Noradrenaline	Antagonist	α_2	↓	Cognitive	Associative Learning
			Hydrocortisone	Cortisol	Agonist	MR/GR	≠		
Kluen et al. (2017b)	Human	Oral	Yohimbine	Noradrenaline	Antagonist	α_2	↑	Motivational	Risk-Taking
			Hydrocortisone	Cortisol	Agonist	MR/GR	↓		
Warren et al. (2017)	Human	Oral	Atomoxetine	Noradrenaline	Antagonist	NAT	↑	Motivational, Predictability	Exploration-Exploitation, Entropy
Georgiou et al. (2018)	Rat	Intraperitoneal injection	Eticlopride	Dopamine	Antagonist	D_2	↓	Motivational	Risk-Taking
			Quinpirole	Dopamine	Agonist	$D_{2/3}$	↑		
			Yohimbine	Noradrenaline	Antagonist	α_2	↓		
			Antalarmin	CRF	Antagonist	$CRF_{1/2}$	↑		
Staton et al. (2018)	Mouse	Intracranial microinfusion	MK-1064 [Ala11, D-Leu15]-OrxB	Orexine	Antagonist	Orx_2	≠	Affective	Innate Preference
				Orexine	Agonist	Orx_2	≠		
Bryce and Floresco (2019)	Rat	Intracranial microinfusion	SKF 81297	Dopamine	Agonist	D_1	≠	Motivational	Effort Discounting
			Quinpirole	Dopamine	Agonist	$D_{2/3}$	↓		
			PD 128,907	Dopamine	Agonist	D_3	≠		
			CRF	CRF	Agonist	$CRF_{1/2}$	↕		
Loughnane et al. (2019)	Human	Oral	Methylphenidate	Dopamine/ Noradrenaline	Antagonist	DAT/NAT	↑	Cognitive	Discrimination
			Atomoxetine		Antagonist	NAT	↑		
			Citalopram	Noradrenaline Serotonin	Antagonist	SERT	≠		

DREADD – designer receptors exclusively activated by designer drug; CRF – corticotropin-releasing factor; NAT – noradrenaline transporter; DAT – dopamine transporter; SERT – serotonin transporter; GABA – gamma-aminobutyric acid; MR – mineralocorticoid receptor; GR – glucocorticoid receptor; n/a – not available.

[a] Pharmaceutical agents could affect decision-making processes by either enhancing (↑) or impairing (↓) them, while simultaneous effects (↕) or no effects (≠) were also possible.

antagonizing either the α_1 or the β adrenoceptor improved impulse control in stressed rats, pertaining to both cognitive and motivational decision-making domains, while NAT antagonists seem to improve cognitive (i.e. working memory) and motivational (i.e. exploration-exploitation) decision behaviour.

3.4.2. Dopamine

Studies that examined dopaminergic modulation of decision-making, usually involved the $D_{1/2}$-family of dopamine receptors or the dopamine transporter (DAT). Following intracranial microinfusion of different doses of dopamine directly into the mPFC of rats, both enhancing and impairing effects on decision-making were found. Agonism of all dopamine receptor subtypes expressed in the mPFC with a dose of 5 μg of dopamine improved choice performance on a T maze task, while a higher dose of 20 μg impaired performance (Dent and Neill, 2012). As stated earlier, these dose-dependent effects of dopamine agonism is reminiscent of the inverted U-curve relationship also seen in noradrenergic signalling.

Targeting the D_1 specifically, intracranial microinfusion of the agonist SKF 81297 directly into the NAcc core and shell of rats did not affect effort discounting behaviour (Bryce and Floresco, 2019). In addition, local microinfusion of the D_1 receptor antagonist SCH 23390 in the vHC or OFC of rats did not seem to affect delay discounting behaviour (Abela and Chudasama, 2014; Pardey et al., 2013), while infusing directly into the mPFC did increase impulsive behaviour in a delay discounting task (Pardey et al., 2013). This gives the inclination that dopaminergic signalling affects impulsivity via the D_1 receptor specifically in the mPFC. Looking at the D_2 receptor, similar effects of antagonism on impulsive behaviour were found in the mPFC as with D_1 receptor antagonism, with additional local effects in the OFC (Pardey et al., 2013). However, intracranial microinfusion of the $D_{2/3}$ agonist quinpirole into the NAcc core and shell increased impulsive tendencies and reduced effort discounting behaviour in rats, unlike D_1 agonism via SKF 81297 (Bryce and Floresco, 2019). Interestingly, intraperitoneal injection of quinpirole revealed a sex specific effect of risk-taking behaviour of rats, as female rats significantly chose the less ideal option through less risky behaviour compared to males (Georgiou et al., 2018). Additionally, when intraperitoneally injected with eticlopride, a more specific D_2 antagonist, males display more risky behaviour, while females remain unaffected (Georgiou et al., 2018), suggesting that dopamine receptor expression may be sex specific. Lastly, as previously mentioned, oral administration of methylphenidate in humans showed improved information processing, by blocking both the NAT and DAT (Bryce and Floresco, 2019).

