Modeling the brain

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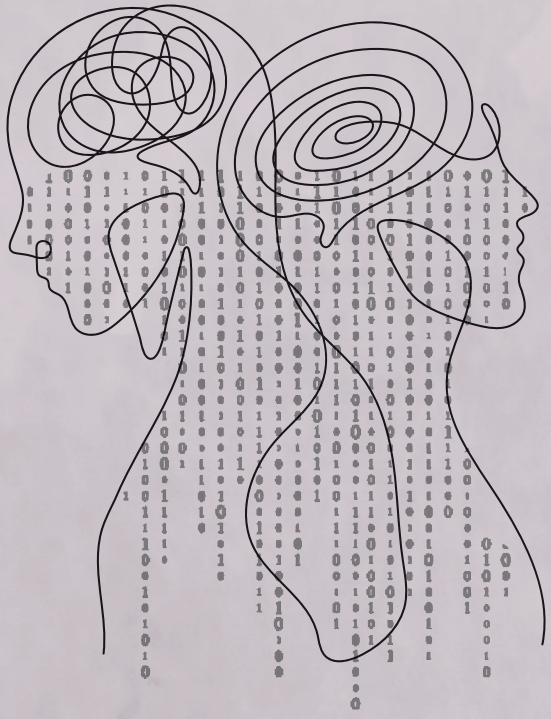
Mechanisms underlying the interplay between the multiple facets of stress and cognition



STELLA VOULGAROPOULOU

Doctoral Thesis

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Mechanisms underlying the interplay between the multiple facets of stress and cognition

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Mechanisms underlying the interplay between the multiple facets of stress and cognition

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CHAPTER 1

General Introduction & Outline of the thesis

Psychological stress

We all know the feeling of being overwhelmed, pressured by certain situations or unable to manage too many responsibilities. However, when it comes to stress research, it can be surprisingly difficult to pinpoint what exactly “stress” is, mainly due to the ambiguities and connotations around the term. The World Health Organization, WHO (2023) has defined stress as “a state of worry or mental tension caused by a difficult situation”. Although everybody experiences stress, the way people respond to it may vary significantly.

In many countries, stress is considered a major public health concern. In the United Kingdom, the Mental Health Foundation's research (2018) has found that 74% of UK adults have experienced stress at some point in their lives. The most commonly reported sources of stress were health concerns about a loved one, financial pressure, and work-related issues. In the United States, according to the Stress in America survey conducted by the American Psychological Association (2020), 78% of adults reported having experienced stress-related symptoms (with coronavirus pandemic being a significant source of stress). These symptoms included physical and emotional manifestations ranging from irritability and fatigue to changes in appetite and headaches.

Stress can affect specific populations differently. For example, students and young adults may experience stress related to career uncertainties and pressure to succeed (Foundation, 2018). Women may face higher levels of stress about their body image compared to men (Foundation, 2018). Individuals from marginalized communities may experience stress due to discrimination and inequality (Duru et al., 2012; Merkin et al., 2009). The diverse causes and consequences of stress highlight the challenges around stress research but also emphasize the importance of unraveling this complex construct by investigating both its underlying (molecular) as well as observed (cognitive/ behavioral) effects.

Acute and chronic stress

Stress can be seen as a double-edged sword. From an evolutionary perspective, it is an adaptive response. It helps us avoiding harm or pain but also prepare for an important meeting or presentation. On the flip side, if experienced extensively and/or repeatedly, it can be impairing, especially when it reaches a level that starts interfering with the ability to effectively perform our daily tasks. Stress is often divided into acute and chronic stress. Although strongly correlated, neurobiological and psychological mechanisms differ for acute and chronic stress (see below). Therefore, investigating their effects can yield important insights about their distinct as well as complimentary functions.

Acute stress has a short-term duration (minutes to hours) and arises from immediate threats or challenges, triggering a rapid reaction known as the "fight-or-flight" response. The fight-or-flight response is characterized by the release of hormones and catecholamines such as cortisol - through activation of the Hypothalamus-Pituitary-Adrenal (HPA) axis- and adrenaline -through activation of the Sympathetic-Adreno-Medullar (SAM) axis, producing well-orchestrated physiological changes, such as increased heart rate and blood pressure (Cohen et al., 2007;

McEwen, 2007). While acute stress can have positive effects in moderation (e.g., improved memory performance (Sandi, 2013)), excessive or intense acute stress can contribute to physical and psychological problems. For example, augmented levels of acute stress may result in anxiety, sleep disturbances, and digestive issues (Cohen et al., 2007). In addition, via elevation of associated hormones and catecholamines, acute stress can impact a wide range of cognitive abilities (McManus et al., 2022; Olver et al., 2015; Roozendaal et al., 2009; Smeets et al., 2006).

On the other hand, chronic stress, as the name implies, refers to stress exposure over an extended period of time usually lasting for weeks, months, or even years. Chronic stress results from persistent exposure to stressors such as work pressure, chronic marital difficulties, and even global crises, such as inflation and the COVID-19 pandemic. The prolonged activation of stress response can lead to allostatic load (cumulative strain that challenges our body to maintain homeostasis) resulting in altered endocrine regulation and physiological changes, such as dysregulated pro-inflammatory effects which can impair both neural and peripheral circuits (Brosschot et al., 2005; McEwen, 2007; Seeman et al., 2001). These cumulative and long-lasting effects of stress on various systems highlight its deleterious impact on both physical and mental health (Lupien et al., 2018; Lupien et al., 2009).

Stress as a transdiagnostic risk factor

As mentioned above, both acute and chronic stress trigger a whole-body biobehavioral response, which is associated with a wide range of adverse health effects, for example, gastrointestinal issues, cardiovascular diseases, diabetes, and autoimmune disorders (Cohen et al., 2007; Han et al., 2012; Lupien et al., 1998; Yaribeygi et al., 2017). In addition to increasing the risk of somatic and physical ailments, psychiatric disorders may also develop due to (repeated) stress exposure.

Specifically, stressful events are among the most important risk factors for mental health problems (Monroe et al., 2006). Compelling evidence has linked exposure to stress with increased risk for development of depression and anxiety (Hammen, 2005; Lupien et al., 2009; Pêgo et al., 2010; Plieger et al., 2015; Revollo et al., 2011; Yang et al., 2015). Approximately 25% of people who experience major stressful events develop depression (Praag et al., 2004). In addition, increased levels of stress predict the clinical course of major depression, including duration, symptom exacerbation, treatment resistance, and recurrences (Hammen, 2005; Mazure, 1998). The relationship between psychological stress and anxiety seems intuitive due to their high degree of conceptual overlap (Daviu et al., 2019; Pfaff, 2002). People exposed to chronic stress are more likely to develop anxiety disorders later in life, and similar to depression, stress plays an important role in the onset and clinical course of anxiety disorders (Faravelli et al., 2012; Hammen et al., 2009; Konstantopoulou et al., 2020; Syed & Nemeroff, 2017).

From a transdiagnostic risk factor to transdiagnostic impairments

Stress, and activation of the fight-or-flight response, exert powerful effects on a number of cognitive and affective processes that are essential in everyday life, including motivation (e.g., willingness to pursue desirable outcomes), learning, decision-making, emotion regulation and memory

(Goschke, 2014; Hollon et al., 2015). Disturbances in these processes have been linked to various mental disorders (Kring & Barch, 2014) and associated with poor quality of life and functional outcomes (Llewellyn et al., 2008; Salamone et al., 2015).

For instance, exposure to stress is known to result in motivational impairments. Motivation can be seen as a dynamic process during which individuals consciously or subconsciously weigh the cost (i.e., cognitive, or physical effort) and benefits (i.e., rewards) associated with a particular goal or action (Sidarus et al., 2019). These subjective value computations – that is, integration of costs and benefits associated with obtaining their goal – subsequently inform a given individual's decision to perform or withhold an action, with decisions with positive subjective value (that is, when benefits outweigh the costs) being more likely to be followed by action (Pessiglione et al., 2018). However, motivation does not only involve cognitive "cost-benefit" computations, it also involves the ability to learn from the outcomes of our actions. That is, previous knowledge and experiences shape the expectations we have about the costs and benefits of subsequent actions. For example, previously achieved positive outcomes are more likely to increase the motivation to pursue similar goals/actions in the future (Niv, 2009).

Past research suggests that these aspects of motivation - i.e., value computation and instrumental learning - may be impaired in many stress-related disorders, including psychotic disorders, depression, anxiety (Salamone et al., 2015; Salamone et al., 2016). Two key features of impaired motivation observed in these disorders, anhedonia (i.e., the inability to experience or pursue pleasurable activities) and avolition (i.e., a reduction in the ability to initiate and maintain goal-directed behavior) have been consistently linked to abnormal reward-seeking behavior and altered effort-expenditure respectively (Bonnelle et al., 2015; Der-Avakian & Markou, 2012). However, still little is known about the precise mechanisms through which acute and chronic stress may impact cost-benefit learning and decision-making. Exploring how acute and chronic stress influence and shape these cognitive processes could shed new light on the adaptive and maladaptive effects of stress on motivation.

Previous work has relied on well-validated experimental paradigms to quantify changes in motivation and, more generally, goal-directed behavior by assessing the willingness to perform effortful actions (e.g., investing grip force) in exchange for rewards (e.g., money) (Pessiglione et al., 2018). However, the observed behavior recorded from these tasks (e.g., number of offers accepted) may be rather aspecific. Different cognitive mechanisms may influence behavioral readouts (e.g., choice preference might be attributed to decreased sensitivity to rewards and/or increased sensitivity to effort). More specific insights, however, can be gained by applying state-of-the-art techniques, such as cognitive computational models (Blohm et al., 2020). That is, we can apply mathematical algorithms, in which specific learning or choice-related processes are formalized to behavioral data to understand the latent cognitive processes that participants rely on to complete the task (Wilson & Collins, 2019). The resulting parameters obtained from these algorithms inform us how and to which degree participants relied on particular learning and/or decision-making skills to complete the task. In some parts of this thesis, we will use the above-

described cost-benefit tasks in combination with computational models of learning and decision-making to improve understanding of stress-related alterations in motivation.

As mentioned above, the impact of stress on cognitive processes does not only involve changes in motivation: it involves changes in a wide constellation of cognitive skills including (working) memory, sustained attention, vigilance, recognition, and motor planning (Etkin et al., 2022; McTeague et al., 2016). Such impairments in cognitive functioning can be observed in a wide range of neuropsychiatric disorders. For instance, a study conducted by Caspi et al. (2014) found that higher score on the general psychopathology (p) factor predicted lower performance on these neurocognitive measurements and worse lifespan IQ. Cognitive functions are also known to be modulated by stress (Marin et al., 2011). Accumulating evidence suggest that chronic exposure to stress can impact hippocampal volume and memory performance (Bremner & Narayan, 1998; Gianaros et al., 2007). Preclinical and clinical data indicate that susceptibility to stress can be a risk factor for the development of Alzheimer's disease (AD) (Briones et al., 2012; Wilson et al., 2005), and increased secretion of cortisol has been observed in individuals with AD and Mild Cognitive Impairment (MCI) compared to normal elderly (Marin et al., 2011).

Interestingly, multiple neurochemical systems (e.g., neurotransmitters, such as dopamine and noradrenaline) and molecular pathways (e.g., inflammatory, and oxidative stress mediated pathways) have been implicated in the etiology and progression of stress-related disorders as well as associated impairments with a significant overlap between them. Manipulation of neurochemical systems, either via the use of drug challenges or therapeutic agents to explore these systems, can serve as invaluable tools in clinical research. The use of psychopharmacology in combination with behavioral/cognitive approaches can provide holistic insights into the transdiagnostic mechanisms that may underly (stress-related) central nervous system disorders.

Aim and outline of the thesis

The current thesis aims to investigate mechanisms underlying cognitive functioning in relation to multidimensional facets of stress. Research initiatives such as the transdiagnostic Research Domain Criteria (RDoC) framework of the National Institute of Mental Health (NIMH) aim to understand mental health and illness in terms of varying degrees of dysfunction moving towards a dimensional conceptualization of psychopathology (Insel et al., 2010). Different methods can be utilized to investigate such multidimensional constructs using various units of analysis that range from molecular to behavioral, and self-report assessments (Insel et al., 2010). In agreement with RDoC's conceptualization *(see Figure1)*, the current thesis attempted to incorporate key constructs of this framework including the Negative Valence System (NVS) -acute and chronic stress-, the Positive Valence System (PVS) -reinforcement learning, reward, and effort valuation-, Cognitive System -memory- in order to evaluate parts of their complex interactions. In addition, we utilized different units of analysis including top-down processes, for instance, behavior influenced by one's goals, expectations, and prior knowledge, but also bottom-up processes investigating, for example, neurotransmitters that are influenced by stress and can affect cognition. More specifically:

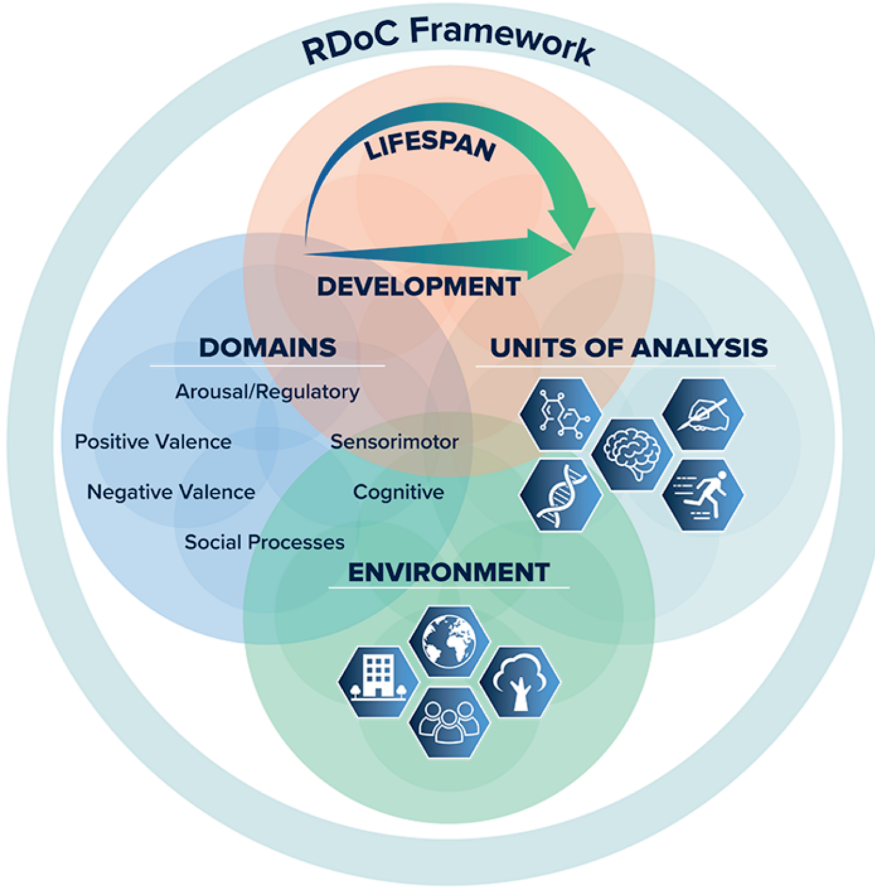

Figure 1 | Graphic description of RDoC's framework. Adapted from Morris et al. (2022).

In **chapter 2**, we aim to investigate whether acute stress changes how humans learn about costs (i.e., physical effort) and benefits (i.e., reward) and we employ computational modeling to investigate latent cognitive mechanisms by which acute stress might affect cost-benefit reinforcement learning. We also use pupillometry and physiological measures to link strategies employed during cost and benefit learning with changes in neuromodulatory systems.

In **chapter 3**, we conducted an online study using a similar cost and benefit reinforcement learning task and investigated how interindividual differences linked to transdiagnostic symptoms and risk factors for psychopathology (i.e., perceived chronic stress, anhedonia, impulsivity, energy) are associated with alterations in learning about the costs and benefits of actions.

Chapter 4 aims to investigate the roles of dopamine and noradrenaline - neurotransmitters that have been strongly associated with stress and motivation - in a cost and benefit decision-making, placebo-controlled pharmacology study. Haloperidol was used to manipulate dopamine, primarily D_2 receptors, while propranolol was used to manipulate the action of noradrenaline at β receptors.

In **Chapter 5**, we used network analyses to unravel complex relationships between COVID-19 related stressors and emotional states during the initial phase of the COVID-19 pandemic.

Lastly, as mentioned above, there is ample evidence that indicate a link between stress with the development of cognitive impairments, dementia, and even AD. **Chapter 6**, presents preclinical and clinical research findings on curcumin, a natural compound, as a potential cognitive enhancer for use in healthy aging and AD.

Chapter 7 contains the general discussion, in which the main findings, conclusions, methodological considerations, and future directions are presented.

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CHAPTER 2

Asymmetric effects of acute stress on cost and benefit learning

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Abstract

Humans are continuously exposed to stressful challenges in everyday life. Such stressful events trigger a complex physiological reaction – the fight-or-flight response – that can hamper flexible decision-making and learning. Inspired by key neural and peripheral characteristics of the fight-or-flight response, here, we ask whether acute stress changes how humans learn about costs and benefits. For this reason, healthy adults were randomly exposed to an acute stress (age mean=23.48, 21/40 female) or no-stress control (age mean=23.80, 22/40 female) condition, after which they completed a reinforcement learning task in which they minimize cost (physical effort) and maximize benefits (monetary rewards). During the task pupillometry data were collected. A computational model of cost-benefit reinforcement learning was employed to investigate the effect of acute stress on cost and benefit learning and decision-making. Acute stress improved learning to maximize rewards relative to minimizing physical effort (Condition-by-Trial Type interaction: $F(1,78)=6.53$, $p=0.01$, $n^2_G= 0.04$; reward > effort in stress condition: $t(39)=5.40$, $p<0.01$). Computational modeling revealed that asymmetric learning could be explained by changes in the learning rates of reward value and action cost [condition-by-learning rate (αR, αE) interaction: $F(1,78)= 6.42$, $p=0.01$, $n^2_G= 0.03$; αE>αR in control condition: $t(39)=-4.75$, $p<0.001$]. This process was associated with distinct alterations in pupil size fluctuations. Data and scripts are available (https://osf.io/ydv2q/). Here we demonstrate that acute stress is associated with asymmetric learning about reward value versus action cost, thereby providing new insights into learning strategies under acute stress, which, depending on the context, may be maladaptive or beneficial. Our pupillometry and physiological results tentatively link asymmetric cost and benefit learning to stress-related changes in catecholamine activity.

Keywords: acute stress, reinforcement learning, computational modeling, costs and benefits, reward, effort

Introduction

Stress is ubiquitous in everyday life. From recurrent, brief events (a work meeting, a public talk) to major life events (pandemic, financial crisis, armed combat), humans are continuously exposed to challenges in their daily environment. The combined psychological and physiological cascade of events triggered by such stressors, termed the *fight-or-flight (or acute stress) response,* serves an allostatic role that enables organisms to adequately respond to environmental demands (de Kloet, Joëls, & Holsboer, 2005). Although beneficial for survival, this allostatic process comes at a cost: stress-induced redistributions of neural resources - e.g., towards vigilance or threat - may hamper the deployment of strategies that support adaptive and optimal decision-making (Joëls et al., 2006).

Optimal decisions essentially depend on the ability to rapidly learn from the positive and negative outcomes of previous actions, also known as *reinforcement learning* (Niv, 2009). Considerable evidence suggests that acute stress modulates aspects of reinforcement learning (Berghorst et al., 2013; Carvalheiro et al., 2020; Lighthall et al., 2013; Petzold et al., 2010; Raio et al., 2017), likely driven by changes in reward sensitivity and the signaling of reward prediction errors (RPEs) (Berghorst et al., 2013; Carvalheiro et al., 2020). Within the context of reinforcement learning, RPEs - the mismatch between actual and expected outcomes - are used to flexibly adjust behavior (Niv, 2009) and are putatively signaled by midbrain dopamine neurons (Bayer & Glimcher, 2005).

Intuitive as it is, the notion that the impact of acute stress on decisions *primarily* involves changes in how reward value influences action may be oversimplified. Decisions are not only motivated by appetitive properties; they equally depend on the - cognitive (e.g., mental effort) or physical (e.g., energy) - *costs* associated with actions (Pessiglione et al., 2017; Schmidt et al., 2012). Expectations about action costs are also updated according to a prediction error rule (Skvortsova et al., 2017; Skvortsova, Palminteri, & Pessiglione, 2014) (henceforth “effort” prediction errors; EPEs). In cost-benefit decisions, the aversive value of action cost is typically subtracted from the reward value to compute a “net”, or subjective decision value (i.e., effort-discounted reward value). Notably, stress exposure impairs cost-benefit decisions in rodents (Friedman et al., 2017; Shafiei et al., 2012). Moreover, in a reinforcement learning context, acute stress blocks the flexible updating of aversive value (Raio et al., 2017), an inherent property of costly actions.

Despite computational similarities, distinct neural correlates of RPEs (e.g., striatal subdivisions, ventromedial prefrontal cortex [vmPFC]) and EPEs (e.g., parietal cortex, insula, dorsomedial PFC) can be observed in cost-benefit reinforcement learning paradigms (Skvortsova et al., 2014). Moreover, the ascending dopaminergic (e.g., RPEs, action cost) (Schultz, Dayan, & Montague, 1997; Skvortsova et al., 2017), noradrenergic (e.g., energizing behavior) (Pessiglione et al., 2017; Varazzani et al., 2015) and serotonergic (e.g., vigor, aversive value) (Meyniel et al., 2016) neuromodulatory systems may encode dissociable aspects of goal-directed actions that involve costs and benefits. These observations are noteworthy because acute stress triggers a large-scale reorganization of brain networks that includes alterations in the firing mode of midbrain dopaminergic and noradrenergic neurons (Arnsten, 2015; Hermans et al., 2014); which additionally

encode reward value, action cost and energy expenditure (Varazzani et al., 2015). Thus, catecholaminergic mechanisms recruited by the fight-or-flight response may differentially impact cost and benefit reinforcement learning.

Although the central effects of the fight-or-flight response trigger a shift in cognitive strategies, its peripheral counterpart mobilizes the energy (i.e., adrenaline-mediated glucose (de Kloet et al., 2005; Russell & Lightman, 2019)) required to exert effortful actions aimed at persevering homeostasis. This could indicate that learning policies regarding physical costs may be *especially* susceptible to stress: both via changes in computational (neural) learning mechanisms, *and* peripheral autonomic mechanisms that control the amount of energy resources that can be directed towards effortful actions. Indeed, preliminary evidence suggests that acute stress alters the willingness to exert physical effort for rewards (Bryce & Floresco, 2016) and reward-associated cues in a Pavlovian-instrumental transfer context (Pool et al., 2015).

The impact of acute stress on instrumental learning involving cost-benefit decisions has not been investigated to date. In light of the above observations, we speculate that the use of computationally frugal heuristics, in concert with increased energy availability during acute stress will asymmetrically prioritize reward (maximization) learning over physical effort (minimization) learning.