In short, direct infusion of dopamine into the rat mPFC, agonizing al dopaminergic receptors, bidirectionally affected cognitive (i.e. working memory) decision-making. Additionally, dopamine receptors seem to be less predictable in their effects on decision-making, as both agonists and antagonists of D_2 receptors, and antagonists of D_1 receptors seem to either have no effect or affect cognitive (i.e. impulse control) and motivational (i.e. impulse control, effort discounting, risk-taking) for the worse. Nevertheless, an increase of dopamine and noradrenaline within the synaptic cleft seems to enhance cognitive processes.

3.4.3. Corticotropin-releasing factor

Now examining neurotransmitters involved in the HPA axis, intraventricular infusion of CRF binding to receptors in the whole brain of rats reduced effort discounting behaviour, increasing impulsivity, like observed in rats exposed to restraint acute stress (Bryce and Floresco, 2016). Furthermore, when infused intracranially in the VTA, similar effects were found compared to central infusion or restraint stress, while infusion in the NAcc core shifted choices from low effort and high reward to high effort and high reward (Bryce and Floresco, 2016, 2019). This gives the inclination that CRF primarily deteriorates motivational decision-making in the VTA. Looking at $CRF_{1/2}$ receptor antagonists, both alpha-helical CRF and antalarmin show enhancing effects on motivational decision-making when exposed to acute stress, as impulsivity was decreased and improved risk-taking behaviour in rats, respectively (Bryce and Floresco, 2016; Georgiou et al., 2018). Thus, besides potential SAM axis associated pharmacological modulators, HPA axis related impairments on decision-making could be counteracted using $CRF_{1/2}$ antagonists.

3.4.4. Glucocorticoids

Only tested in humans, oral administration of hydrocortisone, which binds to both the mineralocorticoid (MR) and glucocorticoid receptor (GR), seems to affect processes relating to the motivational decision-making domain, as motivation for reward decreased and the tendency to take risks in men increased (Kluen et al., 2017b; Montoya et al., 2014). On the contrary, associative learning seems to be unaffected in humans following hydrocortisone administration, suggesting that the motivational domain is particularly affected.

3.4.5. Other agents

Besides the more commonly tested agents, the serotonin transporter (SERT) was blocked in two studies, using citalopram. Antagonizing the transporter and raising levels of serotonin in the synaptic cleft did not seem to affect cognitive and motivational decision-making behaviour in humans (Jepma and Nieuwenhuis, 2011; Loughnane et al., 2019). Zooming in on GABAergic modulation, using a combination of $GABA_A$ agonist muscimol and $GABA_B$ agonist baclofen, intracranial microinfusion in the vHC of rats resulted in more impulsive behaviour and impaired delay discounting (Abela and Chudasama, 2014). Moreover, local infusion of muscimol into the mPFC significantly impaired the ability of rats to learn and adapt to a new choice strategy (Tervo et al., 2014), emphasizing the delicate balance needed in both hippocampal and prefrontal areas for cognitive and motivational decision-making. The $GABA_A$ inverse agonist FG7142, a pharmacological stressor, decreased neuronal firing in the dmPFC and OFC of rats, resulting in both enhanced and impaired set-shifting capabilities, depending on which rule started first (Park et al., 2016). Choice behaviour of rats under pharmacological stress seems to bias sensory-based processes, as the light ruleset took less trials to learn compared to the location ruleset and less mistakes were made (Park et al., 2016). Lastly, an orexin agonist and antagonist were used to induce anxiolysis and anxiogenesis in mice but this was not related to decision-making behaviour (Staton et al., 2018).

Looking at neuromodulation overall, we can observe some clear patterns. Particularly antagonizing the α_2 adrenoceptor using yohimbine seems to impair decision-making across both the cognitive and motivational domains in multiple species (Adams et al., 2017; Georgiou et al., 2018; Kluen et al., 2017a; Sun et al., 2010). Similarly, albeit less frequently observed, antagonizing the D_2 receptor seems to impair the same decision-making domains (Bryce and Floresco, 2019; Georgiou et al., 2018; Pardey et al., 2013), suggesting that some release and binding of both catecholamines is necessary for adequate cognitive and motivational capabilities, as theorized in the inverted U-curve and confirmed *in silico* (Avery et al., 2013). In contrast, using selective noradrenaline reuptake inhibitors (SNRIs) or agonizing the α_{2A} adrenoceptor using guanfacine appears to enhance decision-making by reducing impulsive tendencies and increasing overall choice performance across species (Abela and Chudasama, 2014; Bryce and Floresco, 2019; Kim et al., 2012; Loughnane et al., 2019). Besides receptor signalling involving SAM axis molecules, HPA axis neuromodulation has the capacity to impair decision-making as well. Administration of CRF and hydrocortisone in rats and humans, respectively, resulted in impaired motivational decision-making in particular (Bryce and Floresco, 2016; Kluen et al., 2017b; Montoya et al., 2014), while blocking the $CRF_{1/2}$ receptors seems to alleviate these effects caused by acute stress (Bryce and Floresco, 2016; Georgiou et al., 2018).

3.5. Risk of bias

Overall, the majority of studies showed a relative robustness against bias, based on the Cochrane RoB 2 and SYRCLE risk assessment tools (Hooijmans et al., 2014; Sterne et al., 2019). Particularly, studies using humans as subjects appeared to take several biases of risk into account, while animal studies were less informative about their methods to prevent biases, as indicated in Table 1.

3.5.1. Selection bias

Concerning selection biases, the majority of both the animal and human studies showed low risk of bias. Within studies using animals however, particularly allocation concealment appeared to be a concern, as the majority of animal studies did not provide explicit information on how intervention allocations could have been seen or not. Even so, a decent number of studies did try to counteract allocation bias by implementing randomization techniques minimizing the effect of knowing the allocation. Looking at sequence generation, one study posed a high risk of selection bias. Mice were not randomly distributed to groups, but were allocated based on behavioural phenotype in the task, *a posteriori*, resulting in uneven groups (Staton et al., 2018). Furthermore, considering baseline characteristics of the study sample, in one study no information was given on animal's age, weight and sex, posing high risk of selection bias (Kane et al., 2017). Lastly, one study did not mention any randomization in allocation sequence, complete baseline characteristics, and allocation concealment (Karakilic et al., 2018).

3.5.2. Performance bias

When looking at performance biases, human studies appeared to be very robust, while animal studies were more susceptible. Only one study using humans as subjects showed problems in mentioning concealment or blinding procedures leading to concerns regarding bias (Otto et al., 2013), while unfortunately, a vast majority of animal studies had trouble giving any indication on how caregivers or researchers were blinded to interventions. Luckily, most studies adhered to random housing of animals, although a minority had issues in this area as well. Animal studies that were particularly vulnerable to performance bias showed problems in both housing and concealment procedures, by not clearly mentioning any measures taken to prevent bias (Dent and Neill, 2012; Kane et al., 2017; Tervo et al., 2014).

3.5.3. Detection bias

While there appear to be no vulnerabilities in aspects relating to detection bias in studies with humans, many concerns were found in animal studies. A majority of the experiments showed issues in assessing the outcome randomly, while a majority did not indicate whether outcome assessment proceeded while being blinded to the interventions. Of particular concern were studies lacking on both fronts mostly by not providing information (Bryce and Floresco, 2016; Cieślak et al., 2017; Dent and Neill, 2012; Kane et al., 2017; Karakilic et al., 2018; Pardey et al., 2013; Park et al., 2016; Smith et al., 2014; Staton et al., 2018; Tervo et al., 2014; Tu et al., 2019), with one study even posing high risk of detection bias (Abela and Chudasama, 2014).

3.5.4. Attrition bias

Attrition bias due to problems with incomplete data proved to be fairly uncommon in both human and animal studies. In one study, not all human participants were included due to their lack of sensitivity to the task, while it was also not reported to which experimental group these subjects belonged, posing high risk of bias (Otto et al., 2013). In experiments using animals, two studies did not inform how many animals had been included in the study *a priori*, and the resulting heterogeneous sample sizes reported in various outcomes raises the suspicion if animals have been excluded for the right reasons or not (Garrido et al., 2013; Georgiou et al., 2018). Other concerns involving animal studies mostly resolved around not informing why in some analyses a different sample size was used (Kane et al., 2017; Karakilic et al., 2018; Tervo et al., 2014; Tu et al., 2019; Xiang et al., 2019).

3.5.5. Reporting bias

Reporting biases are the most difficult to investigate, as for most studies included in this review, no protocol was available online. However, some publications of both human and animal experiments appear to be more vulnerable to reporting bias than others, by using suspicious statistical procedures or contradicting the main results with additional information provided in the supplementary material. In studies involving human subjects, one study reported no main effects in drug treatment or interaction effects, and then computed a new variable in which drug sequence is investigated, potentially *a posteriori*, revealing a significant effect of drug sequence (Montoya et al., 2014). Additionally, in another study multiple paired sample T tests were used instead of an analysis that takes multiple testing into account (Salam et al., 2017). Lastly in one human study, the research group decided, potentially *a posteriori*, to only include subjects that self-reported effects of stress, while in the supplementary information it was stated that more subjects had initially been included (Carvalheiro et al., 2021). In some animal studies we could not determine if outcomes or certain statistical analyses had been selected *a posteriori*. (Bryce and Floresco, 2016; Dent and Neill, 2012; Garrido et al., 2013; Kane et al., 2017; Karakilic et al., 2018; Staton et al., 2018; Sun et al., 2010; Xiang et al., 2019).