Methods

Participants

A total of 100 adult participants were recruited via paper and online advertisements. All participants were screened for a DSM-5 psychiatric and/or neurological disorder, substance use, endocrine and/or vascular disorder, abnormal BMI (>40 or <18), smoking and drinking (>10 cigarettes/units per week), psychotropic medication use (lifetime) and hormonal contraceptive use (current; female participants only). All participants completed the ~2-hour experiment between 12:00h and 18:00h to minimize diurnal cortisol fluctuations (Bailey & Heitkemper, 2001). Participants were instructed to refrain from alcohol (starting the evening before the day of the experiment), smoking, food, caffeine intake, strenuous physical activity and brushing their teeth (all >2 hr prior to experiment), which was verified verbally at the start of the session. Four participants were excluded due to an equipment failure (n=4). Three participants quit during stress induction (n=2) or task procedures (n=1). Because chance-level performance on reinforcement learning tasks might indicate a successful manipulation, a lack of motivation, or a failure to comprehend the task instructions, participants that performed at or below chance level (0.5) on both RL and/or both EL pairs near the end of the experiment (final 10 presentations) were excluded (n=13; 6 acute stress, 7 no-stress control), bringing the final sample to 80 participants. Including these participants did not alter our key finding that acute stress was associated with asymmetric cost versus benefit learning (*see Supplemental Results, "Task performance analyses including chance-level performers"*). Pupillometry and neuroendocrine data were not processed further for these participants. G*Power calculations suggested that in order to detect an effect of η^2 p = 0.04 (η^2 G ~ 0.03) with 95% power in a mixed ANOVA (2x2, alpha = 0.05), we would need 40 participants in each group (N = 80). All

participants completed the BIS (behavioral inhibition system)/BAS (behavioral activation system) scale before the stress induction (Gray, 1982). No-stress and acute stress subjects did not differ in BIS/BAS subscales, namely: BIS [$t(77.50)=1.29$, $p=0.20$], which measures motivation to avoid aversive outcomes; BAS Reward Responsiveness [$t(71.92)=0.34$, $p=0.74$], BAS Drive [$t(77.82)=0.26$, $p=0.79$], and BAS Fun Seeking $t(72.80)=-0.54$, $p=0.59$], which measure reward sensitivity, motivation to approach goals and motivation for novel reinforcers, respectively. The study was approved by the ethics committee of the Faculty of Psychology and Neuroscience, Maastricht University (ERCPN-197_03_08_2018) and carried out in accordance with the Declaration of Helsinki. Participants were remunerated in gift vouchers or research participation credits.

Acute stress induction

The MAST is a validated stress-induction paradigm combining both psychological and physiological stressors, and robustly increases neuroendocrine, physiological, and subjective indices of acute stress (Smeets et al., 2012). During a 5-min preparation phase, participants were informed about the upcoming task via oral and visually displayed instructions, followed by a 10-min stress-induction phase consisting of alternating blocks of cold-water immersion (non-dominant hand; 2°C) and backward counting in steps of 17 (while receiving negative evaluative feedback from an experimenter), with a (non-recording) camera continuously directed at the participant's face, which was displayed to the participant on a second monitor. During the MAST no-stress control condition, participants immerse their hand in lukewarm water (36°C) and perform simple mental arithmetic, e.g., counting from 1 to 25 without receiving feedback or fake camera recordings.

Neuroendocrine, physiological, and subjective stress measurements

Salivary cortisol (sCORT) and alpha-amylase (sAA) were collected to measure stress-induced increases in hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes activity, respectively (Dickerson & Kemeny, 2004; Nater et al., 2005). Saliva samples were obtained using synthetic Salivette® devices (Sarstedt, Etten-Leur, the Netherlands) during 3-min sampling periods at 6 time points. A baseline sample was collected 10 min prior to the MAST (baseline: $t_1 = t_{-10}$) and five samples post-MAST ($t_2= t_{+00}$, $t_3= t_{+10}$, $t_4= t_{+20}$, $t_5= t_{+30}$, $t_6= t_{+40}$). SAA assessments were obtained only for t_1-t_4, due to the rapid decay of sAA post-stress induction (Nater et al., 2005). For all participants, t_2 marked the starting point for the reward value maximization/action cost minimization task. Samples were stored at -20°C immediately after the completion of each session. SCORT and sAA levels were determined using the luminescence immune assay kit (IBL, Hamburg, Germany) and kinetic reaction assay (Salimetrics, Penn State, PA, USA), respectively.

Systolic blood pressure (SBP) and heart rate (HR), indices of autonomic nervous system (ANS) arousal, were assessed at t_1 and t_2 using an OMRON M4-I blood pressure monitor (OMRON Healthcare Europe B.V., Hoofddorp, The Netherlands). Subjective affect ratings were assessed at t_1 and t_2 using the 20-item Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988).

Experiment design

Immediately post-MAST, and within the confines of the acute stress response (Hermans et al., 2014), all participants completed a ~ 40-minute probabilistic cost-benefit reinforcement learning paradigm, adapted from Skvortsova et al. (Skvortsova et al., 2017; Skvortsova et al., 2014), in which they learned to select stimuli with high reward value (€0.20) and avoid stimuli with high action cost (exerting grip force above a pre-calibrated individual threshold of 50% maximum voluntary contraction for 3000ms).

On each of 120 trials, participants chose between two paired distinct black-and-white images (stimuli) that were probabilistically associated with both the receipt of a monetary reward and exertion of physical effort. In total, four distinct image pairs were presented, 30 presentations each. For 2/4 pairs, participants could regularly acquire rewards by selecting one (optimal) stimulus over the (suboptimal) other (henceforth, "reward learning"/RL pairs), while the probability of having to exert effort was identical for both stimuli. For the other two pairs, choices of one stimulus were more frequently followed by the avoidance of effort ("effort learning"/EL pairs), while the probability of reward was kept constant between both. For all pairs, the probability of the stimulus property that was *kept constant* (reward/effort) was set to a 33.3% chance of positive outcome upon selection (reward/ effort avoidance) and 66.6% chance of negative outcome (no reward/effort).

To assess whether acute stress effects on reward maximization (RL pairs) and effort cost minimization (EL pairs) learning were potentially mediated by task difficulty, we employed different difficulty levels for each RL and EL pair. That is, for one RL and one EL ("easy") pair, a choice for the optimal stimulus was followed by a positive outcome in 83% (vs 17% negative outcome) of all trials (83% negative/17% positive outcome for suboptimal stimulus); for the other RL and EL ("hard") pair a choice for the optimal stimulus was followed by a positive outcome in 70% (vs 30% negative outcome) of all trials (and 70% negative/30% positive outcome) for the suboptimal stimulus. This approach allowed us to disentangle whether acute stress primarily impacted domain specific (RL vs EL) or general (easy vs hard) reinforcement learning.

For every participant, stimuli were randomly assigned to pairs, optimal/suboptimal stimulus orientation was balanced (50% of all optimal stimulus presentations occurred on the left-hand side) and misleading outcomes (e.g., negative outcomes for optimal stimuli) were equally spaced out across the thirty presentations (and balanced for left/right side). Trial presentation order was pseudo-randomized such that I) a given pair would never be presented more than twice in a row and II) the gap between two presentations of a given pair was never greater than four trials. After the learning task, a surprise test phase followed, during which no feedback was delivered upon choice (Hernaus et al., 2018). All participants received standard verbal instructions pre-MAST and completed a 16-trial practice round before starting. Participants were not informed about stimulus-outcome contingencies. They were only advised to accrue as much money as possible and avoid exerting unnecessary effort, as they would not be able to skip any trial events.

A more detailed overview of the paradigm is provided in *Figure 1* and the *Supplemental Methods* (*"Reward maximization versus action cost minimization reinforcement learning task"*).

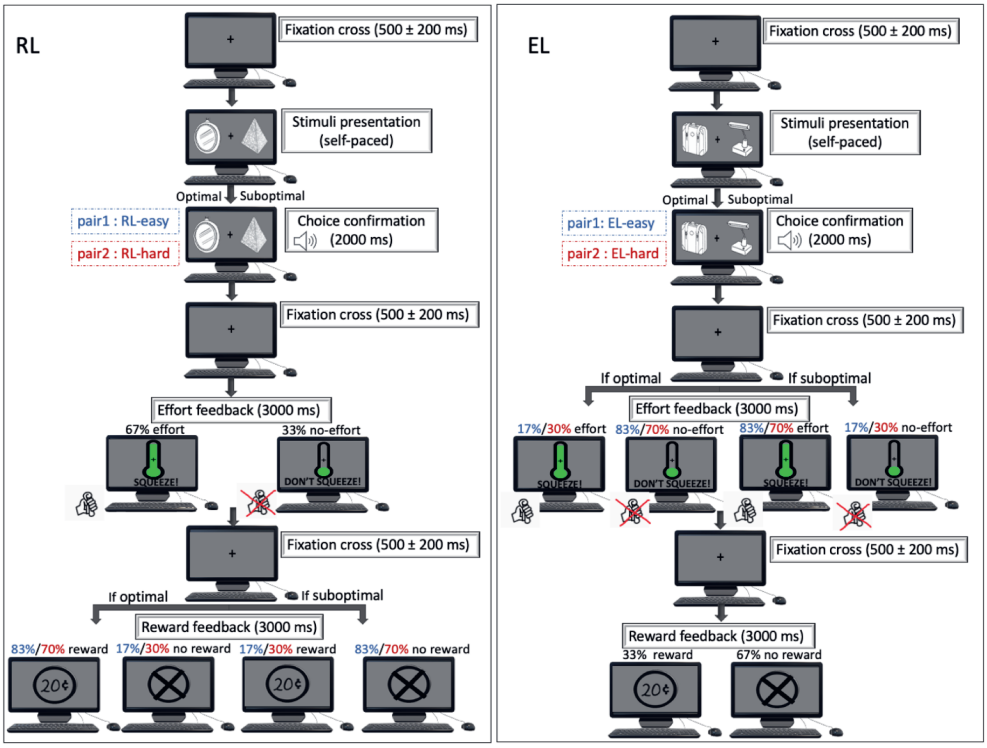

Figure 1 | **Reward maximization/action cost minimization reinforcement learning task**.
Visual depiction of the learning phase. Participants were presented with four distinct stimulus pairs, and all stimuli were associated with a predetermined chance of a €0.20 monetary reward (versus no reward) and a chance of having to exert physical effort (grip force) using a dynamometer (versus no grip force required). Both panels: all 120 trials (30 presentations per pair) started with a fixation cross, followed by the presentation of a stimulus pair, upon which a self-timed choice was necessary. Following choice confirmation (tone immediately upon button press), stimuli remained on-screen for 2000ms, upon which action cost (effort) outcomes and reward outcomes were presented sequentially. An example of RL trials is presented on the left and an example of EL trials is presented on the right. Percentages in blue and red refer to outcomes for the Easy RL/EL and Hard RL/EL pair, respectively.

Computational modeling of cost and benefit reinforcement learning

To uncover latent mechanisms by which acute stress affects cost-benefit reinforcement learning, we turned to cognitive computational modeling. In total, six candidate models were tested (*Supplemental Methods, "Computational cost-benefit reinforcement learning model: model space"*). The models contained between three and six free parameters, including learning rates for reward (αR) and effort (αE), parameters that assign weight to the prediction error, and thus capture learning speed, an inverse temperature parameter (β) to assess choice stochasticity, a linear discounting parameter (γ) to assess how the presence of action cost impacts reward valuation,

and reward/effort weights (W_R, W_E) to assess sensitivity to reward value and/or action cost (all bounds [0, 1]).

Best-fitting parameters were identified using fmincon in MATLAB v.2019B (Mathworks, Natick, MA, USA). Bayesian Model Selection using Akaike's Information Criterion (AIC) (deLeeuw, 1992) suggested that 2LR_γ was the most likely model (exceedance probability*: pxp,* φ = 0.99; expectation of the posterior: $p(r|y)$= 0.70), which contains four free parameters: two separate learning rates that weigh the importance of RPEs and EPEs (αR, αE), an action cost discounting parameter (γ), and an inverse temperature parameter (β). In this model trial-by-trial expectations of participants were updated according to Eqs. 1A and 1B:

$$Q_{R(t)}(s, a) = Q_{R(t-1)}(s, a) + \alpha R * RPE_{(t-1)}(s, a) \quad (1A)$$

$$Q_{E(t)}(s, a) = Q_{E(t-1)}(s, a) + \alpha E * EPE_{(t-1)}(s, a) \quad (1B)$$

Here, $Q_{R(t-1)}$(s, a) and $Q_{E(t-1)}$(s, a) represent the expected reward value and action cost at trial *t-1*, where *s* reflects the given pair and *a* refers to the more abstract action of selecting a stimulus, αR and αE represent the reward and effort learning rates, and lastly, $RPE_{(t-1)(s, a)}$ and $EPE_{(t-1)(s, a)}$ reflect the reward and effort prediction errors calculated as shown in Eqs. 2A and 2B.

$$RPE_{(t)} = r_{(t)} - Q_{R(t)}(s, a) \quad (2A)$$

$$EPE_{(t)} = e_{(t)} - Q_{E(t)}(s, a) \quad (2B)$$

Here, $r_{(t)}$ and $e_{(t)}$ represent the reward and effort outcome for the chosen stimulus at trial *t.* $Q_{R(t)}$(s, a) and $Q_{E(t)}$(s, a) represent the expected reward value and action cost (i.e., effort) for the chosen stimulus at trial *t*. For each choice option*,* a subjective decision value was calculated according to the following equation (Eq. 3):

$$Q_{(t)}(s, a) = Q_{R(t)}(s, a) - \gamma * Q_{E(t)}(s, a) \quad (3)$$

This equation weighs costs against benefits (represented by the difference between the expected reward [$Q_{R(t)}$(s, a)] and action cost value [$Q_{E(t)}$(s, a)] at trial *(t)*, and takes into account the observation that humans tend to discount or prioritize certain types of information in their decisions (γ) (Apps et al., 2015; Inzlicht et al., 2018). Based on previous work using a similar task design (Skvortsova et al., 2017; Skvortsova et al., 2014), here we only considered linear discounting (γ).

Model fit was obtained via the log likelihood, which was updated trial-wise by the log of the probability of the observed choice, calculated via a softmax rule (Eq. 4):

$$pr(s, a) = exp(Q_{(t)}(s, a)) / sum(exp(\beta * Q_{(t)}(s))) \quad (4)$$

Here, pr is the probability of selecting an action, β is the inverse temperature parameter that captures choice stochasticity, $Q_{(t)}(s, a)$ is the net value of the chosen option and $Q_{(t)}(s)$ represents the net values of both stimuli in the pair.

To demonstrate the effect of changes in parameter values on choice preferences within the 2LR_γ architecture, we simulated choices from 50 artificial agents (averaged across 10 repetitions) performing the reward maximization/action cost minimization reinforcement learning task using a range of parameter values. As expected, greater values of αR and αE impacted the speed of RL and EL choice preferences, while low values of γ lead to asymmetric choice preferences through discounting of action cost, and lower values of β lead to non-selective increases in random sampling (*Figure 2*).

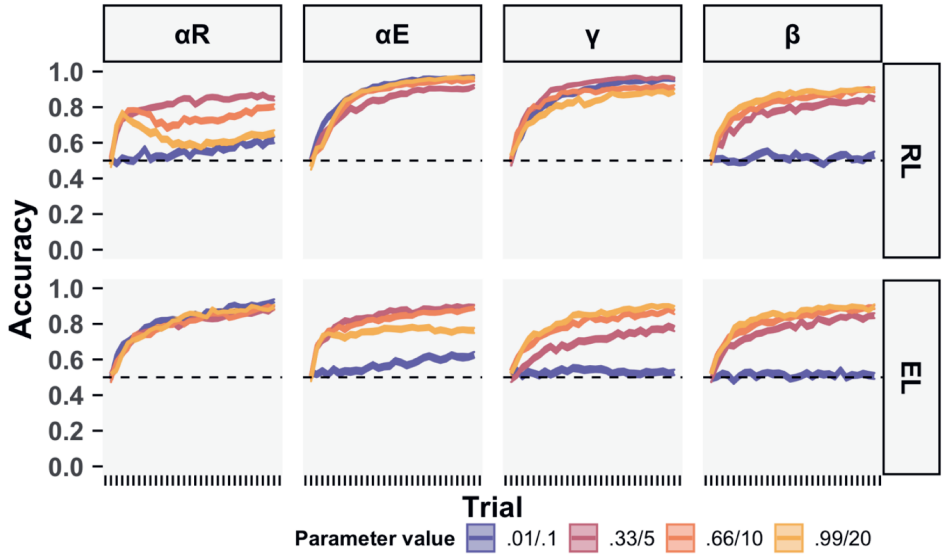

Figure 2 | Model demonstrations of the winning model.
To demonstrate how different parameter values within the 2LR_γ architecture impact choice preferences for the optimal stimulus ("accuracy"), αR, αE, and γ were set to 0.01/0.33/0.66/0.99, while β, a non-linear parameter, was set to 0.1/5/10/20. Parameter effects were always demonstrated for a single parameter (columns), while all other parameter values were kept constant (αR and αE=0.25, γ=1, β=25). Greater values of αR and αE selectively increase the speed with which the agent develops a preference for the optimal RL and EL stimulus, respectively. Lower values of γ produce an asymmetric decision-making policy that emphasizes reward value over action cost, leading to better performance on RL versus EL trials, while greater values of γ correct this asymmetric choice bias. Finally, greater β values lead to more deterministic sampling of optimal stimuli. Colored lines represent mean ± SD.

Data simulation, model recovery and hierarchical model fitting were performed to validate the model. Further information on the details of model fitting, model selection, and validation can be found in the *Supplemental Methods* (*"Computational cost-benefit reinforcement learning model: Model Fitting, Selection, and Simulations"*).

Pupillometry

Fluctuations in pupil diameter were continuously measured using an SR-Research Eyelink 1000 Tower Mount infrared eye tracker while participants performed the reward maximization/action cost minimization reinforcement learning task (1000Hz sampling rate, except for three participants, whose data were obtained at 500Hz). Participants placed their head on an adjustable chin rest and against a forehead bar to minimize motion. Eye-tracker (9-point) calibration was performed at the start of the paradigm, and subsequently every 10 min. Stimulus luminance was matched using the SHINE toolbox (Willenbockel et al., 2010) in MATLAB (v. 2014B; The MathWorks, Inc., Natick, Massachusetts, United States). Due to the COVID-19 pandemic, pupillometry data were not collected for the final eight participants. Three participants, moreover, failed the quality control for eye-tracking data (2 no-stress control/1 acute stress) leaving a final sample of 69 participants with eye-tracking data (34 no-stress control/35 acute stress).

Eye-tracking data were pre-processed using an open-source pre-processing toolbox (Kret & Sjak-Shie, 2019) according to previous work (Jackson & Sirois, 2009). For each subject, blinks, and other invalid samples, due to dilation speed, deviation from the trend line, and extreme values (Kret & Sjak-Shie, 2019) were removed and the remaining data were interpolated, smoothed (4Hz low-pass filter, fourth-order Butterworth filter) (Jackson & Sirois, 2009), z-scored (epoch-wise for choice, effort outcome and reward outcome; see below) and down-sampled to 50Hz (i.e., 20ms). Bins with fewer than 80% valid samples were removed (Lawson et al., 2020). For analyses, we considered three epochs of interest: choice (-1500ms pre-choice - 1500ms post-choice), effort outcome (0 - 1000ms post-outcome), and reward outcome (0 - 2000ms post-outcome). We reduced the duration of the effort outcome epoch to 1000ms to minimize force exertion-related effects on pupil size. Recent work has shown that prediction errors are encoded by pupil size fluctuations within this timeframe (Lawson et al., 2020). Given that we observed large grip force-associated effects on the pupillometry signal *(see Supplemental Figure 3 middle row, for a comparison between effort and effort avoidance trials)*, we limited effort outcome analyses in the main text to effort avoidance trials, although we also report analyses involving all effort outcome trials in *Supplemental Figure 3*.

Statistical analyses

Statistical analyses were conducted using R, version 3.6.2 (Team, 2020). Acute stress measurements were analyzed using mixed ANOVAs involving Condition (between-factor: no-stress control, acute stress induction) and Time (within-factor: 2 pre/post-MAST or 6 levels for sCORT).

For the learning task, an accuracy score was calculated dividing the number of optimal choices by the total trial amount (n=30 per pair). Mixed ANOVAs involving Condition, Trial Type (RL, EL) and Difficulty (Easy, Hard pairs) were carried out. For analyses involving Time effects, accuracy scores were averaged per bin of ten presentations (presentation 1-10, 11-20, and 21-30). Win-stay (repeating a choice following a positive outcome) and lose-shift (choosing the other stimulus following a loss) rates were also calculated for RL (yes/no reward outcomes) and EL trials (yes/no

effort outcomes) (den Ouden et al., 2013). Model parameter differences were investigated using Condition-by Learning Rate (αR, αE) mixed ANOVAs and independent samples t-tests.

Post hoc analyses for all ANOVAs were conducted using independent sample (Condition), paired-samples (Time, Trial Type, Win-stay), and one-sample (≠0.5) t-tests. Greenhouse–Geisser-corrected statistics were reported when sphericity assumptions were violated. We report statistical significance as $p<0.05$ (two-sided). In case of statistically significant results, generalized eta square (ges; n^2_G) was reported.

With respect to pupillometry, we conducted both standard and model-derived analyses. We investigated group differences in pupil size during choice, effort, and reward outcome stages, for every bin of interest. In model-derived analyses, we used GLMs to regress computational parameters from the winning (2LR_ γ) model (Lawson et al., 2020) onto pupil size, for every participant, epoch, and bin (*see Supplemental Methods, "Pupillometry"*). In group-level comparisons using t-tests, we compared the resulting beta weights I) against zero (for the two conditions separately) to investigate when the pupil encoded computational processes, and II) between groups, to assess stress-induced changes in associations between pupil size and computational processes.

We conducted permutation tests at the bin- and cluster-level (2000 permutations, $\alpha_{permute}=0.05$) to control the false-positive rate. All correlations were performed using Spearman's *ρ* correlations. When assessing correlations between acute stress measures and pupil encoding of predictions errors permutation tests were used.

Results

Acute stress manipulation

We first ascertained whether the acute stress manipulation was successful. Acute stress and no-stress control groups did *not* differ on physiological, subjective stress, or neuroendocrine measurements pre-MAST (all *p-values*>0.05). We observed significant Condition-by-Time interactions for subjective stress ratings [PANAS negative: $F(1,78)=52.66$, $p<0.01$, $n^2_G=0.10$; PANAS positive: $F(1,78)=9.82$ $p<0.01$, $n^2_G=0.02$] and physiological measures [systolic blood pressure (SBP): $F(1,78)=15.50$, $p<0.01$, $n^2_G= 0.04$; heart rate: $F(1,78)=6.83$, $p=0.01$, $n^2_G= 0.02$]. Simple main effect analyses revealed that only the acute stress group exhibited pre-to-post *increases* in negative affect [control pre-post: $t(39)=4.21$, $p<0.01$; stress pre-post: $t(39)=-6.17$, $p<0.01$; control-stress post-MAST: $t(55.1)=-5.78$, $p<0.01$], and greater pre-to-post *decreases* in positive affect [control pre-post: $t(39)=4.09$, $p<0.01$; stress pre-post: $t(39)=6.45$, $p<0.01$; control-stress post-MAST: $t(72.8)=2.53$, $p=0.01$]. Similarly, only the acute stress group exhibited stress-induced *increases* in SBP [control pre-post: $t(39)=1.60$, $p=0.12$; stress pre-post: $t(39)=-3.66$, $p<0.01$; control-stress post-MAST: $t(69.1)=-3.27$, $p<0.01$] and heart rate [control pre-post: $t(39)=1.21$, $p=0.23$; stress pre-post: $t(39)=-2.78$, $p=0.01$; control-stress post-MAST: $t(76.9)=-3.14$, $p<0.01$] (*Figure 3A-D*).

A Condition-by-Time interaction was found for salivary cortisol (sCORT) responses [$F(5,390)=18.05$, $p<0.01$, $n^2_G= 0.04$] with the acute stress group displaying greater sCORT levels 10 min post-MAST and onwards (all *p-values*<0.01). We additionally observed a main effect of Condition on sCORT area-under-the-curve with respect to increase: (AUCi) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) [$t(56.32)=-5.28$, $p<0.01$] and salivary alpha-amylase (sAA) AUCi [$t(67.45)=-2.50$, $p=0.02$; after excluding one extreme outlier from the control group], suggesting greater sCORT and sAA levels in response to acute stress (*Figure 3E-G*). These results confirm that the MAST robustly induced stress on all levels of inquiry. No systematic gender effects on stress parameters were observed (see *Supplemental results, "Gender analyses"*).

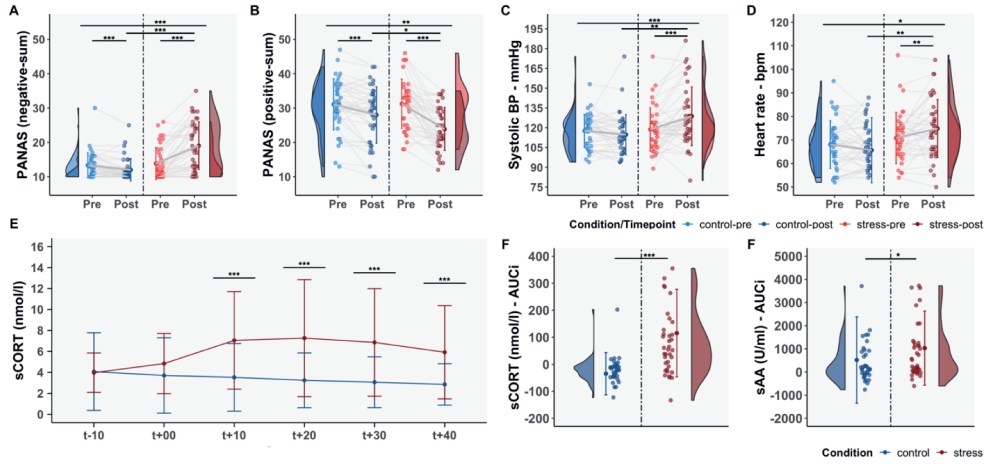

Figure 3 | **Neuroendocrine, physiological, and subjective stress ratings.**
PANAS negative (**A**) and positive (**B**) subscale sum scores, systolic blood pressure (mmHg: millimeters of mercury; **C**) and heart rate (bpm: beats per minute; **D**) are displayed for no-stress control (blue) and acute stress (red) groups separately for pre (light blue/red) and post (dark blue/red) MAST time points. SCORT responses for both conditions across the 6 timepoints are displayed in panel **E** ("t_{+00}" represents the first post-MAST measurement, and the start of the reward maximization/action cost reinforcement learning paradigm; "t_{-10}" represent a baseline sample). Panel **F** and **G** show AUCi for sCORT (nmol/l: nanomoles per liter) and sAA (U/mL: Units per milliliter) responses for both MAST conditions**.** Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$). In the upper panel, the top line denotes a significant Condition-by-Time interaction; lower lines represent simple main effects of Condition or Time.

Participants use reinforcement learning to optimize decisions

Initially, we investigated whether participants in both conditions exhibited evidence of learning to optimize actions. This was confirmed by a main effect of Time on two distinct trial types: RL trials, selecting the stimulus more frequently associated with a reward [control: $F(2,78)=10.16$, $p<0.01$, $n^2_G= 0.06$; stress: $F(2,78)=20.44$, $p<0.01$, $n^2_G=0.17$] and EL trials, selecting the stimulus more frequently associated with avoidance of physical energy expenditure [control: $F(2,78)=12.35$, $p<0.01$, $n^2_G= 0.07$; stress: $F(2,78)=9.76$, $p<0.01$, $n^2_G= 0.05$] (see *Supplemental Figure 4*).

Asymmetric cost-benefit reinforcement learning during acute stress

After having observed evidence for reward (maximization) and action cost (minimization) learning, we tested our key assumption; that acute stress would induce a reprioritization in learning to maximize reward value versus learning to minimize action cost. Crucially, we observed a significant Condition-by-Trial Type interaction [$F(1,78)=6.53$, $p=0.01$, $n^2_G= 0.04$] (*Figure 4A*) with pairwise comparisons indicating that the acute stress group performed significantly better on RL than EL trials [$t(39)=5.40$, $p<0.01$], while the control group performed similarly on both trial types [$t(39)=1.01$, $p=0.32$]. Simple main effects of Condition on RL [$t(65.9)= -1.75$, $p=0.09$] and EL [$t(77.5)=1.80$, $p=0.08$] performance showed numerical trends for group differences that failed to reach significance (although see *Supplemental Results, "Task performance analyses including chance-level performers"*).

We found no Condition-by-Trial Type-by-Difficulty [$F(1,78)=1.05$, $p=0.31$] or Condition-by-Difficulty interactions [$F(1,78)=0.36$, $p=0.55$; *Supplemental Figure 7*], confirming that asymmetric cost vs benefit learning in the acute stress group did not reflect a more general impairment in learning about more difficult stimulus-response associations.

When we investigated the use of win-stay and lose-shift strategies (den Ouden et al., 2013), we observed a significant Condition-by-Win/stay[$F(1,78)=5.20$, $p=0.03$, $n^2_G= 0.02$], but not a significant Condition-by-Lose/shift interaction [$F(1,78)=0.05$, $p=0.82$, $n^2_G= 0.00$]. *Post hoc* comparisons revealed that participants in the acute stress condition were more likely to win-stay for rewards (RL trials) than for avoidance of action cost (EL trials) [$t(39)=-4.91$, $p<0.01$], while no-stress controls exhibited similar win-stay rates on both trials [$t(39)=-1.68$, $p=0.10$]. Separate Condition (main effect) analyses failed to reach significance [WS_reward: $t(71.9)= -0.37$, $p=1.00$; WS_effort: $t(76.6)=2.03$, $p=0.09$] (*Figure 4B*).

Altogether, the behavioral results indicate that acute stress leads to a reinforcement learning strategy that favors learning to maximize reward value over minimization of action cost, potentially due to changes in sensitivity to positive (reward delivery) versus negative (avoidance of effort) reinforcement. In analyses using surprise test phase data, the acute stress group again exhibited a reward maximization-over-action cost minimization choice strategy, although here the Condition-by-Trial Type interaction was not significant ($p=0.29$; *see Supplemental Results, "Asymmetric cost-benefit reinforcement learning biases actions in acute stress subjects"*).

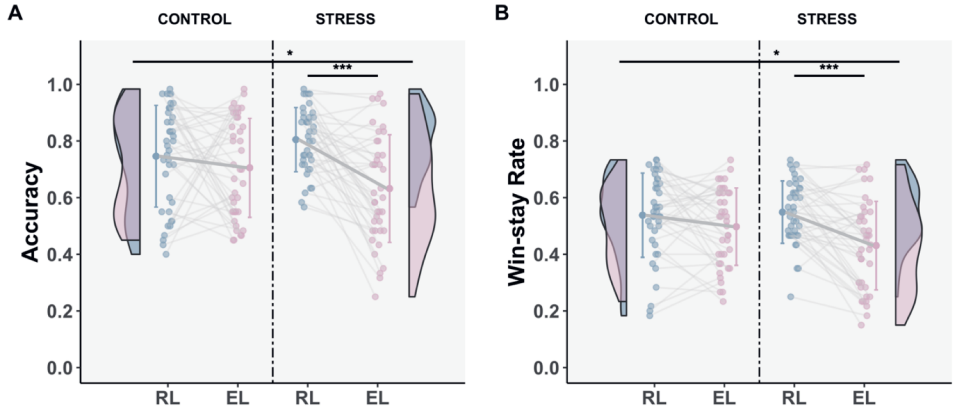

Figure 4 | Acute stress leads to improved benefit versus cost learning.
Panel **A**: Average accuracy (choices of the optimal stimulus) for RL and EL trials, for each condition separately. Panel **B:** Win-stay rates (choices following a positive outcome) for RL and EL trials, for each condition separately. Means ± SD, individual data points, distribution and frequency of the data are displayed. The top lines indicate significant interactions. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

Acute stress selectively reduces the difference between reward and action cost learning rates

Comparing parameters of the winning model (2LR_γ) between conditions, we observed a significant Condition-by-Learning Rate (αR, αE) interaction [$F(1,78)= 6.42$, $p= 0.01$, $n^2_G= 0.03$], with greater EPE relative to RPE learning rates in no-stress control participants [$t(39)= -4.75$, $p< 0.01$], while learning rates in the acute stress group did not significantly differ [$t(39)= -1.61$, $p= 0.12$]. No between-group differences in αR and αE or in the other parameters (γ, β) were observed (all *p-values*>0.05) (*Figure 5*). Parameters obtained following hierarchical fitting recovered the same pattern of the results, and additionally revealed that the no-stress relative to the acute stress group displayed greater values of αE (*Supplemental Results, "Hierarchical model fit"*).

Paradoxically, symmetric reward value and action cost learning rates in the presence of lower values of γ will lead to more efficient RL compared to EL. This is because lower values of γ bias decisions towards reward value (via *greater* discounting of action cost) and similar absolute values of αR/αE will not counteract this bias. *Asymmetric* learning rates (αE>αR) in combination with lower values of γ, however, will lead to more symmetric performance on RL and EL trials via more efficient updating of action cost versus reward expectations. This interpretation is supported by our demonstration of model parameters and *post hoc* simulations (*Figure 2 and Supplemental 1B respectively*), as well as the observation that lower values of γ (i.e., greater action cost discounting) were associated with greater learning rate asymmetry (αE>αR; more efficient EL) in no-stress controls [$\rho(38)= -0.40$, $p= 0.04$], who displayed similar RL and EL performance. These results demonstrate that, in a context where all decisions involve a potential cost and benefit, acute stress selectively reduces the difference between EPE and RPE learning rates, while leaving action cost discounting and choice stochasticity unaffected. The direction of the change in learning rates (i.e.,

greater similarity) implies a stress-induced failure to modulate learning rates in the service of overcoming an asymmetric choice bias that emphasizes reward value.

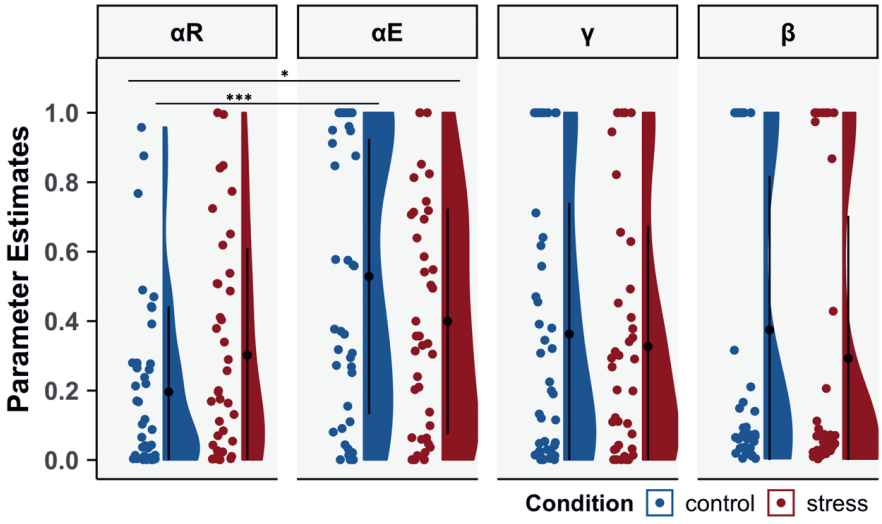

Figure 5 | Acute stress reduces the difference between reward and effort prediction error learning rates. Free parameters (αR, αE, γ, β) of the winning 2LR_ γ model for both groups. Black lines denote means ± SD, dots represent individual data points, and the violin-like shape denotes distribution and frequency of the data. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Pupil size fluctuations track asymmetric cost-benefit reinforcement learning during acute stress

We employed pupillometry to understand whether task-relevant computational processes may be encoded by fluctuations in pupil dilation, which are thought to be controlled by ascending midbrain modulatory systems that play a role in value-based decision-making and the acute stress response.

We observed no main effect of Condition on pupil size fluctuations during choice, effort outcome, and reward outcome epochs, suggesting that acute stress was not associated with more general changes in pupil size (all bin-level $p>0.05$; *Figure 6*, A. Standard analyses; *Supplemental Figure 3* for all effort trials; also see *Supplemental Figure 2* for non-z-transformed pupil responses to task events).

Next, we conducted model-derived pupillometry analyses (Lawson et al., 2020). These analyses revealed effects of Condition on pupil encoding of subjective decision value, EPEs and RPEs (*Figure 6*, B: Model-derived analyses) in a manner commensurate with task performance results. Immediately prior to the stimulus choice, acute stress reduced pupil encoding of subjective decision value (pupil size-subjective decision value association control>stress; stress n.s.,

control>0). Briefly following presentation of effort avoidance outcomes, groups exhibited different pupil size-EPE associations, with no-stress controls showing a non-significant numerically positive pupil size-action cost prediction error association (control>stress, both groups n.s. different from 0). When using all effort outcome trials, we were unable to uncover group differences in pupil encoding of EPEs, due to prominent grip force-related effects on pupil size (*Supplemental Figure 3*). Finally, during reward outcomes, acute stress participants exhibited greater positive associations between pupil size and RPEs compared to no-stress controls (stress>control, stress>0, control n.s.). The average pupil size-RPE slope for bins in which no-stress control and acute stress participants differed (*Figure 6B*), correlated significantly with stress-induced changes in SBP [$\rho_{stress}(38)$= -0.41, *p(permutation)*=0.02] and PANAS negative affect changes [$\rho_{stress}(38)$= -0.46, *p(permutation)*=0.01] in the stress group. Off note, in computational modeling analyses, αR was also correlated with SBP [$\rho_{\alpha R\_stress}$ (38) =-0.36, *p(permutation)*=0.03], and αR-αE difference was correlated with PANAS negative affect changes $\rho_{\alpha diff\_stress}$ (38) =-0.35, *p*(*permutation*)=0.03] in the stress group, suggesting that moderately stressed individuals drove the learning asymmetry.

Group differences in pupil encoding of subjective decision value, EPEs, and RPEs imply that the ascending neuromodulatory systems may have facilitated a stress-induced shift in asymmetric cost versus benefit learning.

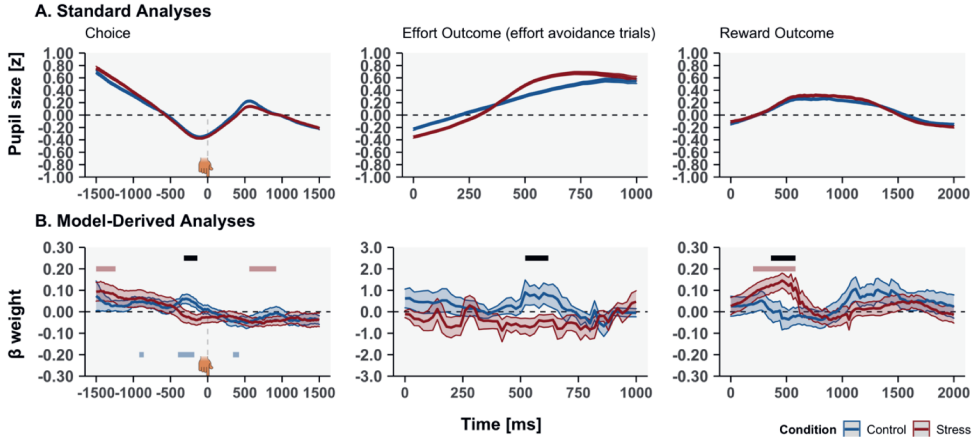

Figure 6 | Model-derived analysis reveals altered pupil encoding of prediction errors and decision value during acute stress.

A. Standard analyses of pupil size during choice, effort outcome, and reward outcome phase revealed no main effect of Condition (no-stress control, acute stress). **B.** Model-derived analyses revealed a stress-induced shift in pupil encoding of subjective decision value (left), action cost prediction errors (middle) and reward prediction errors (right). Black line indicates significant main effect of Condition; blue and red line indicate significance against zero for no-stress control and acute stress groups, respectively (cluster and bin level $\alpha_{permute}$<0.05, 2000 permutations). Group differences in pupil encoding of action cost and reward prediction errors were observed at similar times (note the x-axis differences for effort outcome and reward outcome epochs).

Discussion

Stress-induced alterations in adaptive decision-making are commonly studied using paradigms that isolate positive and negative reinforcement, such as the receipt of a reward or avoidance of a loss. However, it remains poorly understood how acute stress affects the complex process that entails learning about costs *and* benefits, a critical feature of everyday decisions. In this study, participants completed a paradigm in which all stimulus choices contained a potential cost (exerting physical effort) and a financial benefit (€0.20). Acute stress induced a shift in reinforcement learning strategies that improved maximization of monetary rewards relative to minimization of energy expenditure.

Relative improvements in reward versus action cost learning align well with previous reports of enhanced reward learning during acute stress (Byrne, Cornwall, & Worthy, 2019; Lighthall et al., 2013; Petzold et al., 2010), although such effects may depend on stressor timing (Joëls et al., 2006), type (Carvalheiro et al., 2020), and/or sample characteristics (Evans & Hampson, 2015). While reports on action cost learning during acute stress are scarce, acute stress impairs cost-benefit decisions in rodents via changes in physical effort sensitivity, a process mediated by corticotropin-releasing factor and dopamine (Bryce & Floresco, 2016). Our win-stay/lose-shift analyses indicate that asymmetric cost-benefit learning can result from increased sensitivity to monetary gains versus avoidance of costly deterrents.

How might maximization of reward value take precedence over minimization of action cost? Acute stress leads to a redistribution of finite cognitive resources (Hermans et al., 2014): this process limits availability of computationally intensive strategies, including working memory (Qin et al., 2009) and goal-directed instrumental actions (Lars Schwabe & Wolf, 2011). Assuming that acute stress does not merely increase random responding - which we verified via the choice stochasticity model parameter - a computationally cheap heuristic in our task should present itself as better learning for one modality over the other. Increased energy availability (Hermans et al., 2014), insensitivity to aversive stimuli (Timmers et al., 2018), and impaired aversive value updating (Raio et al., 2017) under stress may have reduced the ability – or urgency – to dedicate cognitive resources to strategies that minimize action cost. Importantly, effort expenditure can increase the perceived value of rewards (Inzlicht, Shenhav, & Olivola, 2018). Thus, frequent expenditure of physical effort may increase the perceived value of rewards, and tilt learning towards the maximization of reward value.

Whether this interpretation generalizes to the domain of cognitive efforts is currently unclear. Bogdanov et al. (2021) recently showed that acute stress reduced the willingness to exert cognitive effort, which may be explained by divergent neural versus peripheral effects of stress or could even point to redistribution of resources towards bodily processes. These seemingly divergent results for cognitive and physical effort under stress may align with the reticular-activating hypofrontality model. This model proposes the existence of opponent cognitive and procedural systems, the latter dominating the former during physically-demanding tasks (Dietrich & Audiffren, 2011) – a process that acute stress may further facilitate. Moreover, studies evaluating prolonged physical activity

have reported reduced activity in brain areas associated with mental effort (although physical activity intensity is important (Schmit et al., 2015)), and reduced attention towards physical activity resulting in attenuated feelings of fatigue (Radel, Brisswalter, & Perrey, 2017). Formal comparisons of physical and cognitive effort under stress (or their trade-off) could provide valuable insights.

Using computational modeling (Skvortsova et al., 2017; Skvortsova et al., 2014), we confirmed that biased cost-benefit learning can arise when inappropriate (i.e., similar) importance is afforded to signals that convey information about reward value (RPEs) and action cost (EPEs). Humans presumably display instinctive biases, such as more efficient learning from better-than-expected (vs worse-than-expected) outcomes (Lefebvre et al., 2017) and asymmetric "Go"/approach (vs "No-Go"/avoidance) learning (Guitart-Masip et al., 2012), the latter being a bias modulated by acute stress (de Berker et al., 2016). From this perspective, no-stress controls, who assigned greater importance to EPEs than RPEs, may have used a computationally costly learning strategy that provides counterweight to decisions that are biased towards maximizing reward value (captured by the discounting parameter γ). Paradoxically, when decisions are by default tilted towards reward value, similar reward and action cost learning rates will facilitate reward learning but hamper action cost learning. Reduced learning rate asymmetry in the presence of action cost discounting may, therefore, represent a computational heuristic that is employed when cognitively demanding learning strategies are unavailable and the policy towards energy expenditure is more liberal, such as during acute stress.

Importantly, stress-induced changes in task performance may crucially depend on catecholamine release in neural circuits that support motivation and learning. Dopamine's actions at basal ganglia D1 and D2 mediate approach and avoidance learning (Frank, Seeberger, & Reilly, 2004), and acute stress improves associative learning by augmenting reward-evoked dopamine bursts in selective striatal subdivisions (Stelly et al., 2020). Dopamine's enhancement via L-DOPA administration, moreover, improves reward but not action cost learning (Skvortsova et al., 2017). To the degree that pupillometry can be considered a proxy measure of neuromodulatory activity, these findings are consilient with greater encoding of RPEs by pupil size fluctuations during acute stress. Negative correlations between SBP and PANAS negative affect with RPE-pupil size slopes (and αR) suggest that primarily moderately stressed participants displayed a preference for maximizing reward value, consistent with an inverted U-shape relationship between cognitive performance and DA transmission, which is modulated by stress (Baik, 2020). Noradrenaline, however, mobilizes available energy to complete effortful actions and *locus coeruleus* neurons track energy expenditure (Varazzani et al., 2015). Stress-induced sAA concentrations, increased heart rate, and group differences in the association between pupil size fluctuations and EPEs all point to involvement of the noradrenaline system. Thus, model-derived pupillometry and stress-induction results hint at stress-sensitive dopaminergic and noradrenergic mechanisms that may regulate cost-benefit learning, which could be explored in future work.

The results presented here may improve understanding of stress-related psychopathology. While asymmetric cost-benefit learning during acute stress may be beneficial to reach a desired goal state (e.g., safety) despite high action cost, such strategies could also be maladaptive. For

example, stress exposure can lead to drug or smoking relapse (Schwabe, Dickinson, & Wolf, 2011), a context in which reward value and action cost may be misaligned. Cost-benefit reinforcement learning may provide a useful framework to test hypotheses regarding stress-related impairments in learning and decision-making.

Some study limitations need to be acknowledged. First, pupil dilation associated with effort expenditure greatly reduced our power to detect robust associations between EPE encoding and pupil size fluctuations. Future studies should, therefore, consider greater temporal delays between effort outcome and expenditure phases. Second, while our computational model could recover overall task performance patterns, group differences were subtle and dependent on other (non-learning) parameters, highlighting the importance of interindividual differences in model parameters. Third, although between-group differences on separate trial types failed to reach significance, it is important to note that in the presence of costs and benefits for all choices on every trial, participants might adopt a task-general learning policy, which is reflected in the difference between performance on reward maximization and action cost minimization trials. Lastly, collection of sex hormones and additional psychometric (character/trait-like) data would have facilitated identification of additional moderators of the observed stress-induced performance changes.

Conclusion

To summarize, we present evidence of asymmetric effects of acute stress on cost versus benefit reinforcement learning during acute stress, which computational analyses explain as a failure to assign appropriate importance to RPEs versus EPEs, and our model-derived pupillometry tentatively link to activity of ascending midbrain neuromodulatory systems. These results highlight how learning under acute stress can be tilted in favor of acquiring rewarding things and away from the avoidance of physically costly things.

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Supplemental Information

Supplemental Methods

Reward maximization versus action cost minimization reinforcement learning task

Upon completion of the MAST (stress/ no stress condition), all participants completed a probabilistic stimulus selection paradigm during which they learned to select stimuli with high reward value (20 Eurocents) and avoid stimuli with high action cost (exerting force above a pre-calibrated individual threshold for a duration of 3000 ms). The paradigm was designed in PsychoPy v3.0.0b11 (Peirce et al., 2019) and presented on a 24″ monitor (iiyama ProLite b2483HSU). Physical effort (in mV/kgf) was registered using a hand-held dynamometer in combination with a transducer amplifier (DA100C) and data acquisition system (MP160; all manufactured by BIOPAC Systems, Inc). Individual effort thresholds used throughout the task were obtained by calculating 50% of each participant's maximal voluntary contraction (MVC) (Le Heron et al., 2018) reached over three calibration trials by squeezing the dynamometer with the dominant hand.