3.5.6. Other sources of bias

Finally, some miscellaneous forms of bias have been found across animal studies. Other sources of bias included potential conflict of financial interest (Amemiya et al., 2016; Kim et al., 2012; Sun et al., 2010), potential issues regarding study designs (Amemiya et al., 2016; Bryce and Floresco, 2016; Garrido et al., 2013; Kane et al., 2017; Kim et al., 2012; Staton et al., 2018; Tu et al., 2019; Varazzani et al., 2015), and potential contamination or pooling effects of drugs (Abela and Chudasama, 2014; Bryce and Floresco, 2016). Full risk assessment study profiles of each potential bias can be found in the Supplementary Materials. Results of studies that proved to be less robust against potential bias, as indicated in Table 1, should be considered with caution as more research is needed to verify these findings.

4. Discussion

Our goal was to give an overview on how acute stress affects decision-making processes and behaviour, while relating these effects to local brain areas and examining the modulatory properties of specific pharmaceutical agents in this paradigm. Out of the included articles, specific decision-making themes emerged which we categorized into 4 domains. Acute stress, elicited through various means across species, affected decision-making subtypes by activating the SAM and/or HPA axis, predominantly resulting in impaired decision-making behaviour. Looking at both rodent and human brains in particular, certain brain areas seem to be more involved in a specific decision-making subtypes (e.g. dmPFC for cognitive decision-making), while other areas are involved across multiple domains. Finally, neuromodulation through pharmacological means revealed possible pharmacological agents that can impair and enhance decision-making across species, especially by activating or supressing the SAM or HPA axes. Yohimbine in particular was found to show the most robust impairing effects as a consequence of increased SAM axis activity both in rats and humans (Adams et al., 2017; Georgiou et al., 2018; Kluen et al., 2017a; Sun et al., 2010).

4.1. Decision-making domains

Out of the decision-making processes that were investigated in the included articles, we proposed to categorize each in either the cognitive, motivational, affective or predictability domain. Although a complete

delineation is not feasible, overall, these 4 domains seem to encompass and structure the involved processes which are part of a much broader definition. Indeed, looking at other investigations, decision-making in many different contexts is mentioned (e.g. risk, ambiguity, shared, social) (Bartholomeyczik et al., 2022; Elliott et al., 2023; Gangopadhyay et al., 2021; Garrigan et al., 2016; Starcke and Brand, 2012), but an overall grouped categorization similar to ours is absent. Although social decision-making, while being abundant in the literature (Gangopadhyay et al., 2021; von Dawans et al., 2021; Wallace and Hofmann, 2021), was not included as a separate category in our subdivisions due to low frequency, we opted to merge this term with the affective domain, considering the more instinctual nature of the processes investigated (Karakilic et al., 2018; Salam et al., 2017). Following our categorization, looking at the predominantly investigated species, humans and rats, we find similar observations across both species, as both cognitive and motivational domains are investigated predominantly, and the predictability domain to a lesser extent, while the affective domain is scarcely investigated. However, some processes of decision-making, such as delay discounting, have been found to entail different brain areas when comparing healthy humans with results from animal lesion studies (Varma et al., 2023). Although a wide selection of articles was included in this review, some findings might have been missed.

4.2. Effects of acute stress on behaviour

Studies inducing acute stress with a focus on the SAM axis abundantly found deteriorated decision-making across multiple domains, while a minority of HPA axis-focused research showed some enhancing properties of acute stress, as shown in Table 1. As previously reported, higher levels of glucocorticoids seem to be associated with more altruistic or empathetic behaviour (Duque et al., 2022; Karakilic et al., 2018; Singer et al., 2017). Overall, it is implied that both SAM and HPA enhanced activity deteriorates decision-making processes in the cognitive, motivational, and predictability domains across species, in agreement with the literature (Duque et al., 2022; Morgado et al., 2015; Starcke and Brand, 2016). However, contrasting findings have been reported, as acute psychosocial stress which heightens both SAM and HPA axis activity has been proven to enhance impulse control in humans (Chang et al., 2020; Dierolf et al., 2017, 2018; Qi et al., 2017; Schwabe et al., 2013). This could be attributed to the inverted U-curve of catecholamines and cognitive performance, as participants might have been on the ideal levels of both noradrenaline and dopamine (Arnsten, 2009, 2015).