During the task at trial onset, a fixation cross flanked by two images was presented; participants chose one image by pressing the V/B button for the left/right option, respectively. A 440Hz/600 Hz tone for left/right choice (200 ms) was presented to confirm the participant's choice. Next, a thermometer with the command "SQUEEZE" or "DON'T SQUEEZE" was displayed. If participants were required to exert effort, they were instructed to squeeze the dynamometer until the mercury level reached the top. The mercury bar only moved if participants exerted above-threshold levels of force and stopped moving if exerted force fell below. The cumulative above-threshold time was 3000 ms. If no effort production was required, an animation of a rising mercury bar was displayed (3000 ms). Finally, a screen was presented showing either a €0.20 coin or a crossed-out coin, indicating no reward (3000 ms).

The task contingencies described in the manuscript were based on extensive pilot tests to identify a reinforcement schedule that would enable us to detect stress-induced improvements *and* decreases in task performance. We selected task contingencies based on pilot sessions involving a no-stress control condition and chose a reinforcement schedule associated with non-ceiling/floor performance on RL and EL trials. The selection of these contingencies was also chosen to make it challenging for the participants to adopt a *pair-specific* policy towards reward maximization and action cost minimization, since this would require the agent to track reward and effort outcomes for 8 unique stimuli. This is noteworthy, since a pair-specific learning or decision-making policy can be a useful strategy in more common instrumental learning paradigm in which all choices are associated with a single outcome (e.g., separate gain-seeking or loss-avoidance pairs) – in this context, experiencing a single gain, or loss, provides information about the trial type. In contrast, within our paradigm architecture, and to the degree that they do not rely on working memory, participants would typically weigh costs against benefits when making their decision. As such, (stress-induced) alterations in the influence of reward value and action cost on choices can be investigated by comparing accuracy on RL *versus* EL pairs, since this measure would be indicative of the more general policy towards reward maximization versus action cost minimization.

Following the learning phase, participants completed a surprise test phase, similar to previous work (Hernaus et al., 2019; Hernaus, Gold, Waltz, & Frank, 2018). This phase consisted of 64 trials in which participants were presented with the original four, as well as six novel, stimulus combinations. Participants were asked to choose the stimulus with the highest reward value or the lowest action cost - depending on a coin or thermometer image presented in the middle of the screen - and received no choice feedback. This allowed us to assess acquired choice tendencies, as well as generalizability of this information to novel situations. The four original pairs were presented four times (total n = 16), during which we only asked participants to discriminate on the basis on the reward value (for RL) or action cost (for EL). For novel stimulus combinations, we only presented stimuli that differed in reward value/action cost if reward value discrimination/action cost discrimination was assessed (total n = 48: n = 4 presentations for the 6 combinations).

Prior to performing the actual task, participants completed a practice phase. A 60% accuracy performance threshold on both trial types was used to confirm that participants understood the general task procedure. The practice round was repeated if participants failed to reach 60% accuracy. To prevent learning, we used deterministic stimulus-outcome probabilities and different stimuli.

Computational cost-benefit reinforcement learning model: model space

In an attempt to uncover latent mechanisms by which acute stress affects reward maximization and/or action cost minimization, we turned to computational modeling. We employed a modified reinforcement learning framework based on Rescorla and Wagner (Rescorla, 1972), and used in Skvortsova et al. (Skvortsova et al., 2017; Skvortsova et al., 2014) to investigate whether acute stress impacted learning about sensitivity to, and/or discounting of reward value and action cost. We first describe the model space.

Various reinforcement learning models assume that choice preferences of an agent are updated via the prediction error, i.e., the mismatch between outcome and expectation (Eqs. 1A, 1B) and the critical quantity that drives learning (Rescorla, 1972):

$$RPE_{(t)} = r_{(t)} - Q_{R(t)}(s, a) \quad (1A)$$

$$EPE_{(t)} = e_{(t)} - Q_{E(t)}(s, a) \quad (1B)$$

Here, $Q_{R(t)}(s, a)$ and $Q_{E(t)}(s, a)$ represent the expected reward value and action cost (i.e., effort), where *s* reflects the given pair and *a* refers to the more abstract action of selecting a stimulus, $r_{(t)}$ and $e_{(t)}$ represent the reward and effort outcome for the chosen stimulus at trial *t*. $RPE_{(t)}$ and $EPE_{(t)}$, thus, represent the RPE and EPE at trial t, respectively.

In order to allow for the possibility that humans do not calculate the prediction error against the actual outcome but, rather, what the outcome "feels" like (Huys, Pizzagalli, Bogdan, & Dayan, 2013), we considered a scenario in which reward and effort outcomes are first multiplied by a free parameter that captures the weight that reward and effort outcomes receive ("W_R" and "W_E" in Eqs.

2A and 2B). As the value of these parameters approaches 1, reward is increasingly valued more positively, and effort more negatively. These parameters, therefore, control the maximum size of the prediction error.

$$RPE_{(t)} = (r_{(t)} * W_R) - Q_{R(t)}(s, a) \quad (2A)$$

$$EPE_{(t)} = (e_{(t)} * W_E) - Q_{E(t)}(s, a) \quad (2B)$$

In various formulations of reinforcement learning, such as Q-learning (Watkins & Dayan, 1992) and the actor-critic framework (Niv, 2009; Rescorla, 1972), the degree to which prediction errors update choice preferences is represented by α, the learning rate (Eq. 3A), which determines how current prediction errors update choice preferences on the subsequent trial. High values of α allow for rapid updating of choice preferences, while a low α implies that choice preferences are updated at a slower pace and are thus co-determined by outcomes further into the past.

$$Q_{R(t)}(s, a) = Q_{R(t-1)}(s, a) + \alpha R * RPE_{(t-1)}(s, a) \quad (3A)$$

$$Q_{E(t)}(s, a) = Q_{E(t-1)}(s, a) + \alpha E * EPE_{(t-1)}(s, a) \quad (3B)$$

Extensive evidence suggests that organisms use different learning systems for different types of information, including reward value and action cost (Palminteri & Pessiglione, 2017; Skvortsova et al., 2017; Skvortsova et al., 2014) (Eqs. 3A/B). Thus, the use of separate learning rates for RPEs and EPEs allows for asymmetrical learning about these types of information.

While the learning rate controls the *speed* at which choice preferences are updated, learning rate (nor reward/effort weight) alone does not explain how learned estimates of reward value and action cost may compete at the decision stage (i.e., when participants choose between two stimuli). Agents weigh costs against benefits to calculate a subjective decision value (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2017; Skvortsova et al., 2017), which is used to guide choices (Eq. 4).

$$Q_{(t)}(s, a) = Q_{R(t)}(s, a) - Q_{E(t)}(s, a) \quad (4)$$

In its simplest form, Q, the subjective decision value of a stimulus is represented by the difference between the expected reward and action cost value at trial *t* (Eq. 4) (Skvortsova et al., 2014). However, this particular operationalization of subjective value does not take into account the observation that humans tend to discount or prioritize certain types of information in their decisions (Apps, Grima, Manohar, & Husain, 2015; Inzlicht, Shenhav, & Olivola, 2018). We, therefore, allowed for variation in the calculation of subjective decision value via action cost discounting (Eq. 5). While discounting rates can be linear or hyperbolic (Hartmann, Hager, Tobler, & Kaiser, 2013), here we only considered linear discounting in light of previous work using a similar task design (Skvortsova et al., 2017; Skvortsova et al., 2014). As the value of γ approaches zero, action cost

discounted increases leading the agent to ignore action cost/only utilize reward value to make a decision.

$$Q_{(t)}(s, a) = Q_{R(t)}(s, a) - \gamma * Q_{E(t)}(s, a) \quad (5)$$

Once the subjective decision value has been computed, the degree to which participants deterministically sample the optimal stimulus is captured by a softmax decision function (Eq. 6).

$$pr(s, a) = exp(Q_{(t)}(s, a)) / sum(exp(\beta * Q_{(t)}(s))) \quad (6)$$

Here, pr is the probability of selecting an action, β is the inverse temperature parameter that among others captures the balance between exploration and exploitation (Nassar & Frank, 2016), $Q_{(t)}(s, a)$ is the net value of the chosen option and $Q_{(t)}(s)$ represents the net values of both stimuli in the pair.

Within the above-described model space our predictions of acute stress effects on reward maximization and action cost minimization could, thus, be explained by changes in sensitivity to reward value and/or action cost (W_R, W_E), changes in how much weight RPEs and EPEs are afforded (i.e., learning rates, αR, αE), and/or changes in the discounting of reward value by action cost (γ). If acute stress leads to more random responses, such effects should be captured by β.

Based on our predictions and the obtained pattern of results (most notably asymmetrical RL/EL performance in the acute stress condition), we considered six candidate models that could capture these various scenarios: I) a model with 2 distinct learning rates for reward and effort (αR, αE) [2LR]; II) a model with 2 learning rates (αR, αE) and a discounting parameter (γ) (2LR_ γ); III) a model with 2 learning rates (αR, αE), a reward weight (W_R) and an effort weight parameter (W_E) (2LR_W_R_W_E), IV) a model with a *single* learning rate (α), reward weight (W_R), effort weight (W_E), and a discounting (γ) parameter (LR_ W_R__W_E_ γ); V) a model with 2 learning rates (αR, αE), a reward weight (W_R), and a discounting (γ) parameter (2LR_W_R_γ); VI) a model with 2 learning rates (αR, αE), a reward weight (W_R), effort weight (W_E) and discounting (γ) parameter (2LR_ W_R_ W_E_ γ).

All models contained a β parameter. Consistent with previous work (Skvortsova et al., 2017; Skvortsova et al., 2014), reward and action cost outcomes were set to [0,1 for no/yes reward] and [-1,0 for no/yes effort avoidance], respectively.

Computational cost-benefit reinforcement learning model: Model Fitting, Selection, and Simulations

Bayesian Model Selection (BMS; spm_BMS function in SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) using the AIC as a fit statistic that penalizes for the number of model parameters (Myung, Tang, & Pitt, 2009), suggested that the 2LR_γ model was the most likely model, as indicated by the protected exceedance probability (*pxp,* φ = 0.99) (Rigoux, Stephan, Friston, & Daunizeau, 2014) and expectation of the posterior [$p(r|y)$ = 0.70]

(*Supplemental Figure 1A for p(r|y) of all candidate models*). We note that 2LR_γ remained the most likely model when we considered additional models with greater redundancy and/or lesser biological plausibility (e.g., models with all combinations of reward value/action cost discounting *and* weight parameters).

In *post hoc* simulations, i.e., generating participant choices using the obtained parameters, we observed moderate-to-high correlations between simulated and empirical RL/EL for the acute stress and no-stress control group [$\rho_{RL\_control}$ = 0.55, p < 0.01; ρ_{RL_stress} = 0.84, p < 0.01; $\rho_{EL\_control}$ = 0.56, p < 0.01; ρ_{EL_stress} = 0.77, p < 0.01; *see Supplemental Figure 7*], although the canonical performance difference in RL versus EL accuracy was not selective to the acute stress group [$t_{control}(39)$ = -6.72, p < 0.01; $t_{stress}(39)$ = -6.01, p < 0.01]. However, after we fixed β and γ to group-level averages to better demonstrate the effect of group differences in the learning rate parameters, we recovered a small but significant simulated difference in RL versus EL performance for the acute stress group [$t(39)$ = 2.27, p = 0.03], which was not predicted in the no-stress control group [$t(39)$ = 0.91, p = 0.37] (Condition-by-Trial Type interaction: [$F(1,78)$ = 0.77, p = 0.38, n^2_G = 0.01]; *Supplemental Figure 1B for empirical versus simulated data, averaged across 100 repetitions per subject*).

Importantly, even if a given model is the most likely one based on model fitting and post hoc simulation results from the entire sample, there is still the possibility that different models can better explain task performance in the no-stress control and acute stress condition. When repeating BMS for each condition separately, 2LR_γ was the most likely model in the no-stress control group [φ = 0.99, $p(r|y)$ = 0.83], while for acute stress subjects 2LR_γ was not convincingly the most likely model [φ = .47, $p(r|y)$ = 0.46]. Here, the 2LR model (containing αR, αE, and β parameters) was equally likely to be the optimal model [φ = 0.53, $p(r|y)$ = 0.47]. Post-hoc simulations from the 2LR model also correlated with actual data, both for no-stress control [ρ_{RL} = 0.65, p < 0.01; ρ_{EL} = 0.60, p < 0.01] and acute stress participants [ρ_{RL} = 0.81, p < 0.01; ρ_{EL} = 0.75, p < 0.01].

Similar to the 2LR_ γ model, the 2LR model seemingly also explained stress-induced changes in cost-benefit reinforcement learning via changes in learning rates; in the 2LR model, the acute stress group exhibited greater values of αR versus αE [$t(39)$ = 2.65, p = 0.01], while no-stress control subjects did not [$t(39)$ =. 0.69, p = 0.50] (Condition-by-Learning Rate interaction: [$F(1,78)$ = 2.88, p = 0.09, n^2_G = 0.01]. The difference in learning rates between 2LR_γ (where αR and αE are similar for the acute stress group, *see Results*) and 2LR (where αR > αE for the acute stress group) can be explained by the absence of discounting parameter γ: 2LR is a special case of 2LR_γ, where γ = 1, and thus asymmetric effects of acute stress on reward value maximization and action cost minimization can only be explained by *dissimilarity* in learning rates.

Although the effects of acute stress on reward value and action cost learning rates are opposite in 2LR_ γ versus 2LR architectures, these results bolster our confidence in the overall model space, as well as the interpretation that acute stress primarily impacts reward value and action cost learning rates, and *not* discounting. The observations that I) 2LR_ γ fit better in the entire group of

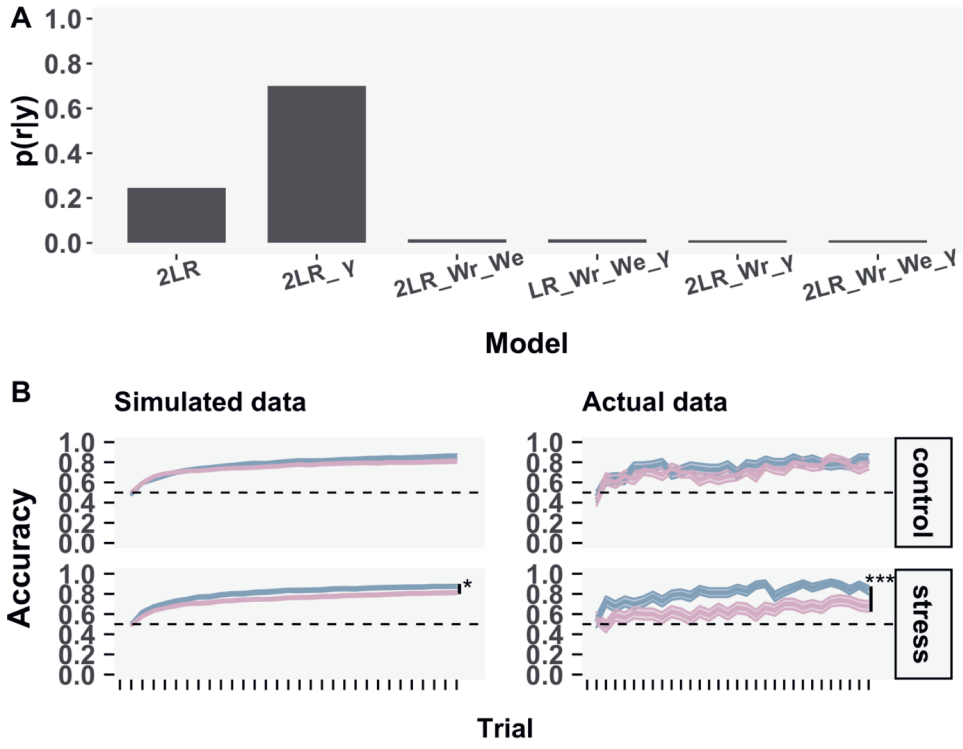
participants, II) 2LR is fully contained within the 2LR_ γ model, and III) 2LR_ γ displayed good recoverability (see *below)* motivated our choice to focus on the 2LR_γ model.

In model recoverability analyses i.e., re-fitting the simulated data from the model to all candidate models (Wilson & Collins, 2019), BMS confirmed that the simulated 2LR_γ data (that is, simulations *without* fixed parameters) were most likely to be generated from 2LR_γ [$\varphi = 0.99$, $p(r|y) = 0.71$].

To assess the stability of 2LR_γ parameters, we repeated model fitting using a Bayesian hierarchical model fitting approach consisting of two steps, as described previously (Daw, 2011; Frey, Frank, & McCabe, 2019). In the first step, we fit the 2LR_γ model to trial-wise choices to obtain subject-specific parameters; in a second step, we again fit the model to trial-wise choices, but this time we used the group-level average and covariance matrix of every parameter as priors, thereby shrinking the parameter search space. Motivated by recent work showing that group-specific priors, compared to a single prior for the entire sample, can better account for between-group differences in task performance, as well as improve parameter robustness and recoverability (Valton, Wise, & Robinson, 2020), we used separate mean and covariance matrices for the acute stress and no-stress control groups.

Highly similar parameter estimates were obtained after hierarchical fitting (for parameter estimates after Bayesian hierarchical model fitting; *see Supplemental Figure 9*). Similar to *post hoc* simulations using parameters from the non-hierarchically fit 2LR_γ model, we observed moderate-to-high correlations between empirical and simulated data using parameters obtained from the hierarchically fit model [$\rho_{RL\_control} = 0.65$, $p < 0.01$; $\rho_{RL\_stress} = 0.84$, $p < 0.01$; $\rho_{EL\_control} = 0.37$, $p = 0.02$; $\rho_{EL\_stress} = 0.78$, $p < 0.01$; *see Supplemental Figure 9*]. All in all, these results confirm parameter stability within the 2LR_γ architecture.

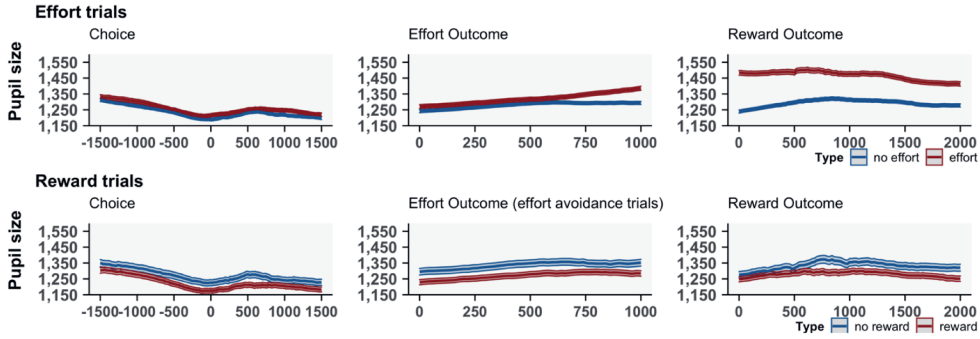
In light of model fitting results, post-hoc simulations, model and parameter recoverability analyses, we used parameters and trial-by-trial predictions of the non-hierarchically fit 2LR_ γ model in the main analyses.



Supplemental Figure 1 | Model selection and *post hoc* simulations of the winning model.
Panel **A**: Expectation of the posterior for all candidate models. Panel **B**: Post-hoc simulations after fixing β and γ to group-level averages. Colored lines represent mean ± SD. Dashed lines denote chance level (0.5). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

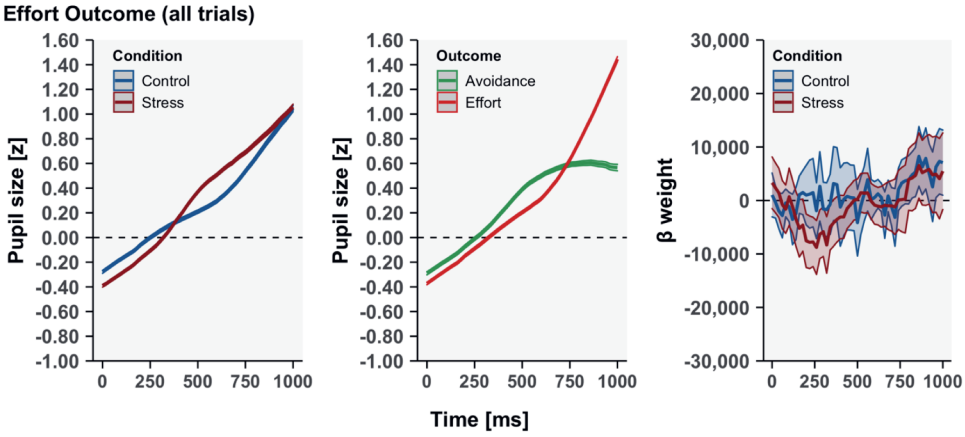
Pupillometry

Raw (here: preprocessed, non-baseline-corrected, non-z-scored) pupillometry data are visualized in *Supplemental Figure 2*.



Supplemental Figure 2 | **Pupil dilation track on raw data.**
Top: Raw pupillometry data for effort/no effort outcomes for effort learning trials. **Bottom:** Raw pupillometry data for reward/no reward outcomes for reward learning trials. To clearly visualize the effect of yes/no reward outcomes, we include only reward learning trials in which no effort was required.

With regards to model-derived analysis, for the choice phase we regressed trial-wise measures of pupil size against trial-wise estimates of the subjective decision value (i.e., effort-discounted reward value) of the chosen stimulus. For the effort and reward outcome phase, trial-wise EPEs and RPEs were the primary predictors of interest, respectively. Trial number (1-120) and presented images/pair (RL_easy, RL_hard, EL_easy, EL hard) served as additional predictors of interest for all models. Additional epoch-specific variables of interest were included for the choice (optimal choice yes/no), effort (action cost of chosen stimulus, effort avoidance yes/no), and reward (reward value of chosen stimulus, reward yes/no) outcome phase. Similar results were obtained when repeating the analyses with more elaborate GLMs (e.g., the addition of yes/no most likely outcome based on reward/effort outcome probabilities [“surprise”] and reward/action cost for EL/RL trials).

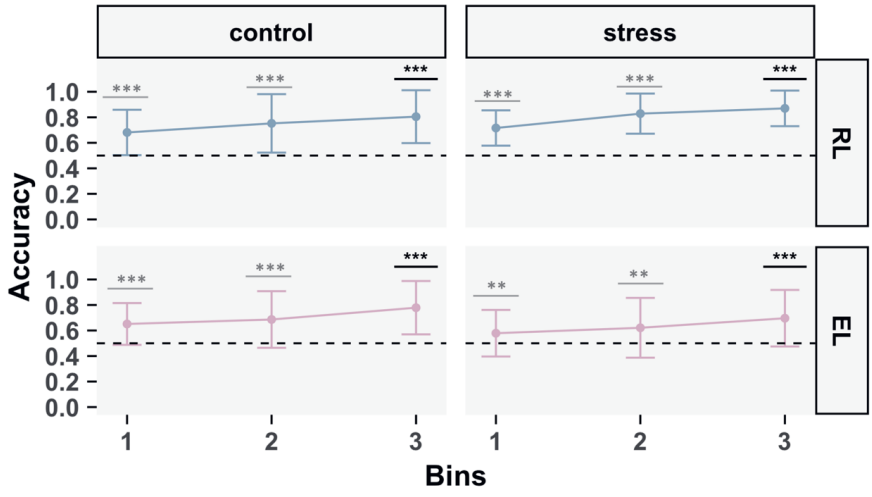


Supplemental Figure 3 | **Pupillometry analyses using all effort outcome trials.**
Left: Standard analyses of pupil size using all effort outcome trials. **Middle**: Pupil size differences during effort/effort avoidance outcomes in the entire sample; force exertion was associated with large effects on pupil size and were therefore excluded from analyses. **Right**: Model-derived action cost prediction error analyses using all effort outcome trial.

Supplemental Results

Participants use reinforcement learning to optimize decisions

First, we explored whether participants exhibited evidence of reinforcement learning to optimize actions, which in this paradigm should be reflected by an increased tendency to select stimuli with high reward value and avoid stimuli with high action cost as a function of increasing number of stimulus pair presentations (i.e., "time").



Supplemental Figure 4 | Evidence of reward and action cost reinforcement learning.
Optimal stimulus choices ("accuracy") on reward learning (RL) and effort learning (EL) (rows) trials for both conditions (columns). Trials were binned into groups of 10 presentations. Participants performed significantly better than chance level (0.5) in all bins. Means ± SD. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

Task performance analyses including chance-level performers

Repeating key task performance analyses including participants that performed at chance level (≤ 0.5, total n = 93), we were still able to recover a Condition-by-Trial Type performance in the model of accuracy [$F(1,91) = 7.30$, $p = 0.04$, $n^2_G = 0.04$], with the acute stress group displaying better RL vs EL performance [$t(46) = 5.83$, $p < 0.01$], while no-stress controls performed similarly on both trial types [$t(45) = 1.24$, $p = 0.22$]. Participants in the acute stress group outperformed participants in the no-stress control group on RL [$t(91) = 2.04$, $p = 0.04$], but no simple main effects of Condition were observed for EL [$t(91) = -1.67$, $p = 0.1$].

Gender analyses

We performed a series of additional mixed ANOVAs and t-tests to analyze potential gender differences in psychological and physiological measures (PANAS negative, PANAS positive, SBP, heart rate, sCORT_AUCi, sAA_ AUCi) as well in the dependent variables (accuracy and Win/stay rate).

SBP and heart rate showed no significant Gender-by-Condition-by-Time, Gender-by-Condition nor Gender-by-Time interactions (all p-values>0.05). PANAS negative subscale analyses revealed significant Gender-by-Condition-by-Time [$F(1, 76) = 7.03$, $p = 0.01$, $n^2_G = 0.01$] and Gender-by-Time [$F(1, 76) = 5.95$, $p = 0.02$, $n^2_G = 0.01$] interactions, but a non-significant Gender-by-Condition interaction [$F(1, 76) = 3.47$, $p = 0.07$, $n^2_G = 0.04$]. Post- hoc comparisons indicated a significant difference in the stress condition post-MAST [$t(37.7) = -2.26$, $p = 0.03$] with females scoring higher than males on PANAS negative subscale. In addition, PANAS positive subscale showed a significant Gender-by-Condition-by-Time [$F(1, 76) = 5.67$, $p = 0.02$, $n^2_G = 0.01$] but no Gender-by-Condition nor Gender-by-Time interactions (all p-values>0.05). Post-hoc analyses revealed no gender differences (all *p-values* > 0.05). No significant gender differences were observed for sAA_AUCi [$t(32.4) = -0.52$, $p = 0.61$]. However, there was a marginally significant difference after stress induction in sCORT_AUCi [$t(34.5) = 2.07$, $p = 0.05$] with males having higher cortisol levels than females.

Lastly, with regards to task performance variables, overall accuracy, and Win/stay rates, we observed no Gender-by-Condition-by-Trial Type, Gender-by-Condition, nor Gender-by -Trial Type interactions (all *p-values* > 0.05).

Overall, these analyses provided no systematic evidence for gender on stress-induction or task performance measures.

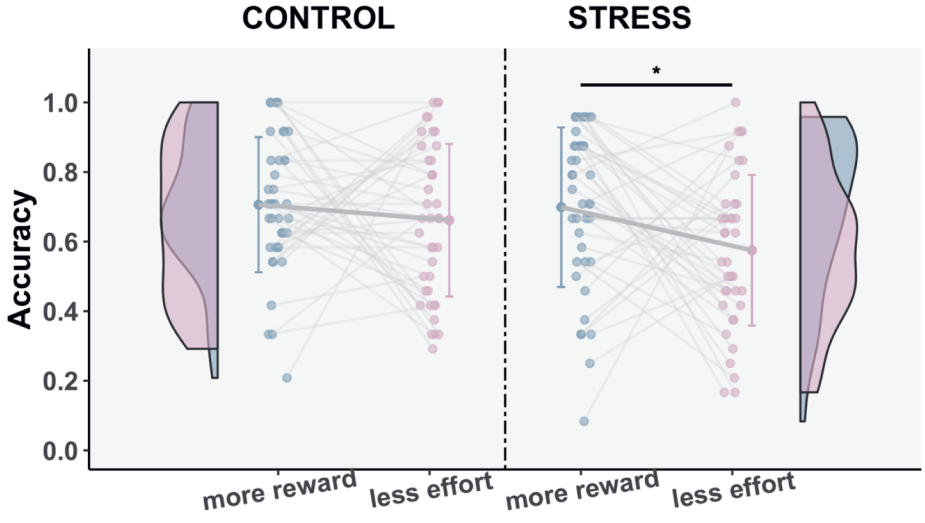
Asymmetric cost-benefit reinforcement learning biases actions in acute stress subjects

During a surprise 64-trial test phase (Hernaus et al., 2018), we asked participants to discriminate original and novel combinations of stimuli on the basis of reward value or action cost without receiving feedback (n = 16 trials for original combinations; n=48 for novel combinations). The surprise test phase allowed us to assess learned choice tendencies without having to arbitrarily choose a given number of final learning phase trials, during which participants may still learn. This

approach also allowed us to assess the degree to which learned tendencies would carry over to novel contexts.

First, both groups chose the optimal (most rewarding/effort avoiding) stimulus on surprise test phase trials involving the original four pairs [one-sample t-test against chance; $control_{RL}$: $t(39) = 8.73$, $p < 0.001$; $control_{EL}$: $t(39) = 3.72$, $p = 0.02$; $stress_{RL}$: $t(39) = 13.54$, $p < 0.01$; $stress_{EL}$: $t(39) = 4.47$, $p < 0.001$], confirming that both groups had developed a preference for the optimal stimulus.

Although we observed no Condition-by-Trial type (reward value, action cost discrimination) interaction or main effects of Condition for novel stimulus combinations [$F(1,78) = 1.10$, $p = 0.30$, $n^2_G = 0.01$; stress vs controls reward value discrimination: $t(75.9) = 0.15$, $p = 0.88$; stress vs controls action cost discrimination: $t(78) = 1.77$, $p = 0.08$], pairwise comparisons revealed that the acute stress group performed better on reward discrimination compared to action cost discrimination trials [$t(39) = -2.23$, $p = 0.03$], while no-stress controls performed similarly on both trial types [$t(39) = -0.87$, $p = 0.39$]. These results provide some evidence that a reward maximization-over-action cost minimization reinforcement learning policy might bias future actions in novel contexts (*Supplemental Figure 5*). Although, in the absence of interaction this result should be interpreted with caution.

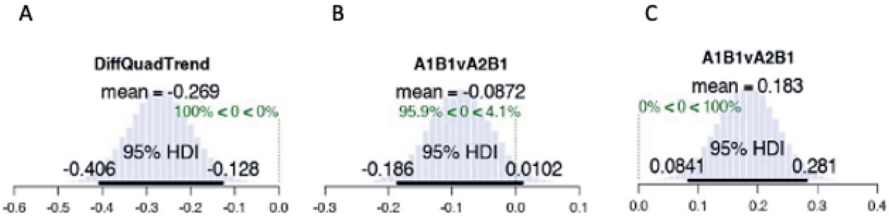


Supplemental Figure 5 | Surprise test phase performance.
The acute stress group performed better on reward than action cost discrimination trials. Means ± SD, individual data points, distribution and density of the data are displayed. Significant differences are depicted with asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

Hierarchical model fit

Given that we used separate priors for the two groups, we report the Bayesian analogue of a t-test and mixed-ANOVA (Kruschke, 2014) - a more robust test of group differences - for posterior parameters obtained from the hierarchically fit model (for reference, we also report these analyses for the non-hierarchical data).

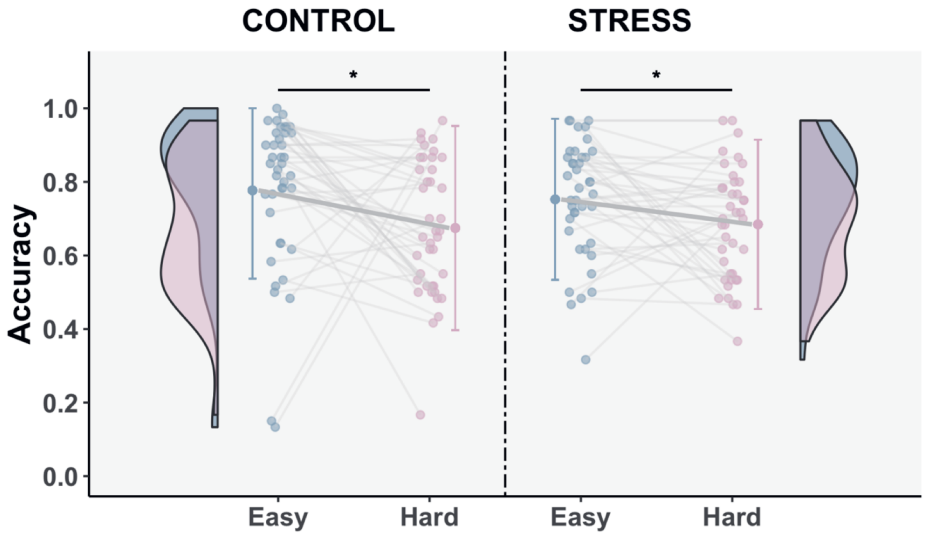
Using posterior parameters we recovered the key Condition-by-Learning Rate interaction (95% HDI for Bayesian mixed ANOVA = -0.41 to -0.13, mean = -0.27; non-hierarchical data: 95% highest density interval (HDI) for Bayesian mixed ANOVA = -0.41 to -0.02, mean = -0.22). Acute stress and no-stress control subjects differed from each other on αE (95% HDI = 0.08 to 0.3, mean = 0.18) but not αR (95% HDI = -0.19 to 0.01, mean = -0.09) (*Supplemental Figure 6*). Similar to the non-hierarchically fit parameters, acute stress and control subjects did not differ on posterior estimates of γ (95% HDI = -0.09 to 0.14, mean = 0.02) and β (95% HDI = -0.03 to 0.2, mean = 0.09).



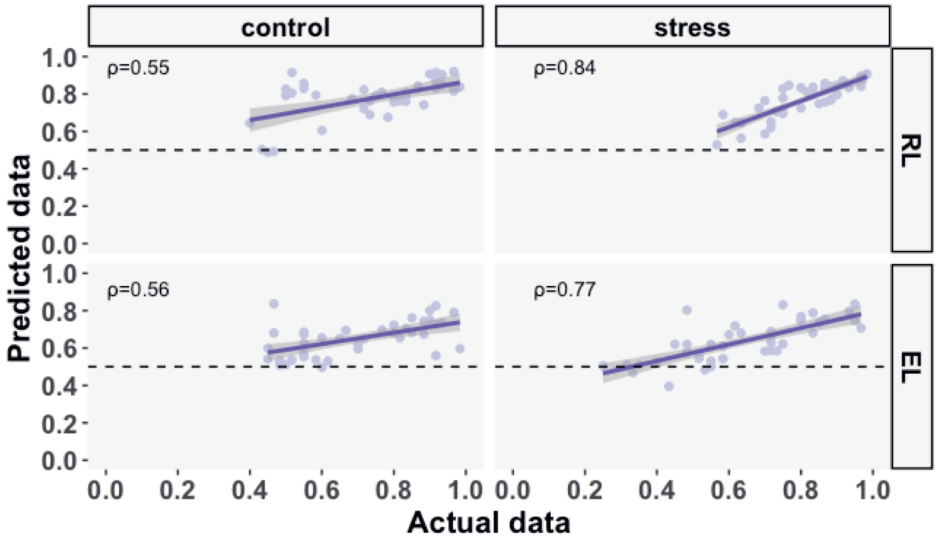
Supplemental Figure 6 | Bayesian estimation analysis to evaluate group differences in posterior parameter distributions.

Panel A. Bayesian estimation (mixed-ANOVA) using posterior parameters (following hierarchical fitting) revealed evidence for a credible Condition-by-Learning Rate interaction. The observed mean difference from zero that falls outside the 95% HDI suggests that the difference between αE and αR was greater in no-stress controls compared to acute stress subjects. **Panel B**. Both groups did *not* differ in the magnitude of αR, as indicated by a 95% HDI that included 0. **Panel C**. Acute stress compared to no-stress control subjects exhibited a lower value of αE, as indicated by a 95% HDI that falls well above zero.

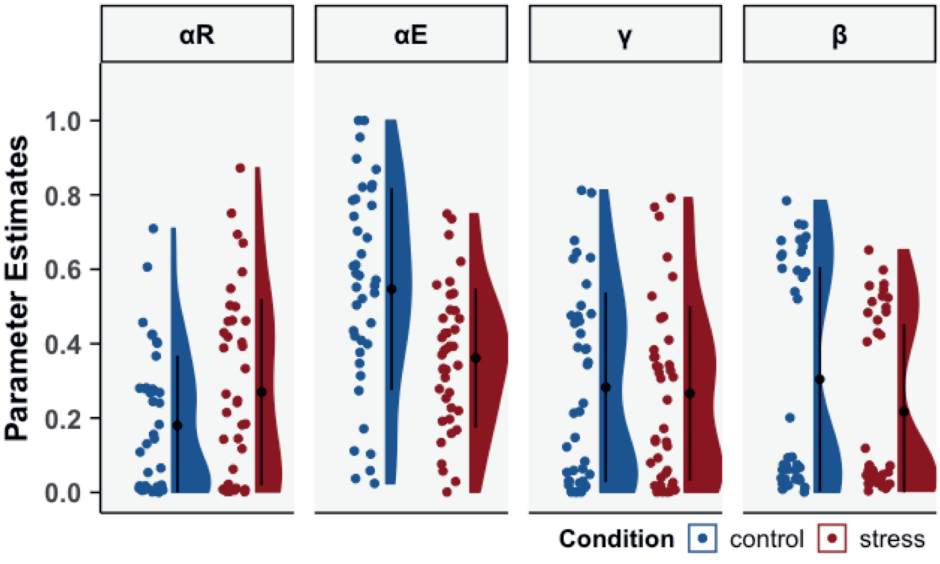
Supplemental Figures



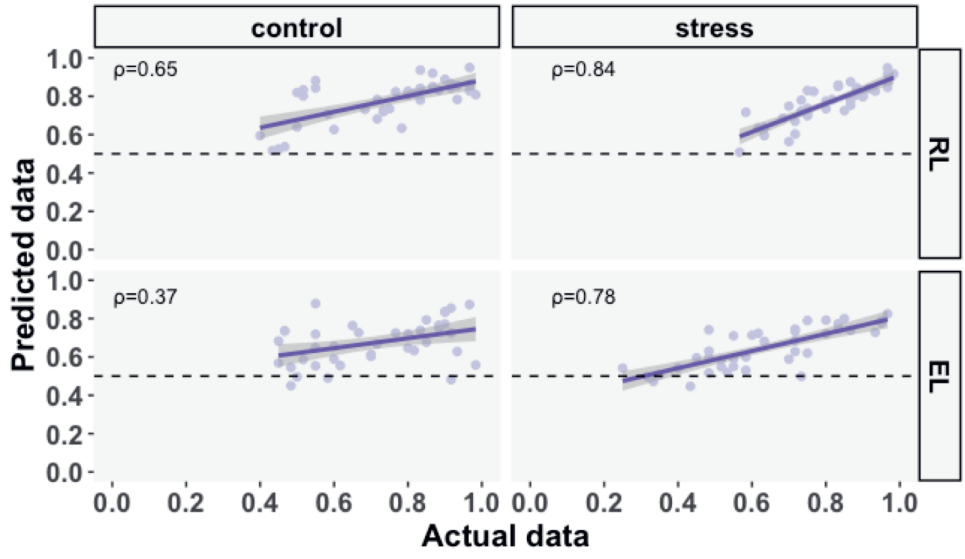
Supplemental Figure 7 | Acute stress does not affect difficulty learning.
Easy and hard pairs collapsed across RL/EL trials depicted for each condition separately. While all participants sampled the optimal choices more frequently for Easy vs Hard pairs, no significant Condition-by-Difficulty interaction or between-group differences were observed. Means ± SD, individual data points, distribution and density of the data are displayed. Significant differences are denoted with asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).



Supplemental Figure 8 | Correlations between empirical and simulated 2LR_γ choices.
Actual and post hoc simulated choices for RL and EL (rows) were moderately to highly correlated, both for no-stress control and acute stress subjects (columns). Simulations were averaged across 10 repetitions per subject. Solid and shaded lines represent mean ± $CI_{95\%}$. Dots represent individual data points. Horizontal dashed lines indicate chance level (0.5).



Supplemental Figure 9 | Parameter estimates after Bayesian hierarchical model fitting.
Hierarchical model fitting reproduced the overall pattern of parameter estimates (*Figure 5* for comparison).



Supplemental Figure 10 | Correlations between empirical and simulated 2LR_γ choices after Bayesian hierarchical model fitting.

Correlations between actual and post hoc simulated choices for RL and EL (rows) for no-stress control and acute stress subjects (columns). Simulations were averaged across 10 repetitions per subject. Solid and shaded lines represent mean ± $CI_{95\%}$. Dots represent individual data points. Horizontal dashed lines indicate chance level (0.5).

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CHAPTER 3

Perceived chronic stress and impulsivity are associated with reduced learning about the costs and benefits of actions

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Abstract

Many psychiatric conditions have been linked with deficits in cost-benefit reinforcement learning. However, previous results have been mixed, partly due to significant symptom heterogeneity within distinct psychiatric conditions and symptom overlap between them, making it difficult to disentangle whether alterations in cost-benefit reinforcement learning are condition- or symptom-specific. Here, we investigate whether transdiagnostic (sub)clinical symptoms and risk factors for psychopathology are associated with reinforcement learning and cost-benefit integration. For this reason, we use an online cost-benefit reinforcement learning task in combination with self-rated measures of common transdiagnostic factors (chronic stress, anhedonia, impulsivity, energy/fatigue) in 360 subjects (18-46 years old) with(out) a diagnosis of a psychiatric condition. Increased chronic stress and impulsivity were associated with poorer reinforcement learning, independent of whether participants were learning to minimize costs (physical effort) or maximize benefits (monetary rewards). These associations were selectively driven by a reduction in learning from positive and negative reinforcement, not punishment. The use of mobile phone (compared to laptop/PC) was also associated with lower performance accuracy. Data and scripts are available (https://osf.io/w3mvq/). Our work emphasizes the importance of chronic stress and impulsivity as potential drivers of altered motivation and goal-directed behavior beyond diagnostic labels, in addition to methodological challenges associated with data collection via online platforms.

Keywords: reinforcement learning, cost-benefit, chronic stress, impulsivity, transdiagnostic factors

Introduction

Humans are required to act within a complex and dynamic environment on a daily basis. Within this environment, individuals must often learn to make appropriate actions, that maximize benefits (e.g., rewards), and minimize costs (e.g., effort or punishment). This ability to optimize our behavior based on the outcomes of previous actions, and to use this knowledge to guide future decisions, is known as reinforcement leaning (Lee et al., 2012; Niv, 2009).

Reinforcement learning is a key construct within the Positive Valence System (PVS) domain of the Research Domain Criteria (RDoC) project, a well-established transdiagnostic approach to psychiatric conditions (Cuthbert, 2014; Insel et al., 2010; Kozak & Cuthbert, 2016). The PVS focuses on reward-seeking behavior and has been strongly linked to motivational impairments (Olino, 2016). Aberrant use of reinforcement learning to guide actions that maximize benefits and minimize costs, and impairments in integrating (learned) costs and benefits into a net value (Pessiglione et al., 2017; Pizzagalli et al., 2005; Treadway et al., 2009), are considered to be among the key mechanisms that drive motivational dysfunction and impaired goal-directed behavior across a wide range of psychopathological conditions (Pessiglione et al., 2017; Zald & Treadway, 2017).

For instance, previous work has demonstrated that individuals with depression exhibit impairments in reinforcement learning, blunted sensitivity to rewards, and increased aversion to exerting effort (Cléry-Melin et al., 2011; Geugies et al., 2019; Huys et al., 2013; Pizzagalli et al., 2008; Reinen et al., 2021; Treadway et al., 2012). A similar pattern has been reported in individuals with schizophrenia (Barch et al., 2014; Gold et al., 2013; Hernaus et al., 2018; Reddy et al., 2015), although the underlying mechanisms of such deficits are hypothesized to differ compared to those in mood disorders (e.g., cognitive control deficits versus reduced reward responsivity) (Barch et al., 2016; Culbreth et al., 2018). In addition, individuals with drug addiction show increased reward sensitivity (Dawe & Loxton, 2004) and impaired learning from negative outcomes (Myers et al., 2017), while attention deficit hyperactivity disorder (ADHD) has been associated with deficits in reward learning (Parvaz et al., 2018; Thoma et al., 2015) but not reduced effort aversion (Mies et al., 2018). Combined, these results suggest that a wide range of psychopathological conditions characterized by altered motivational states may be associated with distinct changes in reinforcement learning and cost-benefit integration.

Importantly, the majority of previous work has relied on case-control designs, in which individuals with a diagnosis of a psychiatric disorder are contrasted against healthy volunteers (i.e., those without such a diagnosis). Even though “cases” may share the same diagnostic label, it is well known that significant heterogeneity (e.g., in terms of symptom severity and profile) exists within these groups (Brolsma et al., 2022), which may at least partly account for inconsistencies or contradicting results between studies (Berwian et al., 2020; Chen & Takahashi, 2017; Leyton & Vezina, 2013; Luman et al., 2005; McCarthy et al., 2016).

Fewer studies have investigated how transdiagnostic measurements of psychopathology and associated risk factors are accompanied by deficits in motivation and goal-directed behavior in the general population, independent of diagnostic status and label. These measures play an important role in the RDoC framework of psychopathology (Krueger & Eaton, 2015), suggesting that finding links between particular clinical features and cognitive/behavioral constructs could pave the way for future revisions of the current diagnostic system (Insel et al., 2010).

In terms of risk factors, it is well known that stress and stressful life events increase the risk for psychopathology in a transdiagnostic fashion (Harkness et al., 2014; Lynch et al., 2021; Sinha, 2008). Many studies have found evidence that chronic stress impacts PVS-associated behavior either directly, or as a mediator (Olino, 2016). Particularly, exposure to both acute and chronic stress has been associated with abnormal reward-seeking (Polter & Kauer, 2014; Schwabe et al., 2011; Vidal-Ribas et al., 2019) and effort expenditure (Bogdanov et al., 2021; Voulgaropoulou et al., 2022; Yang et al., 2014).

In terms of psychopathology, impulsivity or disruptive impulse control are thought to be transdiagnostic impairments linked to psychopathology characterized by externalizing problems (Freis et al., 2022). In online studies, compulsivity and impulsivity have been shown to be associated with deficits in goal-directed control (Gillan et al., 2016) and increased random exploration strategies (Dubois & Hauser, 2022) in the general population. In addition, anhedonia and low energy (fatigue) are constructs highly linked with PVS (Medeiros et al., 2020) and have been associated with disrupted reward learning and effort valuation respectively (Huys et al., 2013; Müller et al., 2021).

In the current study, we aimed to explore which transdiagnostic measures of impaired motivation and goal-directed behavior were associated with distinct aspects of reinforcement learning and cost (physical effort) – benefit (monetary reward) integration in a sample that spanned several diagnostic spectra as well as non-clinical individuals. Based on the above considerations, we selected constructs with strong *a priori* links to a transdiagnostic risk of psychopathology (i.e., chronic stress, anhedonia, energy/fatigue, impulsivity). We collected self-reported ratings of these measures, in combination with a simplified version of a previously-validated cost-benefit reinforcement learning task (Voulgaropoulou et al., 2022) using the (digital) Gorilla platform (Anwyl-Irvine et al., 2020) to collect a sample size that was well-powered to detect (differential) associations between self-report measures and task performance. Guided by previous work, we hypothesized the presence of associations between self-rated measures of psychopathology and distinct aspects of reinforcement learning and cost-benefit integration. Specifically, we expected lower energy/greater fatigue to be associated with a greater emphasis on learning to minimize costs (Müller et al., 2021), chronic stress and anhedonia to be primarily associated with reduced learning about rewards (Huys et al., 2013; Ironside et al., 2018), while impulsivity may be associated with a more general deficit in reinforcement learning (i.e., independent of outcome) (Cáceres & San Martín, 2017; Peck & Madden, 2021).