Unfortunately, about half of the studies investigating SAM axis-dependent effects did not actually include an acute stressor in its design while relating this to decision-making outcomes. Nonetheless, during both selection steps, these studies proved to adhere to the inclusion criteria that were set (view Supplementary Material) and provided valuable information regarding our research questions. Specifically, a selection of included investigations without an acute stressor confirmed the inverted U relationship of the levels of catecholamines in the rat brain and using computational models with regard to enhanced and impaired decision-making (Avery et al., 2013; Dent and Neill, 2012; Sörensen et al., 2022), as previously stated to be present in humans as well (Arnsten, 2009, 2015; Starcke and Brand, 2016).

One of the main goals in this review was to differentiate between SAM and HPA axis-dependent effects on decision-making processes. To achieve this, studies were categorized based on outcome measurements and interventions. In many cases, acute stress was elicited through non-pharmacological means, effectively activating both SAM and HPA axes indiscriminately, while only taking measurements indicative of one of the stress systems (Amemiya et al., 2020; Bellebaum et al., 2017; Carvalheiro et al., 2021; Karakilic et al., 2018; Kimura et al., 2013; Otto et al., 2013; Salam et al., 2017; Smith et al., 2014; Staton et al., 2018). Consequently, acute stress might have affected decision-making through mechanisms caused by a stress system that was not taken into account in the outcome parameters, thus not providing the complete picture. To this end, studies eliciting acute stress through pharmacological specific agents and/or measuring outcomes indicative of both the SAM and HPA axes, can more completely predict how stress influences decision-making processes.

4.3. Neurobiology of the impact of acute stress on decision-making

Following the subdivision of decision-making into 4 domains, we hoped to observe involvement of specific brain areas and neurotransmitters for each category. Although many areas appeared to be related to multiple domains, patterns of activity are noticeably in agreement with preconceived notions, as can be seen in Table 2 and Fig. 4. The frontal cortex was predominantly associated with cognitive decision-making, although motivational processes appear to be primarily investigated in frontal areas as well (Hiser and Koenigs, 2018; Klein-Flügge et al., 2022). More precisely, the PFC was associated with working memory, set-shifting, place preference, delay discounting, empathy, VTE and entropy. Working memory seems to be located in the mPFC/dmPFC and dlPFC specifically, with the catecholamines affecting performance depending on dose in both humans and rats, in accordance with the inverted U-curve (Avery et al., 2013; Dent and Neill, 2012; Grueschow et al., 2020). Furthermore, dopamine in particular seems to play a key role in motivation and activity in the mPFC, as place preference and delay discounting behaviour seem to be affected depending on dose and receptor type (Dent and Neill, 2012; Pardey et al., 2013). On the other hand, noradrenaline seems to be involved during VTE in the mPFC of rats and during heightened entropy in decision-making in the dlPFC in humans, suggesting heightened stress to elicit VTE and more entropy in decisions (Amemiya et al., 2016; Ohira et al., 2014). Interestingly, following low acute stress, higher levels of vasopressin and oxytocin were found in the PFC of rats, resulting in higher displays of empathy (Karakilic et al., 2018). In humans, similar enhanced empathy has been reported in the literature following the TSST, which is attributed to the effects of cortisol (Buchanan et al., 2012; Wolf et al., 2015).

The OFC was involved in attention, impulse control and delay discounting, with activity specifically in the mOFC relating to entropy. By increasing levels of noradrenaline as seen in acute stress, both attention and impulse control seem to be impaired through connections in the OFC in rats (Sun et al., 2010). Interestingly, this effect can be reversed by using specific adrenoceptor antagonists (Adams et al., 2017). Blocking the D_2 receptor in the OFC also increases impulsive choice in a delay discounting framework (Pardey et al., 2013), suggesting again that a certain balance of catecholamines is needed for appropriate decision-making. As for humans, in fMRI, the BOLD response related to contemplations with higher entropy, indicated higher activity in the mOFC, along with wider pupil dilations, suggesting connections between arousal, entropy and both the mOFC and dlPFC (Muller et al., 2019; Ohira et al., 2014).

The ACC was associated with working memory, reinforcement learning, and exploration-exploitation. Similarly to the effects observed in the dmPFC, during conflict resolution in a working memory task, the ACC is activated as arousal is increased (Grueschow et al., 2020; Muller et al., 2019). Authors speculate a functioning coupling between the LC noradrenergic system and areas such as the dlPFC, dmPFC and the ACC. Indeed, LC signalling to the ACC mediates whether choices should be made following learned behaviour or stochastically (Tervo et al., 2014), Likewise, during acute stress, decreased activity in the ACC is found, which is likely a result of noradrenergic signalling (Tu et al., 2019). Overall, these findings come as no surprise, as dopamine is strongly innervated in the frontal cortex and plays a key role in cognition, motivation, and in the SAM axis stress response, alongside noradrenaline (Arnsten, 2009, 2015; Datta and Arnsten, 2019). Indeed, acute stress is presumed to shift the brain from a balanced state toward a less segregated and more integrative state with the frontal-temporal regions taking precedence (Wang et al., 2022).