Methods

The study was performed according to the Declaration of Helsinki and was granted ethical approval by the ethics committee of the Faculty of Psychology and Neuroscience of Maastricht University (ERCPN- 220_38_03_2020). Informed consent was provided by every participant prior to the start of the experiment.

Participants

In total, 483 adults, 18-45 years of age, participated in this study between 24/04/2020 and 02/09/2020. Recruitment strategies were focused on young adults and students with targeted advertisements via Sona, mailing lists, and Facebook student and social groups. The only inclusion criteria were sufficient understanding of the English language and availability of a laptop, PC, or smartphone. Due to the emphasis on latent transdiagnostic factors, participants were not excluded based on a psychiatric/psychological disorder. However, after excluding participants based on a number of performance criteria (catch items n=20, task performance n=103; discussed below), the final sample consisted of 360 participants (age: M = 24.31; SD = 4.27). Power analyses conducted in G*Power (Faul et al., 2009) indicated that a sample of 351 participants would yield a power of 95% to detect an effect of Cohen's $f^2 \approx 0.07$ ($\eta^2 G \approx 0.04$) in a linear multiple regression analysis (9 predictors, $\alpha = 0.05$). All participants completed the ~30 min web-based study session hosted on the online platform Gorilla Experiment Builder (www.gorilla.sc) (Anwyl-Irvine et al., 2020). At the end of the session, they were reimbursed in the form of gift vouchers (5 euro), research participation credits (equivalent of 0.5 hours) or they could choose to donate their earnings to Doctors Without Borders.

Self-report questionnaires

During the session, participants filled out several demographic questions and a set of four self-rated questionnaires based on the constructs highlighted in the introduction, including the Perceived Stress Scale (Cohen et al., 1983), Snaith–Hamilton Pleasure Scale (Snaith, 1993), Vitality Scale (Bostic et al., 2000), and Abbreviated Impulsiveness Scale (Coutlee et al., 2014), which captured the transdiagnostic constructs/risk factors discussed in the introduction. Socio-demographic information including age, gender, diagnosis of a DSM-5 psychiatric disorder by a health care professional (lifetime) and device type used during the session (smartphone, PC or laptop) were additionally collected. To ensure that all participants paid attention during the session, we included four catch items, one at each self-rated questionnaire (e.g., “If you are paying attention to these questions, select "agree" as your answer”; four in total). Participants that responded inaccurately to one or more of these catch items were excluded (n=20). To minimize the possibility of order effects, self-rated questionnaires were presented using Latin square randomization and all possible permutations of questionnaire orders were presented equally often.

Perceived stress scale (PSS)

The PSS was used to assess perceived chronic stress over the past month. The scale consists of 10 items and each item is rated on a 5-point Likert scale ranging from 0=“never” to 4=“very often” (Cohen et al., 1988). The PSS items assess the degree to which participants experience their life

as being unpredictable, uncontrollable, and overloading. Previous research has found that chronic stress and distress potentiates the development of internalizing problems such as anxiety and depression (Appleyard et al., 2005; Krueger et al., 2018).

Based on their total PSS scores, participants were divided into three categories according to corresponding guidelines (Cohen et al., 1983). Participants with total PSS scores lower than 14 and greater than 26 were allotted to the low and high perceived stress group, respectively. Participants with scores ranging from 14-26 were allotted to the moderate perceived stress group.

Snaith–Hamilton Pleasure Scale (SHAPS)

The SHAPS is a 14-item self-report scale with four possible responses ranging from 0= “strongly disagree” to 4= “definitely agree”. The SHAPS is used to assess anhedonia, the inability to experience pleasure from different activities (Snaith, 1993). Anhedonia has been proposed as a transdiagnostic feature of several disorders including depression, psychosis, and anxiety (Conway et al., 2019; Krueger et al., 2018).

Vitality Scale

We used the vitality scale to assess the degree to which participants felt energetic and alert. The vitality scale comprises 7 items that range from 1= “not at all true” to 7= “very true” (Bostic et al., 2000). The main outcome measure includes having energy available to the self. Reduced energy or fatigue are hallmark features of generalized anxiety and major depressive disorders (Merrell, 2008).

Abbreviated Impulsiveness Scale (ABIS)

The ABIS was used to measure impulsivity. The ABIS is a 13-item scale and each item is rated on a 4-point Likert scale ranging from 0=“rarely/never” to 4=“almost always/always” (Coutlee et al., 2014). ABIS data from 90 participants were missing as this questionnaire was not included in the initial (pilot) round of data collection (see below). Main outcome measures include attentional, motor, and non-planning impulsiveness, and these were summed to a total score (i.e., the sum of all items) (note: both subscale and total scores were used in separate analyses, discussed below). Lack of impulse control has been excessively linked with vulnerability to disorders such as ADHD, drug abuse, antisocial personality disorder (Beauchaine et al., 2017; Krueger et al., 2018).

Reinforcement Learning Task

To assess the degree to which deficits in reinforcement learning (about the costs and benefits of actions) and cost-benefit integration were associated with the transdiagnostic self-report measures discussed above, we used a probabilistic reinforcement learning task adapted from previous work (Voulgaropoulou et al., 2022). Because of the online nature of the study, a simplified version was utilized to avoid difficulties in comprehending the task. All participants were instructed that the aim of the task was to maximize their earnings (monetary rewards) and avoid a physically effortful action (finger tapping), and that they should treat these goals as being of equal importance. Participants were, moreover, instructed to complete the task on their smartphone (touch screen) or laptop using a touch pad. Participants could also make use of a mouse, although use of this

device was explicitly discouraged in the instructions phase. The task consisted of three phases: a practice phase, a learning phase, and a surprise test phase.

At the start of the practice phase, participants were first asked to rapidly tap 30 times on a virtual button as fast as possible to familiarize themselves with the finger tapping procedure of the task, which was repeated twice. Thirty button presses had to be completed for the task to progress. Afterwards, all participants completed a stepwise interactive introductory phase followed by a practice trial.

After the practice phase, participants moved to the learning phase. Here, they were presented with two stimulus pairs, each consisting of 2 unique fruit images, and with each pair indicating a specific trial type, i.e., a reward learning (RL) trial, or effort learning (EL) trial. Thus, a pair of stimuli was uniquely associated with RL or EL trials. On RL trials, choices of the "optimal" stimulus frequently led to the receipt of €0.10 reward (80% of all choices lead to receipt of a €0.10 monetary reward; 20% no money), while choosing the "suboptimal" stimulus rarely led to a monetary reward (20% of all choices lead to receipt of a €0.10 monetary reward; 80% no money). However, independent of choice, participants always had to exert effort (i.e., 30 virtual button presses completed via finger tapping). On EL trials, participants could frequently avoid having to exert effort (80% of all choices lead to avoidance of 30 virtual button presses; exert effort on 20%), while choosing the suboptimal stimulus rarely led to avoidance of effort (20% of all choices lead to avoidance of 30 virtual button presses; exert effort on 80%). Independent of choice, EL trials never lead to receipt of a monetary reward. *Figure 1* provides a graphical overview of an RL and EL trial. These two trial types, therefore, independently assessed the degree to which participants were able to maximize rewards and minimize effort. Tapping speed (reaction time [RT] in milliseconds [ms]) served as an assessment of interindividual differences in tapping speed during the actual task, which was averaged across all trials. Previous research has shown large interindividual differences in tapping speed (Ohmann et al., 2020), and we therefore included this measurement as a covariate in our statistical models.

Participants completed three blocks of 10 RL trials and 10 EL trials (i.e., 30 presentations of RL/EL trial types in total, total trial number = 60) in each session. Trial types were never repeated more than twice in a row, misleading outcomes (e.g., no reward for optimal RL stimulus) were equally dispersed across the three trial blocks, and the position of the optimal/suboptimal stimuli was counterbalanced. To ensure that stimuli (i.e., fruit images) were not consistently coupled to the same trial type (i.e., RL, EL), two playlists were created in which the same set of stimulus pairs were coupled with different trial types. For every participant, one playlist was randomly selected using a 1:1 ratio.

The main outcome measures were accuracy scores -for each trial type separately, which we calculated by dividing the number of optimal choices (i.e., choosing the most frequent rewarding stimulus for RL and the most frequent effort avoiding stimulus for EL) by the total trial amount per pair (n=30). In addition, an overall accuracy score was calculated by dividing the number of optimal choices by the total trial amount (n=60). To investigate time-related (i.e., learning) effects, accuracy

scores were averaged per bin of ten trials (e.g., bin1: trial 1-10, bin 2: trial 11-20, and bin 3: trial 21-30). Win-stay (repeating a choice after receiving positive feedback) and lose-shift (choosing the other stimulus after receiving negative feedback) rates were also calculated for both RL and EL trials (den Ouden et al., 2013). Participants that performed at or below chance level (0.5) on both RL and EL pairs on every time bin were excluded from further analyses (n=103) (Voulgaropoulou et al., 2022), as low accuracy scores may reflected lack of attention to the task, difficulty comprehending task instructions, or lack of interest in engaging with the task, possibly due to the online nature of the experiment (also see Discussion).

Upon completion of the learning phase, a surprise test phase followed to explicitly evaluate knowledge acquired from the learning phase (Hernaus et al., 2018; Voulgaropoulou et al., 2022). This phase comprised 20 trials during which the original stimulus pairs (4 presentations) as well as new stimulus combinations (16 presentations) were displayed. For new stimulus combinations, images from all pairs were mixed across trials. Specifically, pairs of 1) optimal RL and EL images, 2) optimal RL images and suboptimal EL images, 3) optimal EL images and suboptimal RL images, and 4) suboptimal RL and EL images were presented (four times each). Contrary to the learning phase, participants did not receive feedback after choosing a stimulus. This phase of the task investigated the ability of participants to integrate (learned) cost and benefits into a net value. Overall accuracy score (i.e., choosing the stimulus with the highest net value) was calculated by dividing the number of optimal choices by the total trial amount (n=20).

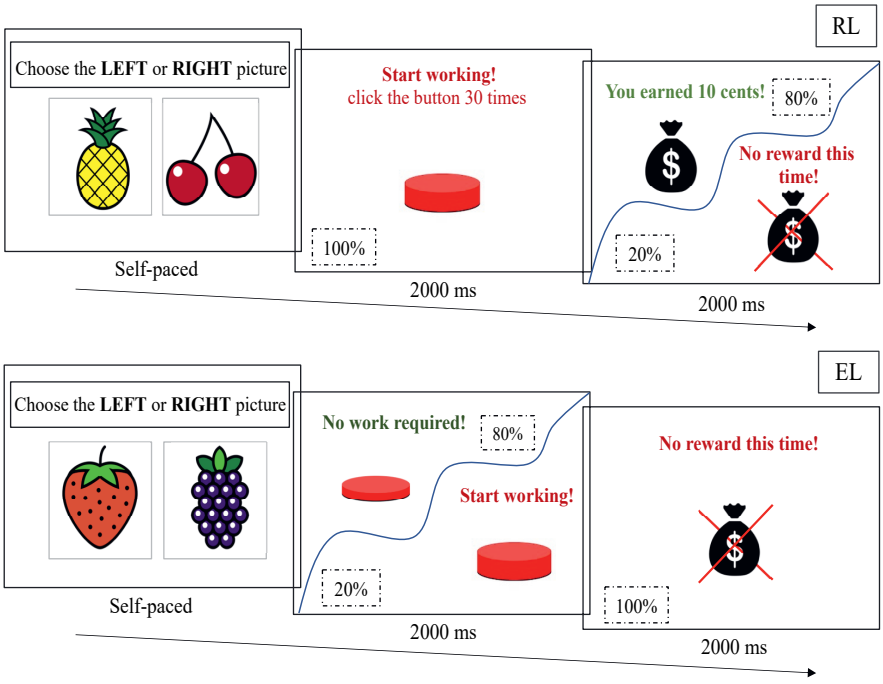

Figure 1 | Reinforcement learning task.
A schematic illustration of the cost-benefit reinforcement learning task. Top/bottom row shows an example of an RL/EL trial. At the beginning of each trial two images were presented on the screen. Participants choose one in a self-paced manner by selecting the right or left option. During the next phase (i.e., the effort outcome phase), participants either saw an unpressed button with the command: "Start working! (Click the button 30 times)", or a pressed button with the command "No work required" (2000ms). During the final phase (i.e., reward outcome phase), a screen showing a money bag, or a crossed-out money bag was presented with the caption "You earned 10 cents" or "No reward this time", respectively (2000ms).

Statistical analyses

Statistical analyses were conducted using R, version 3.6.2 (Team, 2020). Descriptive statistics were used to describe demographic characteristics of the final sample. A series of multiple linear regression models were performed to evaluate which of the variables of interest, including (a) perceived stress, (b) impulsivity, (c) vitality, (d) anhedonia, (e) device type (PC/touch pad, PC/mouse, smartphone/ touchscreen), (f) trial type (RL, EL), (g) psychiatric diagnoses and/or their interaction would predict accuracy, win-stay (WS), and lose-shift rates (LS) (dependent variables). In all analyses we adjusted for potential confounders including gender, age, and tapping speed. To evaluate differences among PSS subgroups (low, moderate, high) on accuracy, we used pre-determined cut-off values as described above. In cases of categorical variables with more than 2

levels, we first evaluated the significance of the overall predictor (e.g., device type, PSS subgroups, diagnoses) conducting F-tests before adding them to the model. When interactions with pair (RL, EL) or bin (trial 1-10, 11-20, 21-30) were not observed, we evaluated main effects. Adjusted R^2, beta coefficients and 95% CIs (for z-scored predictors) are reported for each model.

Results

Sample characteristics

Demographic variables of the final sample are reported in Table 1. The majority of the sample were females (77.78 %) and most participants were 18-24 (60.28%) or 25-31 (32.78%) years of age.

Using pre-defined PSS cut-offs, we observed that a majority of 66.11% reported moderate levels of perceived stress, followed by individuals with low levels of perceived stress (19.17%) and high levels of perceived stress (14.72%).

Most participants in the final sample did not self-report report a psychiatric diagnosis (78.89%), although a considerable percentage indicated having been diagnosed with either depression (10.28%) or an anxiety disorder (6.39%) by a mental health professional. In line with task instructions, all but 12 participants used their dominant hand to complete the task.

A visualization of the distribution of self-rated questionnaire scores, that is ABIS (M = 15.84; SD = 5.20), vitality scale (M = 28.82; SD = 8.05), SHAPS (M = 22.14; SD = 5.49), and PSS (M = 19.14; SD = 7.25) is available in *Supplemental Figure 1*. Importantly, participants who self-reported a diagnosis of depression endorsed significantly higher SHAPS and PSS scores compared to participants who reported no diagnosis (lifetime) [SHAPS: $t(353)=3.54$, $p<0.01$; PSS: $t(353)=3.45$, $p<0.01$]. Participants who reported having been diagnosed with an anxiety disorder exhibited the same trend on the PSS, although this failed to reach significance ($t(353)=2.72$, $p=0.09$).

Finally, as expected, most participants completed the task using a touch pad on a PC/laptop, or smartphone touchscreen (46.11% and 45% respectively). The remaining small percentage of participants (8.89%) disregarded the advice to not use the mouse to complete the session.

Table 1 | Sample characteristics.

Variables	N	Percent (%)
Gender		
Female	280	77.78
Male	79	21.94
Other	1	0.28
Age		
18-24	217	60.28
25-31	118	32.78
32-38	24	6.67
39-46	1	0.27
PSS score [1]		
Low	69	19.17
Moderate	238	66.11
High	53	14.72
Diagnoses		
ADHD[2]	7	1.94
Anxiety	23	6.39
Autism	2	0.56
Depression	37	10.28
No diagnosis	284	78.89
Other	6	1.67
Substance abuse	1	0.27
Device		
Laptop/PC (touchpad)	166	46.11
Laptop/PC (mouse)	32	8.89
Mobile phone (touch screen	162	45.00
Handedness		
Right	314	87.22
Left	37	10.28
Ambidextrous	9	2.50

[1] Perceived Stress Scale score

[2] Attention Deficit Hyperactivity Disorder

Participants improved performance over time using reinforcement learning

First, we verified that participants learned to select the optimal stimulus over time. Confirming this expectation, we observed a main effect of time (i.e., time bins) on both RL [$F(2,359)=83.17$, $p<0.01$, $n^2_G= 0.07$] and EL trials [$F(2,359)=43.08$, $p<0.01$, $n^2_G= 0.04$] (*see Figure 2*), suggesting that participants learned to select stimuli frequently associated with rewards and the avoidance of effort. As suggested by the absence of a bin x trial type interaction [$F(1, 359)=1.51$, $p=0.22$, $n^2_G= 0.00$], participants did not learn to more quickly select the optimal RL versus EL stimulus. However, we did observe a main effect of trial type [$F(1, 359)=15.21$, $p<0.001$, $n^2_G= 0.02$] (*see Figure 2*) suggesting that participants, on average, selected the optimal RL stimulus (M=0.73, SD=0.19) slightly more frequently than the optimal EL stimulus (M=0.69, SD=0.22).

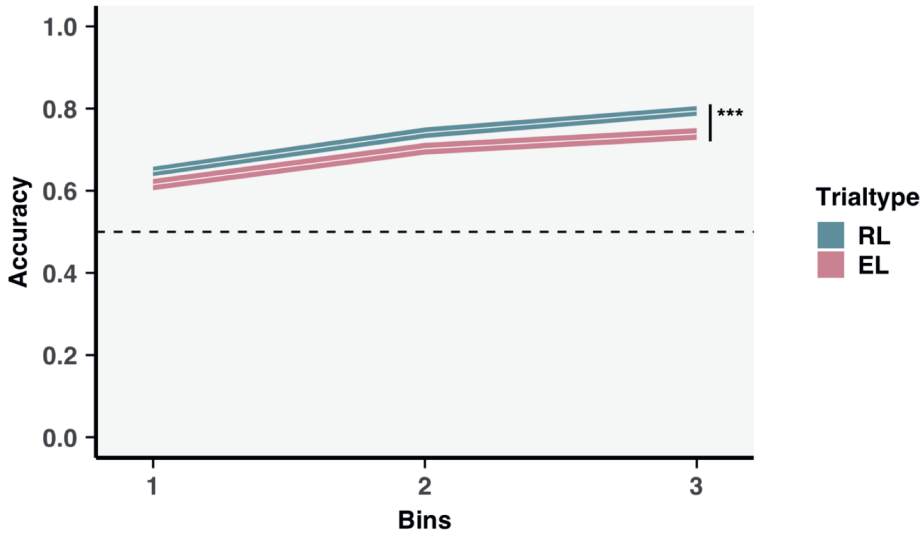

Figure 2 | Employment of reward and effort-cost reinforcement learning over time.
Average accuracy (optimal stimulus choice) on RL (blue) and EL (pink) trials. Trials were grouped into bins of 10 presentations. Participants improved in accuracy on both RL and EL trials over the course of time (bin1, bin2 and bin3). On average, however, they selected the optimal stimulus more often on RL compared to EL trials. Data are presented as means ± SD. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

Limited collinearity between self-report questionnaires

After confirming that participants used feedback to optimize performance on both trial types, we evaluated potential collinearity among self-report questionnaires. We found low to moderate correlations among all questionnaires (*see Supplemental Figure 2*). In addition, we used the generalized variance inflation factor (GVIF) to more thoroughly check for potential collinearity among all measurements (Fox & Monette, 1992). The rule of GVIF < 5 was applied, indicating that there was no substantial collinearity among measurements (*see Supplemental Table 1*). We also investigated how average RTs (tapping speed) were associated with accuracy and questionnaire scores. These analyses revealed no-to-low correlations between these variables (see *Supplemental Results*).

Perceived chronic stress, impulsivity and device type are associated with instrumental learning about costs and benefits

To evaluate whether transdiagnostic factors would (differentially) be associated with measures of cost and benefit learning, we assessed which self-reported ratings predicted performance accuracy during the learning phase. First, to examine if alterations in learning about the costs and benefits of actions may constitute separate pathways that contribute to motivational impairments, we investigated potential interactions between trial type (RL, EL) and self-reported chronic stress, impulsivity, vitality, and anhedonia ratings using the following model: accuracy ~ PSS + ABIS + vitality + SHAPS + device + age + gender + tapping speed + trial type + trial type*PSS + trial type*ABIS + trial type*vitality + trial type*SHAPS. The overall regression was statistically significant

[F (14, 521) = 3.69, p < 0.001, R^2 adj = 0.07], although no trial type -by- self-report rating interaction was observed (all p-values > 0.05). These results indicate that RL and EL were not differently associated with any of the self-report questionnaire scores.

Because significant interactions with trial type interaction were not observed, we repeated the regression excluding these terms (i.e., accuracy ~ PSS + ABIS + vitality + SHAPS + device + age + gender + tapping speed). The overall regression model remained statistically significant [F (10, 258) = 3.01, p = 0.001, R^2 adj = 0.07]. Importantly, chronic stress (β=-0.21, 95% CI= [-0.35 – -0.06], t=-2.75, p<0.01), impulsivity (β=-0.15, 95% CI= [-0.27 – -0.03], t=-2.42, p=0.02), and device type - with laptop/PC touchpad > smartphone (β =0.36, 95% CI= [0.10 – 0.63], t=2.70, p<0.01) and laptop/PC mouse > smartphone (β =0.52, 95% CI= [0.09 – 0.95], t=2.39, p=0.02); *see supplemental Figure 3 and Supplemental Information*) - were associated with poorer overall performance accuracy. No other variables were significantly associated with overall task accuracy (all p-values > 0.05). Results remained the same when running separate models for each factor, i.e., chronic stress (β=-0.16, 95% CI= [-0.27 – -0.06], t=-3.07, p=0.002) and impulsivity (β=-0.14, 95% CI= [-0.26 – -0.02], t=-2.21, p=0.028) were negatively associated with overall performance accuracy. In addition, we seperately evaluated the three ABIS sub-scales (attentional, motor, and non-planning impulsiveness) finding that attentional (β =-0.13, 95% CI= [-0.25 – -0.01], t=-2.15, p=0.03) and motor (β =-0.17, 95% CI= [-0.28 – -0.05], t=-2.6, p=0.01) but not non-planning (β =0.001, 95% CI= [-0.12 – 0.12], t=0.11, p=0.91) implusiveness were associated with reduced performance accuracy. After excluding individuals with a self-reported diagnosis of a psychiatric disorder, chronic stress was the only significant predictor of overall performance accuracy in the model (*see Supplement*).

Since chronic stress was a significant predictor in the model, we additionally compared overall performance accuracy between low, medium, and high stress groups by repeating the regression specified above using PSS cut-off groups (low, medium, high; *see section 2.2.1*) instead of continuous scores. Participants in the low chronic stress group exhibited significantly better overall performance accuracy compared to participants in the high chronic stress group (β =0.66, 95% CI= [0.20 – 1.13], t=2.77, p<0.01). Similarly, participants in the moderate chronic stress group performed significantly better than high chronic stress participants (β =0.38, 95% CI= [0.02 –0.73], t=2.05, p=0.04), while there was no significant difference between moderate and low chronic stress groups (β =0.28, 95% CI= [-0.61 – 0.04], t=1.72, p=0.09) (*see Figure 3*).

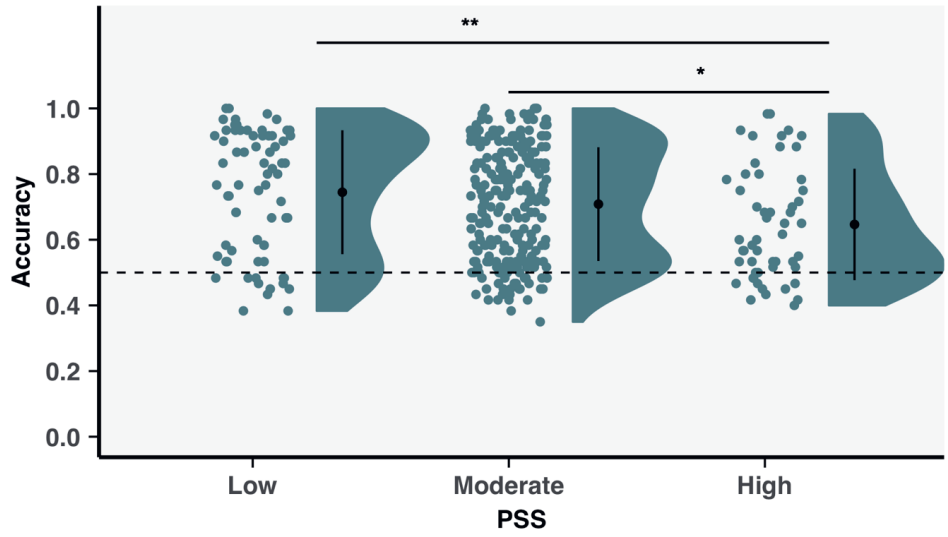

Figure 3 | High chronic stress leads to lower overall accuracy in the task.
Participants with high levels of perceived stress showed reduced overall performance accuracy compared to participants with low and moderate levels of perceived chronic stress. Means ± SD, individual data points, distribution and frequency of the data are displayed. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).

We additionally assessed whether self-reported psychiatric diagnoses were associated with overall performance accuracy by adding it as an independent variable in the model specified in the previous paragraph. ADHD, Autism, substance abuse and "other" diagnoses were removed from the sample due to the very low number of observations (<10), leaving mood and anxiety disorders as the only self-reported diagnostic categories. However, diagnosis was not a significant predictor in the model [$F(2, 254)=2.84$, $p=0.06$] (see *Figure 4* for accuracy based on diagnosis), and diagnosis-by-trial type interactions were also not observed (see *Supplement*).

Overall, these results indicate that chronic stress, impulsivity, and device type (laptop/PC touchpad or mouse > smartphone touchscreen) were significantly associated with lower performance accuracy, independent of trialtype (i.e., reward or effort avoidance), while self-reported diagnosis was not a significant predictor of task performance, although these results should be considered exploratory due to the low number of observations.

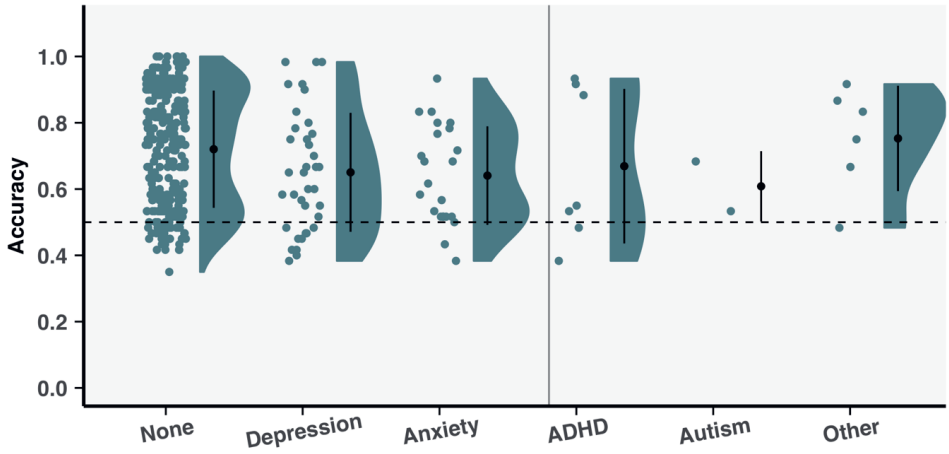

Figure 4 | Overall accuracy based on psychiatric diagnoses.
No group differences were observed in overall performance accuracy based on self-report psychiatric diagnoses by a mental health professional. ADHD, Autism and "Other" (after the vertical line) were not considered in the analyses. "Other" diagnoses include anorexia n=3, borderline personality n=2 and highly sensitive person n=1.Means ± SD, individual data points, distribution, and frequency of the data are displayed.

Chronic stress and device type are associated with win-stay and lose-shift strategies

To obtain insights into specific mechanisms by which transdiagnostic factors may impact reinforcement learning, we investigated associations with win-stay (choosing a stimulus again following the receipt of money -for RL- or avoidance of effort -for EL-, i.e., a measure that represents learning from positive/negative reinforcement) and lose-shift (choosing the other stimulus following no reward -for RL- or following effort -for EL-, i.e., a measure that represents learning from negative/positive punishment).

First, we checked for potential interactions between win-stay/lose-shift rates (WS/LS), as defined in *section 2.3* and self-reported chronic stress, impulsivity, vitality, and anhedonia ratings using the following model: rate (i.e., the rate of WS/LS) ~ PSS + ABIS + vitality + SHAPS + device + age + gender + tapping speed + WS/LS *PSS + WS/LS *ABIS + WS/LS *vitality + WS/LS *SHAPS. WS/LS served as a categorical variable in this model. The overall regression was statistically significant [F (15, 524) = 39.37, p < 0.001, R^2 adj = 0.52]. Importantly, we observed a strategy [win-stay vs. lose-shift] -by- chronic stress (β=-0.27, 95% CI= [-0.41 – -0.12], t=-3.55, p<0.01) and a strategy -by- impulsivity (β =-0.13, 95% CI= [-0.26 – -0.01], t=-2.2, p=0.03) interaction. To better understand the WS/LS interaction with questionnaire ratings we conducted follow-up, stratified, analyses in which win-stay and lose-shift rates were used as dependent variables in separate analyses. We observed that win-stay rates were significantly associated with chronic stress (lower) (β =-0.19, 95% CI= [-0.34 – -0.04], t=-2.52, p=0.01), impulsivity (lower) (β =-0.13, 95% CI= [-0.25 – -0.01], t=-2.22, p=0.03), and device type - with laptop/PC touchpad > smartphone (β =0.37, 95% CI= [0.11 – 0.64], t=2.87, p<0.01) and with laptop/PC mouse > smartphone (β =0.55, 95% CI=

[0.12 – 0.98], *t*=2.53, *p*=0.01). After excluding participants with psychiatric diagnoses only chronic stress remained significantly associated with win-stay rates (*see Supplement).* Lose-shift rates, however, were not associated with chronic stress (β =0.12, 95% CI= [-0.03 – 0.27], *t*=1.63, *p*=0.1) and impulsivity (β =0.08, 95% CI= [-0.04 – 0.21], *t*=1.31, *p*=0.19). Only device type was significantly associated with lose-shift rates with laptop/PC touchpad < smartphone (β =-0.31, 95% CI= [-0.57 – -0.04], *t*=-2.25, *p*=0.03) and laptop/PC mouse < smartphone (β =-0.58, 95% CI= [-1.01 – -0.14], *t*=-2.63, *p*=0.01). When excluding participants with a psychiatric diagnosis the overall regression model was not significant (*see Supplement*).

Chronic stress is associated with performance accuracy in the surprise test phase

We repeated the same statistical model using overall accuracy during the surprise test phase, during which participants were asked to choose stimuli that they preferred the most. Thus, in this phase of the experiment, participants were asked to choose a stimulus based on a comparison on net value (reward – effort cost) for each stimulus. Although the overall regression model was not statistically significant [F (10, 258) = 1.63, p = 0.09, R^2 adj = 0.02], the specific association with chronic stress (β =-0.23, 95% CI= [-0.38 – -0.08], *t*=-3.02, *p*=0.003) was significantly associated with fewer choices of stimuli with (objectively) the highest net value.

Discussion

In this study we investigated whether transdiagnostic ratings of psychopathology and associated risk factors (i.e., chronic stress, anhedonia, energy, impulsivity) were (uniquely) associated with alterations in reinforcement learning and cost-benefit integration; cognitive mechanisms that have been frequently implicated in motivational dysfunction and disrupted goal-directed behavior. We opted to not rely on diagnostic boundaries that may, at least partly, account for previously-reported inconsistent findings. Contrary to expectations, we found no evidence for our hypothesis that different self-ratings of psychopathology were associated with distinct changes in reinforcement learning and cost-benefit integration. Instead, we observed that elevated levels of chronic stress and impulsivity were associated with a more general reduction in reinforcement learning (i.e., independent of whether participants were learning to maximize gains or minimize effort), that was linked to a reduced ability to learn from reinforcement.

Specifically, we observed that self-report measures of perceived chronic stress were a significant predictor of performance accuracy in almost every model, with higher chronic stress being associated with decreased performance accuracy (i.e., decreased selection of stimuli associated with frequent rewards and/or effort avoidance). This finding aligns with previous research showing that stress-related disorders are characterized by reduced reward sensitivity and a reduced influence of previous outcomes on subsequent actions/decisions (Ironside et al., 2018; Olino, 2016; Vidal-Ribas et al., 2019).

Of note, this study was conducted during the first wave of COVID-19 pandemic, a stressful life event, which may explain the relatively high perceived stress reports in the sample (Pashazadeh Kan et al., 2021; Salari et al., 2020). Past research has shown that stressful life events reduce

reward responsiveness (Berenbaum & Connelly, 1993). Thus, these findings add to emerging evidence that chronic stress (potentially due to negative life events) is linked to impaired sensitivity to reinforcers.

Indeed, in analyses investigating whether participants primarily learned from positive/negative reinforcement (here, defined as "win-stay") or positive/negative punishment (here, defined as "lose-shift"), we observed that chronic stress was specifically associated with reduced win-stay rather than lose-shift rates, suggesting that prolonged exposure to stress may specifically blunt learning from positive outcomes. Taken together, these observations hint towards a differential role for chronic stress in learning from reinforcement versus punishment, as opposed to a valence-specific effect (i.e., reward versus effort). Lastly, results from the surprise test phase provide preliminary evidence that participants under chronic stress might have difficulties integrating the costs and benefits of actions into a net value.

Overall, in the current study, higher levels of perceived chronic stress were associated with reduced overall task accuracy and sensitivity to (positive/negative) reinforcers. In contrast, accumulating evidence indicate that acute stress (i.e., via acute stress-induction) can increase reward sensitivity, decrease sensitivity to effort, or lead to reduced use of negative feedback. (Mather & Lighthall 2012; Lighthall et al 2013; Petzold, Plessow et al 2010; Raio, Konova & Otto 2020, Voulgaropoulou et al., 2021). Interestingly, previous work has suggested that acute and longer-term (e.g., chronic) stress might exert different effects on sensitivity to and learning from rewarding outcomes. For example, acute stress has been hypothesized to temporarily increase reward sensitivity, while chronic stress is assumed to result in blunted reward sensitivity, which may be associated with stress-associated psychopathology such as anhedonia (Baik, 2020; Barch et al., 2016). In addition, differences in brain activation have been observed when processing rewards under acute and chronic stress (Vidal-Ribas et al., 2019). Thus, stressor duration, as well as different ways of assessing stress (e.g., self-administered questionnaires versus acute stress induced in lab settings) can offer important complementary perspectives on the association between stress and instrumental learning and/or decision-making.

In addition to chronic stress, increased impulsivity was also a predictor of reduced overall accuracy in most models. Analyses of win-stay/lose-shift rates, as operationalized above, indicated that impulsivity was associated with reduced sensitivity to both positive and negative reinforcement. Our findings align with previous work that has found low impulsivity to be positively correlated with learning to maximize rewards and minimize losses (Cáceres & San Martín, 2017). Moreover, studies in individuals without a psychiatric diagnosis, as well as in individuals whose impulsivity warrants clinical attention, have found impulsivity to be associated with deficits in learning for rewards and punishments as well as difficulties in adapting to new stimulus-reward contingencies (i.e., reversal learning) (Berlin et al., 2004; Franken et al., 2008).

Interestingly, and contrary to our expectations, both chronic stress and impulsivity were associated with the same pattern of performance; that is, reduced learning to maximize monetary rewards and minimize physical effort as well as reduced learning from positive and negative reinforcers.

Previous work that has employed cognitive computational modeling has investigated whether such performance changes are driven by the same latent cognitive mechanisms. For example, past research has indicated that chronic stress can selectively affect learning rates (Wise & Dolan, 2020), whereas impulsivity is associated with increases in random exploration (Dubois & Hauser, 2022). Thus, despite differences in the way learning was quantified (i.e., task accuracy, win-stay, learning rates obtained from computational cognitive models) chronic stress and impulsivity seem to be negatively associated with instrumental learning, potentially due to different underlying cognitive mechanisms. It would be interesting for future research to evaluate the precise mechanisms by which different transdiagnostic characteristics impact reinforcement learning and decision-making.

In contrast to chronic stress and impulsivity, however, neither anhedonia nor energy/fatigue were associated with task accuracy, which is surprising given that past research has found associations with impaired reinforcement learning, motivation to exert effort, and cost-benefit integration (Huys et al., 2013; Müller et al., 2021; Waltz & Gold, 2016). The lack of consistent findings may be attributable to a number of factors. Firstly, the Hierarchical Taxonomy of Psychopathology (HiTOP), which hierarchically summarizes transdiagnostic dimensions (Krueger et al., 2018), describes distress and impulsivity as high-order factors, whereas anhedonia and (low) energy are viewed as lower-order components (Krueger et al., 2018). In addition, converging evidence across species highlights that chronic stress can precipitate anhedonia and low energy/fatigue, which may explain why these factors were not correlated with overall task accuracy in the general population (Pizzagalli, 2014; Stanton et al., 2019).

Secondly, there is increasing evidence that more established findings in clinical samples without comorbidities are weaker, or not observable, in more naturalistic patient samples. For example, enhanced learning from negative feedback (Rodriguez-Thompson et al., 2020) or reduced neural responses to reward (Brolsma et al., 2021), which have often been linked to depression specifically and mood disorders more generally, does not seem to be present in more naturalistic samples that experience anhedonia and/or avolition. In addition, previous findings in individuals with schizophrenia have shown that anhedonia and avolition severity were not linked to a reduction in learning from positive outcomes (Dowd et al., 2016). These observations warrant an increased focus on higher-order psychopathology factors, such as distress and impulsivity, and more naturalistic (or, non-patient) samples.

Interestingly, we also found device type to be an important predictor of task performance. Use of a smartphone was negatively associated with task performance compared to use of a PC/laptop (touchpad or mouse). This reduction in accuracy may be related to the fact that participants are more prone to errors or find it harder to comprehend instructions when using a smaller screen size (Kim & Kim, 2012). Alternatively, they may have trouble concentrating on task performance when using their mobile phones (which can be used in any setting) instead of their PC/laptop. Even though past research suggests that screen size does not affect learning outcomes per se, users have indicated that they prefer to access learning materials through their laptops compared to smartphones (Karam, 2015). These findings underscore the importance of strictly monitoring

device use and encouraging use of a single device to avoid potential interference with task performance.

To sum up, the aim of the study was to investigate whether certain transdiagnostic constructs were associated with independent PVS mechanisms in a reinforcement learning and cost-benefit integration task. We observed that chronic stress and impulsivity were the most consistent predictors of overall performance accuracy due to a selective reduction in learning from reinforcement, suggestive of impaired goal-directed behavior.

Strengths and limitations

One advantage of this study is that we aimed to uncover cognitive mechanisms specifically associated with transdiagnostic measurements of (sub)clinical psychopathology, as opposed to potentially more heterogeneous diagnostic labels. In addition, we used an *a priori* selection of self-rated measurements previously linked to impaired motivation and goal-directed behavior. Third, we used a task design that has the potential to differentiate/assess various PVS constructs within a single task experience. Finally, we conducted our study during the first wave of the COVID-19 pandemic, an ongoing life stressor that may have led to sufficient variability in chronic stress ratings over the past month.

Yet, due to the online nature of the study, some limitations should also be acknowledged. First, the sample was self-selected, resulting in unequal distributions across several measurements, such as gender and age. Moreover, the use of self-administered questionnaires that rely on personal interpretations is often accompanied by potential biases (Althubaiti, 2016). For example, participants self-reported the presence of a psychiatric/psychological diagnosis made by a health care professional, which may have led to misclassification biases (e.g., not reporting a diagnosis, using incorrect terminology). Nevertheless, in an attempt to minimize potential recall bias, instead of using retrospective assessments for events occurred far into the past, we either used questionnaires with short recall period (PSS, vitality scale, SHAPS) or without the temporal component (ABIS). It should be noted, however, that these subjective measures might lead to different results compared to lab-based measures (Gard et al., 2007). In addition, although we used a simplified task design to avoid difficulties in comprehending task procedures, and extensively piloted this design prior to study launch, we nevertheless excluded a substantial group of participants based on stringent *a priori*-selected performance criteria. Such exclusions may be prevented with a more extensive practice session, recruitment on dedicated online crowdsourcing platforms (e.g., MTurk, Prolific), or actively encouraging the use of a laptop or PC. A final limitation of the study is that we did not include measurements of more latent dimensional transdiagnostic symptoms (Conway et al., 2012) and did not explicitly recruit for variation in outcome measures. Future research evaluating additional transdiagnostic factors or with additionally variability in self-report measures may be able to identify specific subgroups that exhibit distinct patterns of impaired task performance, which may offer a more stringent test of our hypotheses.

Conclusion

To conclude, in this online study, we observed that increased levels of perceived chronic stress and impulsivity were associated with a reduced ability to learn from (positive and negative) reinforcement during a reinforcement learning and cost-benefit integration task. Our work emphasizes the importance of chronic stress and impulsivity as potential drivers of altered motivation and goal-directed behavior, as well as various methodological challenges associated with data collection via online platforms.

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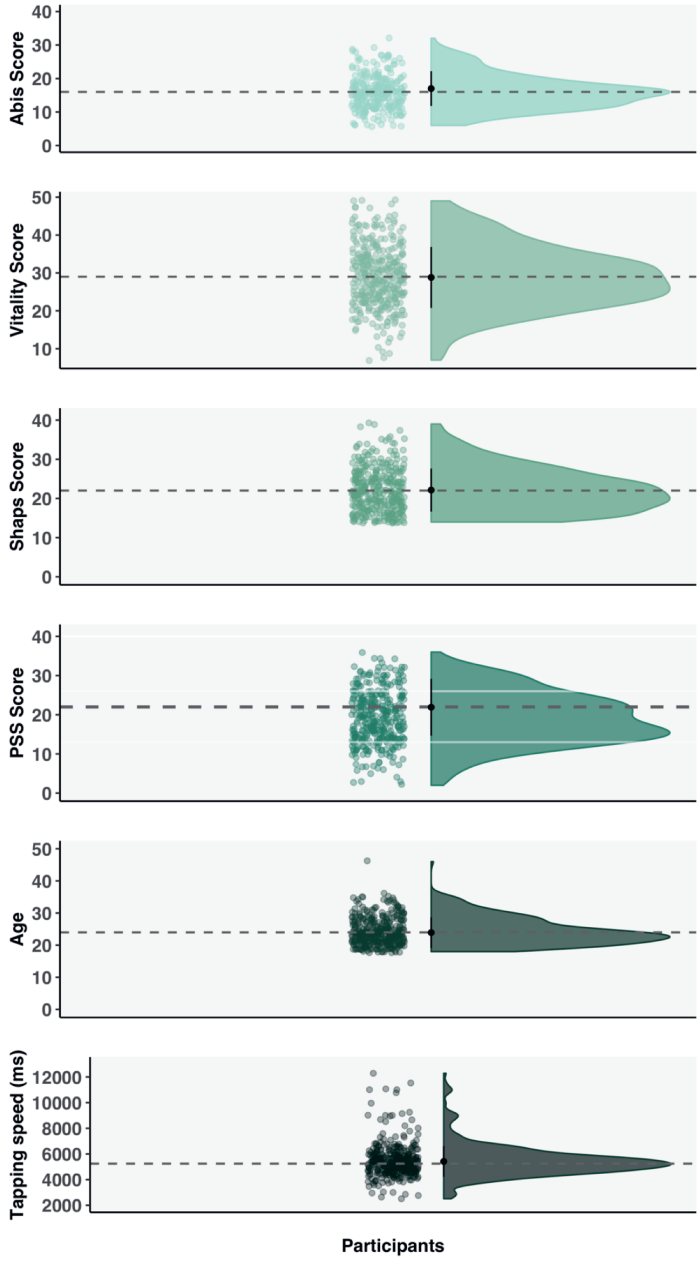
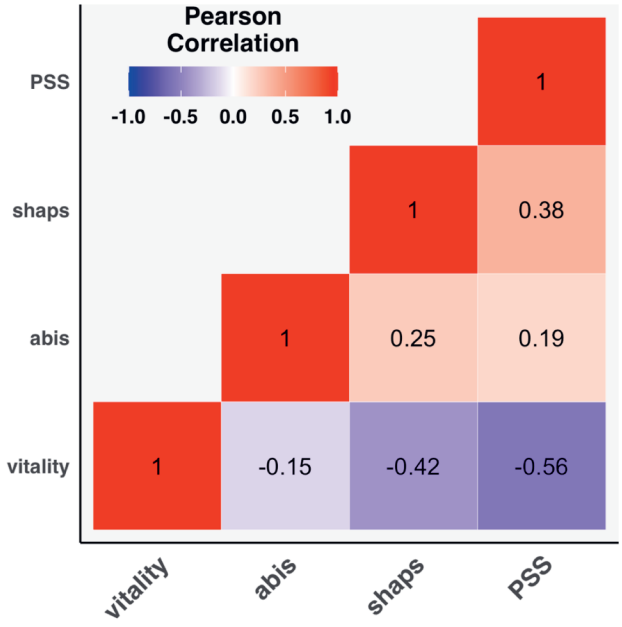
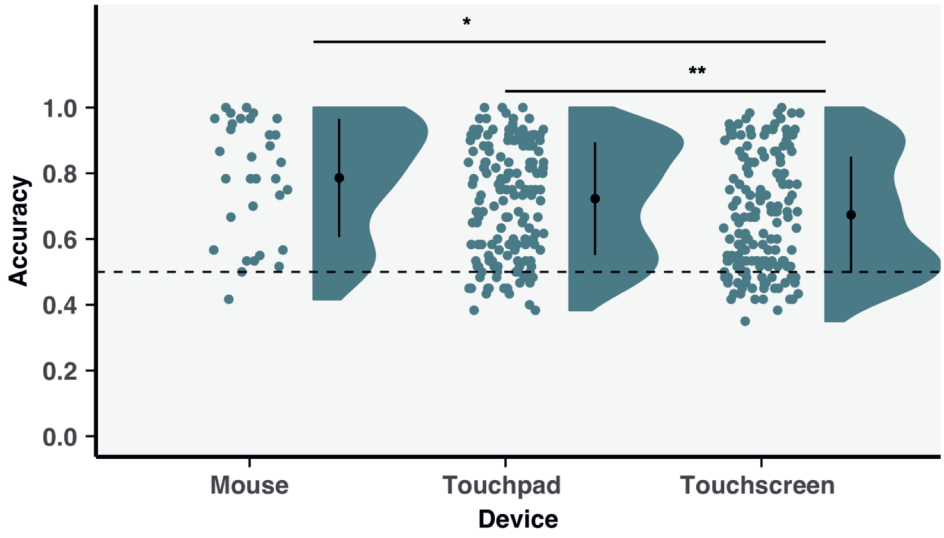
Supplemental Information



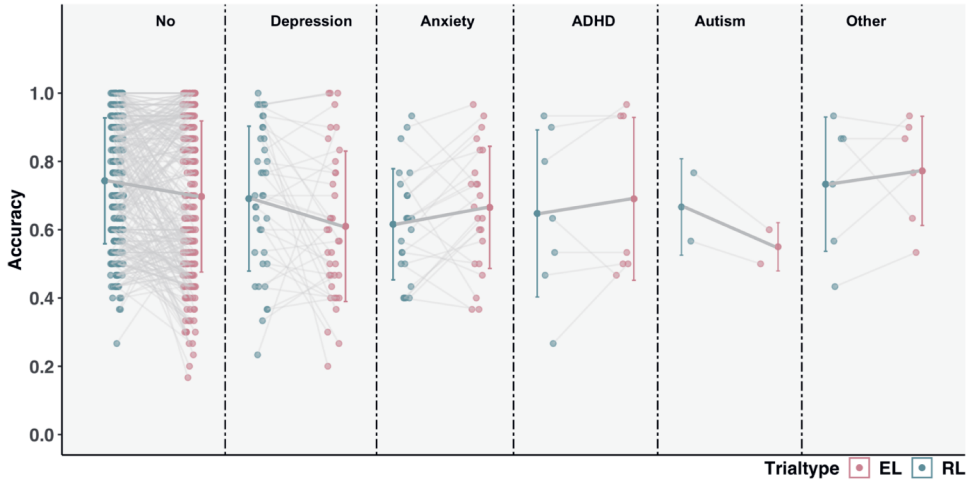
Supplemental Figure 1 | Distribution of individual and averaged items from the questionnaires (ABIS, vitality, SHAPS, PSS), age and tapping speed. White lines on PSS distribution denote the different cut-off groups (low, medium, high).