In a similar vein, the striatum seems to be involved in both motivational and cognitive decision-making processes, as both brain areas have dense connections involved in reward processing and frequently coactivate (Berridge and Kringelbach, 2008; Delgado, 2007; Goulet-Kennedy et al., 2016; Levy and Dubois, 2006). Both ventral and dorsal striatum and its subparts seem to be involved in learning, reward processing and risk taking, although more functional network research is needed as subcortical areas often are underrepresented (Wang et al., 2022). Expected values of stimuli in an associative learning task were correlated with BOLD responses in the human ventral striatum (Kahnt and Tobler, 2013), while prediction errors during a reinforcement learning task were correlated with BOLD responses in the dorsal striatum and NAcc (Carvalheiro et al., 2021). Furthermore, as expected, learning about rewards is also related to the processing of those rewards, as both the NAcc and CN are implicated in reward processing in accordance with the literature (Arsalidou et al., 2020; Yan et al., 2023). However, both are also impaired by cortisol, as administration of hydrocortisone leads to blunted motivation for reward (Montoya et al., 2014), a finding that contradicts the elevated activation in the NAcc found following hydrocortisone in another study in humans (Oei et al., 2014). However, authors speculate that when cortisol levels reach a certain threshold, the NAcc will switch to elevated activation.

Interestingly, the amygdala mostly was associated with the affective domain (Karakilic et al., 2018; Smith et al., 2014), as the amygdala is well known to play a major role in affect across species. Indeed, innate preference and empathy were associated with activation in the amygdala, other than reward processing, risk-taking and VTE. However, unlike similar enhancing effects of corticosterone in the amygdala as seen with cortisol in the human PFC (Buchanan et al., 2012; Smith et al., 2014), corticosterone did not change innate preference behaviour. In contrast, just like in the PFC, increased levels of vasopressin and more empathetic decisions were found in the amygdala of rats following heightened corticosterone after acute stress (Karakilic et al., 2018), in accordance with human behaviour (Buchanan et al., 2012; Wolf et al., 2015). As for motivation, the superficial amygdala showed an increased BOLD response during rewarding conditions, but was unaffected by cortisol (Montoya et al., 2014), while risk-taking behaviour in rats worsened as CRF_1 receptor distribution increased (Georgiou et al., 2018). The amygdala is known to contain many CRF neurons which respond and release CRF in situations of acute stress (Chudoba and Dabrowska, 2023), which in turn might facilitate an heightened limbic response by activating LC noradrenergic neurons (Curtis et al., 2002), while executive control by the prefrontal regions is simultaneously impaired, leading to suboptimal decision-making behaviour. Overall, these findings imply that our categorization of different types of decision-making seems to be an accurate division, despite limitations. However, the affective domain in general was scarcely investigated and conclusions should be made with caution.

On the contrary, the brainstem was a major area of interest across multiple domains, particularly in cognitive context, which is not surprising considering our search strategy and topic of interest. The LC is the primary source of noradrenaline in the brain and widely innervates many areas. Interestingly, the DRN, although densely innervating many brain areas with serotonin, was barely investigated in this selection of articles and was only investigated once in a task examining contemplative behaviour (Amemiya et al., 2020), while serotonin seems to be involved in some aspects of decision-making (Crockett et al., 2015; Ohmura et al., 2021). Nonetheless, the LC was involved in working memory, associative learning, feedback learning, set-shifting, attention, impulse control, effort discounting, exploration-exploitation, and VTE. Predominantly, the LC was found to coactivate with other brain areas during cognitive decision-making processes in arousing conditions, namely the dlPFC/dmPFC (Grueschow et al., 2020), and the temporoparietal junction (Kahnt and Tobler, 2013). Other than that, tonic firing of the LC seems to be responsible for the impairing effects predominantly seen under conditions of acute stress across cognitive and motivational decision-making domains.

Lastly, due to less frequently being included in this selection of articles, areas such as the insula or the parietal cortex have been classified as miscellaneous. Despite this, these cortices seem to be involved in decision-making in an unpredictable environment more so than others (Ohira et al., 2013, 2014). Indeed, other studies seem to establish that the insula is the primary convergent region for other frontal-parietal brain regions activated in different states of ambiguity (Feng et al., 2022), while also being part of the cognitive control network under conditions of uncertainty (Wu et al., 2020).

4.4. Pharmacological neuromodulation

A primary goal of this review was to find potential drug candidates that could enhance decision-making when exposed to the effects of acute stress. Although only investigated once, the α_1 and β adrenoceptor agonists prazosin and propranolol, and $CRF_{1/2}$ receptor antagonist antalarmin could provide means to reduce the detrimental effects of acute stress on decision-making processes in humans (Adams et al., 2017; Georgiou et al., 2018). As previously stated, the α_1 and α_2 adrenoceptors display different binding affinity to noradrenaline, in which the α_2 adrenoceptor is easily agonized by noradrenaline, as seen in a calm wakeful state (Arnsten and Goldman-Rakic, 1985; Li and Mei, 1994), while the α_1 and β adrenoceptors are less sensitive, only being occupied in conditions of stress (Arnsten, 2000, 2009; Birnbaum et al., 1999). Considering the inverted U-curve of catecholamines in cognitive functioning, it would be desirable to only activate adrenoceptors needed for wakefulness, while preventing the lower affinity α_1 and β adrenoceptors from activating, potentially leading to impaired decision-making capabilities. Indeed, blocking the α_1 and β adrenoceptors proved to improve impulse control in rats, reversing the effects of α_2 antagonist yohimbine (Adams et al., 2017). To continue, antagonizing the α_2 adrenoceptor using yohimbine appears to elicit robust stress-like effects in both humans and non-humans (Adams et al., 2017; Georgiou et al., 2018; Kluen et al., 2017a; Sun et al., 2010), showing that activating this adrenoceptor subtype is necessary for optimal functioning. In contrast, agonizing the α_{2A} adrenoceptor via guanfacine in non-stressed conditions improved decision-making in rats and primates (Abela and Chudasama, 2014; Kim et al., 2012), suggesting that for optimal decision-making in humans the α_2 adrenoceptor needs to be activated, while the α_1 and β adrenoceptors need to remain silent (Arnsten, 2009, 2020), as seen in work improving cognitive control in human addiction (Fox et al., 2015; McKee et al., 2014). Interestingly, another α_2 agonist clonidine appears to be less persistent in its enhancing effects on decision-making in rats (Amemiya and Redish, 2016), even leading to impairment (Amemiya et al., 2014, 2016), but this was attributed to potentially activating postsynaptic receptors (Amemiya et al., 2016). Similarly in humans, clonidine has been proven to improve performance in a risk-taking gambling task in heroin addicts, but at the same time impair sustained attention and memory in Alzheimer's Disease (Riekkinen et al., 1999; Zhang et al., 2012). Lastly, the enhancing effects of the NAT inhibitor atomoxetine in humans might be due to increased binding to the α_2 adrenoceptor under normal conditions (Loughnane et al., 2019; Warren et al., 2017), but in conditions of acute stress the α_1 adrenoceptor might also activate, reducing its enhancing properties, as seen in dose-dependent animal work (Higgins et al., 2021; Ozga-Hess and Anderson, 2019).

Similarly to noradrenergic mechanisms, dopamine exerts its inverted U-shaped effects on cognitive processes via the D_1-and D_2-family of receptors (Arnsten, 2009). As such, agonism of the $D_{2/3}$ receptor via intraperitoneal injection of quinpirole appeared to reduce risky behaviour in rats, improving decision-making performance (Georgiou et al., 2018), showing potential as an enhancing drug. However, microinfusing the same drug in the NAcc of rats appears to impair decision-making performance in an effort discounting task (Bryce and Floresco, 2019), suggesting that dopaminergic modulation is a less suitable candidate.

Indeed, the mechanism in which the inverted U relationship of dopamine is realized in different brain areas is more difficult to precisely modulate across a range of arousal conditions, while noradrenergic mechanisms offer more clinical utility (Arnsten et al., 2015). To this end, the enhancing properties observed in non-stressful situations with the non-selective DAT/NAT inhibitor methylphenidate (Loughnane et al., 2019), raising dopamine and noradrenaline in the synaptic cleft, may not prove to be as useful in situations with higher levels of arousal.

Finally, antagonism of the $CRF_{1/2}$ receptors, locally in the VTA or throughout the whole brain was found to enhance motivational decision-making in an acute stress setting in rats (Bryce and Floresco, 2016; Georgiou et al., 2018). In agreement with findings suggesting that both CRF and glucocorticoids impair motivational decision-making processes specifically across species (Bryce and Floresco, 2016, 2019; Kluen et al., 2017b; Montoya et al., 2014), blocking the $CRF_{1/2}$ receptors using antalarmin could prove to be a useful candidate in preventing the impairing effects of acute stress on decision-making in humans. The LC is densely innervated by CRF axons originating from the amygdala amongst others (Curtis et al., 2002; Van Bockstaele et al., 1998), and stimulates the LC in a dose-dependent manner reminiscent of the inverted U-curve (Hupalo et al., 2019a). In addition, local neurons in brain areas important for decision-making processes such as the dmPFC have the capacity to synthesize CRF locally, binding to receptors and impairing behaviour in conditions of stress (Hupalo et al., 2019b). By blocking $CRF_{1/2}$ receptors during acute stress, heightened activity in the LC and local disruption in areas such as the dmPFC could be prevented, not only improving motivational decision-making, but other processes involved as well. Indeed, systematic administration of CRF_1 antagonists improves working memory under basal non-stressed conditions (Curtis et al., 2002; Hupalo and Berridge, 2016), showing cognitive enhancing properties of itself that could also potentially be observed in stressful situations.

4.5. Limitations

In an effort to reduce personal bias when reviewing the literature, a systematic approach according to PRISMA standards was performed (Page et al., 2021). During the construction of the search term, key elements were chosen based on their relevance to the subject, but also on their feasibility. Earlier constructs of the search query resulted in a higher number of potential articles to be included, but such constructs were deemed unrealizable considering the time required. Similarly, a time interval was chosen in which articles before the year 2010 were not included. Due to this, a selection of articles might not be included in the currently used search strategy. Additionally, three databases were selected based on their relevance and quality to capture the most studies fitting the criteria. The databases selected are similar to other systematic reviews following PRISMA standards (Banz et al., 2021; Rossetti et al., 2021; Tamminen et al., 2019). Although we are confident that relevant studies were included, some studies may have been missed.

Although our subdivision of decision-making processes appears to accurately convey superordinate decision-making categories, specific behavioural processes should be examined separately as well. Certain processes (e.g. impulse control, delay and effort discounting) proved to be difficult to effectively attribute to one of our categories and some overlap appears to be inevitable. Nonetheless, we ultimately decided to categorize each process to a domain which would be its most suitable representation, with only impulse control possessing characteristics of relatively equal cognitive and motivational nature.

Finally, to assess the quality of the included articles, risk of bias was assessed using validated tools, as mentioned previously (Hooijmans et al., 2014; Sterne et al., 2019). Although the majority of studies offered at least some robustness against several forms of bias, a significant portion proved to be susceptible to at least one category of bias. Caution should be taken when interpreting results from studies indicated to be susceptible to bias, as these findings might not be due to the suggested intervention. However, on average most studies with human participants appear to take bias risks into account, offering robust findings without any translational issues.

5. Conclusion

This review shows that it is possible to establish several superordinate decision-making domains based on specific processes and behaviour, namely cognitive, motivational, affective, and predictability. As previously discussed, acute stress exerts its effects on both brain and behaviour via SAM and HPA axes, in which both stress cascades predominantly impair decision-making behaviour, with an exemption of the effects of the HPA axis on affective decisions. Additionally, although decision-making processes are complex, clear patterns of neuronal activity can be found that relate to the proposed behavioural subdivisions. First, cognitive decision-making processes seem to be regulated primarily via frontal brain areas and the LC. Second, motivational decision-making predominantly encompasses frontal, striatal, and midbrain areas. The debilitating effects of acute stress on frontal brain area functioning, involved in both cognitive and motivational decision-making domains, seem to be the result of heightened SAM axis activity. In contrast, impaired functioning of striatal and midbrain areas, involved in motivational decision-making, involve the HPA axis. Finally, affective decision-making could potentially be enhanced through changes in the amygdala as a result of the HPA axis during acute stress, although other decision domains regulated by the amygdala might suffer instead. Last, decisions involving strong aspects of making predictions appear to primarily involve cortical structures (i.e. insula, TPJ, mOFC, ACC), seemingly through SAM axis mechanisms, but more precise research robust against potential bias is needed, to effectively pinpoint interactions between stress molecules and decision-making processes.

Considering these interactions of acute stress and impaired behaviour, several drug candidates might countereffect the influence of stress on decision-making, either through SAM or HPA axis modulation. More specifically, prazosin, propranolol, and guanfacine might be good candidates to alleviate the debilitating effects of heightened SAM axis activity, as these drugs have been found to improve cognitive and motivational decision-making, while antalarmin might prove to be a good countermeasure against the deleterious effects of the HPA axis on motivational decision-making. More research is needed to select a suitable pharmacological agent to prevent the effects of acute stress on decision-making. Consequently, occupations confronted with difficult choices, with potential far-reaching consequences, might benefit from the implicit enhancing properties of said pharmacological agents against the harmful effects of acute stress.

6. Contributions

LvH registered the systematic review, performed the literature search and screening, extracted data, assessed study quality, and wrote the initial draft of the manuscript. FS performed the literature screening and AdW, BB, and EG supervised the work and reviewed/edited the manuscript.

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CRediT authorship contribution statement

Lukas van Herk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Frank P.M. Schilder:** Conceptualization, Validation, Writing – review & editing. **Antoin D. de Weijer:** Conceptualization, Project administration, Supervision, Validation, Writing – review & editing. **Bastiaan Bruinsma:** Conceptualization, Project

administration, Supervision, Validation, Writing – review & editing. **Elbert Geuze:** Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100659.

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