Supplemental Figure 2 | Heatmap to evaluate potential collinearity among questionnaires.
Low to moderate correlations were observed among questionnaires. Blue shades display negative correlations. Red shades display positive correlations.



Supplemental Figure 3 | Smartphone usage was associated with less accurate task performance. Participants who used smartphones to complete the task exhibit decreased overall accuracy compared to participants who used a PC or laptop (touchpad or mouse). Means ± SD, individual data points, distribution and frequency of the data are displayed. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$).



Supplemental Figure 4 | Performance on RL and EL trials for each psychiatric diagnosis.
Each column represents a different diagnostic category. The column "other" diagnoses included: anorexia n=3, borderline personality n=2 and hypersensitive person n=1. Dots depict individual data points. Means ± SD.

Supplemental Table 1 | Generalized variance inflation factor (GVIF).

	GVIF	Df	GVIF^(1/(2*Df))
PSS	1.56	1	1.25
ABIS	1.11	1	1.05
Vitality	1.61	1	1.27
SHAPS	1.43	1	1.19
Device	1.31	2	1.07
Age	1.16	1	1.07
Gender	1.24	2	1.06
Tapping speed	1.19	1	1.09

Note: Both GVIF and GVIF^(1/(2*Df)) are indices of collinearity. The standard rules of thumb were applied, namely GVIF < 5 and GVIF^(1/(2*Df)) < 2 suggesting no substantial collinearity among measurements.

Supplemental Results

Tapping speed shows no-to-low correlation with accuracy and self-report scores

We investigated how average RTs are associated with task accuracy and questionnaire scores, which revealed low correlations. Moreover, even at uncorrected p-value thresholds, most correlations, with the exception of vitality x tapping speed (r=0.12, p= 0.03) were not statistically significant (ABIS/tapping speed: r = -0.02, p= 0.75; SHAPS/tapping speed:r= -0.07, p= 0.17; PSS/tapping speed, r = 0.11, p= 0.06; overall accuracy/tapping speed, r=0.06, p= 0.1).

The use of mobile touchscreen leads to reduced overall accuracy

Since device was also a significant predictor in most models, we additionally assessed group differences in task performance based on the device used during the task using the following model: accuracy ~ PSS + ABIS + vitality + SHAPS + device + age + gender + tapping speed. The overall regression model was statistically significant [F (10, 258) = 3.01, p<0.01, R^2adj = 0.07]. We found a main effect of device on average performance accuracy in the learning phase [F(2, 357)=5.00, p<0.01]. Particularly, we observed that participants using PC/laptop (touchpad) performed significantly better than participants using mobile (touchscreen) (β =0.36, 95% CI= [0.10 – 0.63], t=2.70, p<0.01). Moreover, participants who used PC/laptop (mouse) performed better compared to participants who used mobile (touchscreen) (β =0.52, 95% CI= [0.09 – 0.95], t=2.39, p=0.02) (see *Supplemental Figure 3*).

Cumulative stress is associated with task performance after excluding participants with a self-reported diagnosis of a psychiatric disorder

We repeated the regression specified in the main text of this manuscript (i.e., overall accuracy ~ PSS + ABIS + vitality + SHAPS + device + age + gender + tapping speed) after excluding participants who self-reported that they had been diagnosed with a psychiatric diagnosis by a professional. The overall regression was statistically significant [F (10, 199) = 2.27, p = 0.02, R^2 adj = 0.06]. Moreover, cumulative stress was a significant predictor of overall performance accuracy (β =-0.21, 95% CI= [-0.37 – -0.04], t=-2.48, p=0.01), whereas device type (smartphone) failed to reach significance (β =-0.48, 95% CI= [-0.98 – 0.02], t=-1.91, p=0.06). No other predictors were associated with overall performance accuracy (all p-values > 0.05).

Performance on distinct trial types based on psychiatric/ psychological diagnoses

We evaluated a potential diagnosis-by-trial type interaction using the following model: accuracy ~ PSS + ABIS + vitality + SHAPS + device + age + gender + clicks + diagnosis * trial type. Substance abuse was removed from the statistical analysis since there was only one observation. The overall regression was statistically significant [F (20, 513) = 3.1, p < 0.001, R^2 adj = 0.73]. There was no diagnosis-by-trial type interaction F (5, 354) = 0.49, p = 0.78] (see *Figure 4* for RL/EL accuracy based on diagnosis). Also in this model, cumulative stress (β =-0.16, 95% CI= [-0.26 – -0.05], t=-2.96, p<0.01), impulsivity (β =-0.13, 95% CI= [-0.21 – -0.04], t=-2.50, p=0.01) and device type (mobile phone) (β =-0.44, 95% CI= [-0.75 – -0.13], t=-2.99, p<0.01) were significant predictors of overall task performance.

Cumulative stress is associated with win-stay rates after excluding participants with a psychiatric diagnosis

For win-stay rates, the fitted regression model was: WS rate ~ PSS + ABIS + vitality + SHAPS+ device + age + gender +clicks. The overall regression was statistically significant [F (10, 200) = 2.13, p=0 .02, R^2adj =0.05]. Specifically, PSS (β =-0.20, 95% CI= [-0.36 – -0.03], t= -2.30, p=0.02), was significantly associated with win-stay rate.

Regarding lose-shift rates, the fitted regression model was: LS rate ~ PSS + ABIS + vitality + SHAPS + device + age + gender +clicks. The overall regression was not significant [F (10, 200) = 1.75, p=0.07, R^2adj = 0.03].

CHAPTER 4

Exploring the complementary roles of dopamine and noradrenaline in cost-benefit decision-making

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In preparation

Abstract

Dopamine's (DA) and noradrenaline's (NA) involvement in motivation have been extensively studied in animals. To date, however, the distinct and interacting contributions of DA and NA on cost-benefit decision-making have not been compared in humans. Thus, the aim of this study was to explore how DA and NA contribute to two proxy-measures of motivation in humans (i.e., explicit cost-benefit computations and implicit motor vigor). For this reason, healthy volunteers aged 18-35 were assigned to a single dose of placebo (n=45), propranolol (n=48; 40mg; β-norepinephrine receptor antagonist) or haloperidol (n=46; 2mg; dopamine D2 receptor antagonist) according to a randomized double-blind placebo-controlled design. 150 minutes post-administration, they completed a cost-benefit decision-making task, in which they could earn rewards (0.01-0.15 Euro's) in exchange for physical effort (from 40-100% pre-calibrated maximum grip force). We found that low-dose haloperidol may temporarily increase response vigor (B=-0.02, 95% CI= [-0.04 – -0.00], t=-2.32, p=0.02, compared to placebo) at the cost of reduced acceptance over time [t(81.9)=-2.83, p_{holm}=0.01, compared to placebo; t(81.8)=-3.46, p_{holm}=0.003, compared to propranolol]. In addition, we found that propranolol might increase effort sensitivity [t(68.4)=-2.83, p_{holm}=0.02; compared to haloperidol]. These results provide insights into the role of DA and NA in (motor) motivation, the dysregulation of which is implicated in many neuropsychiatric conditions characterized by motivational deficits.

Keywords: dopamine (DA), noradrenaline (NA), haloperidol, propranolol, cost-benefit decision-making, motivation

Introduction

A fundamental aspect of everyday decision-making involves the evaluation of costs and benefits of future actions. The decision to execute or withhold an action depends on a trade-off between maximizing expected benefits (e.g., a reward) versus minimization of the costs (e.g., physical or cognitive effort) required to obtain these benefits (Pessiglione et al., 2017). Existing work suggests that humans and other non-human animals combine benefits and costs into a net value (i.e., reward value discounted by effort cost, i.e., benefit - cost = net value), which represents whether a particular action is "worth it" (Cléry-Melin et al., 2011; Schmidt et al., 2012). A failure to adaptively use reward value and effort cost, and integration of the two into a net value, is associated with the development of negative symptoms such as motivational deficits, reduction in pleasure, anergia, and a more general lack of goal-directed behavior. Such symptoms can be observed across a wide range of psychiatric and neurological disorders (Mueller et al., 2018; Pessiglione et al., 2018; Salamone et al., 2016) and can profoundly impact patients' quality of life (Barone et al., 2009; Pessiglione et al., 2018).

To better understand how negative symptoms may develop, a mechanistic understanding of the neurobiological underpinnings of cost-benefit evaluation is of substantial importance. Accumulating evidence has implicated both dopamine (DA) (Pessiglione et al., 2018) and noradrenaline (NA) (Salamone & Correa, 2012) as key neuromodulators in processes associated with cost-benefit evaluation, such as reward sensitivity (e.g., behavior motivated by rewarding/appetitive stimuli), effort expenditure (e.g., spending energy or time on obtaining a reward) and motivation (e.g. overcoming a cost to obtain a reward).

On a neural level, DA, a neurotransmitter whose projections originate in the midbrain -most prominently the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) – is commonly associated with reward processing and motivation (Bouret & Richmond, 2015; Daniel & Pollmann, 2014; Salamone & Correa, 2012). Abnormalities within its circuits are thought to contribute to reward sensitivity deficits (Muhammed et al., 2016; Schultz, 2007). Indeed, pharmacological agents that modulate DA function, such as levodopa, used for treatment of Parkinson' Disease (PD) and DA subtype receptor 2/3 (D2/3) antagonists such as amisulpride used for treatment of psychosis, alter how people learn to maximize reward, and learning from positive outcomes (Admon et al., 2017; T. T.-J. Chong et al., 2015; Guitart-Masip et al., 2014; Muhammed et al., 2016). Past research on PD patients suggests that alongside the well-documented role of DA in "explicit" reward-seeking behavior (i.e., cost-benefit computations), it may also play a crucial role in implicit forms of motivation such as "motor motivation" or, vigor (i.e., intensity of motor movements) (Mazzoni et al., 2007). In contrast to reward sensitivity, effort expenditure has not only been associated with DA activity, but also with NA signaling. NA, a neurotransmitter that is produced in the locus coeruleus (LC) and adrenal medulla, is thought to play a major role in regulating arousal status (Aston-Jones & Cohen, 2005; T. T.-J. Chong et al., 2015; Glenberg & Gallese, 2012; Sarter et al., 2006; Yacubian et al., 2007) and the energization of behavior (i.e. supporting liberation of energy/resources necessary to perform effortful actions) (Jahn et al., 2018; Varazzani et al., 2015).

Preclinical research has attempted to dissect the unique contributions of DA and NA in cost and benefit computations. For example, abundant studies in rodents and non-human primates support the well-

established idea that DA neurons encode the expected value of future rewards (Hamid et al., 2016). Particularly, greater firing of DA neurons is observed with larger reward magnitudes (Roesch et al., 2007; Philippe N Tobler et al., 2005), whereas reduced DA responses reflect delay or uncertainty of future rewards (Fiorillo et al., 2003; Kobayashi & Schultz, 2008). Importantly, mounting evidence also implicates DA in motor or physical effort cost and particularly, with strength magnitude, vigor, or velocity (speed/reaction time) of responses that are aimed at acquiring rewards (Barter et al., 2015; da Silva et al., 2018; Hughes et al., 2020; Niv et al., 2007; Puryear et al., 2010). On the other hand, increased NA activity seems to be associated with the energization of behavior and effort production at time of executing actions (Borderies et al., 2019b; Varazzani et al., 2015), while a reduction in available NA has been shown to lead to a reduction in completing effortful actions (Jahn et al., 2018). Thus, in animal models, DA (explicit cost-benefit computations, vigor) and NA (executing effortful actions) are thought to contribute somewhat uniquely to cost-benefit computations. However, human studies investigating the role of NA and effort expenditure are surprisingly sparse.

While these promising preclinical findings suggest an important role for DA and NA in motivation (Ranjbar-Slamloo & Fazlali, 2020), overall, they have not been successful in parsing each system's contribution, in part due to lack of direct comparisons. In the current study, we aimed to investigate, for the first time, how DA and NA each play a role in cost-benefit evaluation in healthy humans. To these aims, we used a validated cost-benefit decision-making paradigm to assess explicit cost-benefit valuation and integration, as well as vigor at time of executing effortful actions, in combination with pharmacological challenges of the DA and NA system. More specifically, we used a low single-dose of propranolol to block NA, which is primarily used to treat hypertension by blocking β-adrenergic receptors (Srinivasan, 2019). Past research has shown that modulating β_1- and β_2- adrenergic receptors is linked with energy expenditure (Hoeks et al., 2003). We also used a low single-dose of haloperidol, which mainly exerts its antipsychotic effects by competitively blocking DA D_2 receptors (Davis, 2007), that have been suggested to impact reward processing and motivational drive (Pessiglione et al., 2006; Reuter et al., 2005; Tremblay et al., 2011).

In accordance with previous work, we expected a single dose of haloperidol to reduce willingness to acquire rewards in exchange for effort relative to placebo and propranolol, thus reduce reward sensitivity and/or affect net value computations. Moreover, we expect propranolol to increase the weight of effort on choices (i.e., increase effort sensitivity) compared to placebo and haloperidol. We additionally explored the effect of both agents on response vigor, an implicit form of motivation, hypothesizing that both agents, via the mechanisms mentioned above, might exert a negative effect on invigorating responses compared to placebo.

Methods

The study was approved by the medical-ethical review committee of Maastricht University (NL74735.068.2) and conducted in accordance with the Declaration of Helsinki. Financial compensation was granted for participation. Participants were instructed that they would receive a flat fee of 70 euros. In addition, participants were informed that they could win up to 30 euros depending on their task performance (amount for 2 computerized tasks; here one of them is discussed). These

instructions were given to motivate participants to perform well and stay focused throughout the task. In reality, all participants received 100 euros (70+30 euros) in total at the end of the testing session.

Participants

A total of 168 male and female healthy participants, 18-35 years old, were recruited via (online) advertisements. All participants completed two screening procedures, once before scheduling the session in order to determine major exclusion criteria via an anonymous online link and once on site prior to the start of the testing session using a detailed medical questionnaire. The former determined exclusion criteria, such as age, psychiatric/neurological disorder, substance abuse or dependence, diabetes, use of blood-pressure medication (lifetime), medication use in the past 3 weeks, pregnancy/ nursing (female participants only), abnormal BMI (>40 or <18). During the second screening all answers given during the online screening were checked again. Additionally, questions regarding medical history were asked including presence of cardiovascular disease, obstructive respiratory disease, chronic renal failure, hyperthyroidism, heart arrythmias (lifetime) as well as use of certain medication and antibiotics that could interact with the pharmacological agents used in the experiment e.g., blood-pressure medication, lopinavir/ritonavir (Kaletra), pentamidine (Pentacarinat), clarithromycin (Biaxin), moxiflocacin (Avelox). During a standard medical screening, participants body mass index (BMI: >40 or <18), vital signs (blood pressure/ pulse rate), and pregnancy status (urine sample, female participants only) were assessed. Detection of a medical condition or contra-indication for haloperidol (hypersensitivity to phenothiazines) or propranolol (abnormal blood pressure, i.e., diastolic< 60mmHg; systolic< 90mmHg) prior to testing led to the exclusion of participants. Moreover, all participants were instructed to refrain from alcohol and food intake (24 and 3 hours prior to the experiment respectively), which was verbally verified during the physical screening. In total, 12 participants were excluded before the start of data collection (3 due to abnormal BMI, 1 due to respiratory disease, 8 participants did not reschedule following COVID-19 related reasons). Additionally, 6 participants cancelled their appointment without providing any reason.

Design

The study was conducted according to a randomized double-blind placebo-controlled three-armed parallel-group (between-subjects) design. Participants were randomly allocated to one of three groups (n = 50 per group). One group received a single dose of propranolol (40 mg; temporarily reduces NA function via non-selective blockade of β-adrenergic receptors), one group received a single dose of haloperidol (2mg; temporarily reduces DA transmission by preferentially binding to D_2 receptors), and the third group received placebo (an inactive substance). Previous studies have shown that stimulating β-receptors increases energy expenditure (Hoeks et al., 2003), while inhibiting NA transmission decreases effort processing and effort production (Borderies et al., 2019a; Varazzani et al., 2015). On the other hand, mounting evidence suggests that haloperidol, as well as other antipsychotics that exhibit high affinity D_2 receptor antagonism impact reward processing and are associated with reduced motivational drive (Pessiglione et al., 2006; Reuter et al., 2005; Tremblay et al., 2011) (for detailed drug and dose justification *see Supplemental Methods*). It should be noted, however, that it is possible for dopaminergic antagonists, including haloperidol, to act in an opposite way and enhance DA concentration by increasing extracellular levels of DA (Devoto et al., 2003; Frank & O'Reilly, 2006; Kuroki et al., 1999). The order of drug administration was randomized using block randomization to

ensure balanced sample size across groups. For drug administration, we used a “double dummy” procedure to ensure successful double blinding. Specifically, participants in the haloperidol group received two tablets of haloperidol 1mg. Participants in the placebo group received two placebo tablets, while participants in the propranolol group received 1 tablet of propranolol 40mg and 1 tablet of placebo. All participants received each tablet (which was identical and thus non-discriminable in terms of size, appearance, and structure) in a separate and non-transparent container.

Questionnaires

During the session, participants filled out several questions pertaining to demographic information, such as age, gender, and education. They also completed four baseline questionnaires/tasks, including the Sensitivity to Punishment and Sensitivity to Reward Questionnaire - Revised and Clarified (SPSRQ-RC) (Conner et al., 2018), the Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995), the Abbreviated Impulsiveness Scale (ABIS) (Coutlee et al., 2014) and the digit-span task (Mefferd et al., 1966). In addition, the Bond & Lader Visual Analog Scale (BL-VAS) (Bond & Lader, 1974) was completed at baseline and repeated several times during the session (see below). All questionnaires, except the digit span, were digitized using the Experience Management Software Platform – Qualtrics.

The SPSRQ-RC, a 20-item self-rated scale with answers ranging from 1=“very untrue” to 5=“very true”, was used to assess trait-like sensitivity to reward and punishment at baseline (Conner et al., 2018).

The SHAPS is a 14-item self-report scale rated on a 4-point Likert scale ranging from 0 = “strongly disagree” to 4 = “definitely agree”. SHAPS was used to assess baseline anhedonia/ hedonic tone (Snaith et al., 1995).

The Abbreviated Impulsiveness Scale (ABIS) assessed trait-like impulsiveness and inattentiveness at baseline (Coutlee et al., 2014). ABIS is a 13-item scale with four possible responses ranging from 0 = “rarely/never” to 4 = “almost always/always”. Subscales include attentional, motor, and non-planning impulsiveness.

The digit-span task, a brief neuropsychological working memory task in which participants have to remember digit sequences, served as a measure of baseline working memory (Mefferd et al., 1966). It consists of two parts, the forward (normal order; up to 9 digits) and the backward (reverse order; up to 8 digits) part. The sum score of both parts constitutes the total score of the task.

The Bond & Lader Visual Analog Scale (BL-VAS), a 16-item self-report scale rated on a 100-point scale was used to assess momentary mood states and side-effects (Bond & Lader, 1974). The scale was completed 3 times during the session (before drug intake, 120 and 180 min after drug intake). Individual responses were combined to create three dimensions, namely alertness, contentedness, and calmness (Bond & Lader, 1974).

Decision-making task

After completion of the baseline questionnaires, all participants completed a computerized task designed in PsychoPy v3.0.0b11 (Peirce et al., 2019). Before the task, each participant's maximum voluntary contraction (MVC) was calibrated using a hand-held dynamometer with the dominant hand (Biopac systems, TSD21B-MRI). Participants were asked to exert their maximum grip strength over three consecutive trials. The average score of the above-median force of the 3 trials served as the MVC. Before calculating the above-median average we first removed any extreme values (>2*standard deviation). This approach resulted in an estimated MVC value that participants could sustain over a number of seconds and for multiple trials, since the task described below is a forced choice task.

During the main cost-benefit decision-making task, participants were presented with a high striker game, adapted from Chong et al (2015) (*see Figure 1*). On each trial (i.e., offer), participants were presented with a pre-determined amount of reward (i.e., 1, 5, 10, or 15 eurocents, indicated on a banner) combined with a level of physical effort (i.e., exerting 40%, 60%, 80 %, 100% of their MVC for 1.5 consecutive seconds, with the required force level represented as the red level of the high striker). Next, participants decided to accept or reject the offer, in a self-paced manner, using the corresponding keyboard buttons (V to accept and B to reject). They were instructed to accept an offer if they judged that the reward was worth the effort and reject it if they deemed the reward/effort combination was not worth it.

If the offer was accepted, participants had 5 seconds to squeeze the dynamometer until they reached the target bar and hold for 1.5 seconds to acquire the presented rewards. As soon as they reached the threshold, the red bar (indicating required MVC) turned green and upon successful completion of the trial a high-pitched tone was played, followed by the presentation of the reward amount. However, in case participants failed to exert the necessary amount of effort (intensity and/or duration), a low-frequency tone was played. Finally, if the offer was rejected, participants were asked to wait. To prevent potential time benefits that one would obtain from rejecting offers, the waiting period was kept identical to the trial events (i.e., 5 s). All trials were followed by a 1.5 s feedback phase, during which participants received information about performance (in case of successful completion: "You won *X* cents!"; in case of a failed trial: "Failed!"; in case of rejected trial: "Offer rejected.") and current total earnings. Participants were familiarized with structure of the task and experienced different effort and reward levels during a 4-trial practice phase that took place prior to the main task.

Participants were presented with 80 trials in total. Importantly, sixteen unique combinations of reward/effort level were repeated five times (i.e., five blocks), and during each block the order offer was randomly determined. To standardize the accumulation of fatigue effects, participants experienced a forced break between each block, and they could choose to resume in a self-paced manner whenever they were ready to continue. Participants also completed two questions at three distinct points that asked about fatigue ("Do you feel tired?" (Webster et al., 2003)) and hand discomfort participants were feeling at that moment ('Choose a number that best describes the pain in your hand.' (Katz & Melzack, 1999)) on respectively a 4- and 5- point Likert scale (i.e., 0 = Not at all - 3 = Very much; and 0 = No pain - 4 = Strong pain).

As primary outcome measure, we calculated an offer acceptance rate, defined as the number of accepted trials in proportion to all (i.e., 80) trials (Bonnelle et al., 2015; Klein-Flügge et al., 2016; Le Heron et al., 2018). As an additional, implicit, measure of motivation we also investigated participants' overexertion (i.e., MVC overshoot relative to MVC threshold) during offer completion, which reflects response vigor. To calculate response vigor, we used data from successful trials and extracted values lasting for 1.5 seconds - the amount of time that participants had to stay above threshold. Subsequently, we calculated the average exerted effort (above-threshold for 1.5 secs) and subtracted it from the required effort level. Since consistently and highly elevated values of overexertion could indicate potential problems in calibration procedures instead of drug effects (e.g., participants did not follow the instruction to squeeze as hard as possible), we, first, used the interquartile rule to identify outliers. Eleven outliers were identified (5 placebo, 4 haloperidol, 2 propranolol) resulting in a final sample of 139 participants (n=45 placebo, n=46 haloperidol, n=48 propranolol).

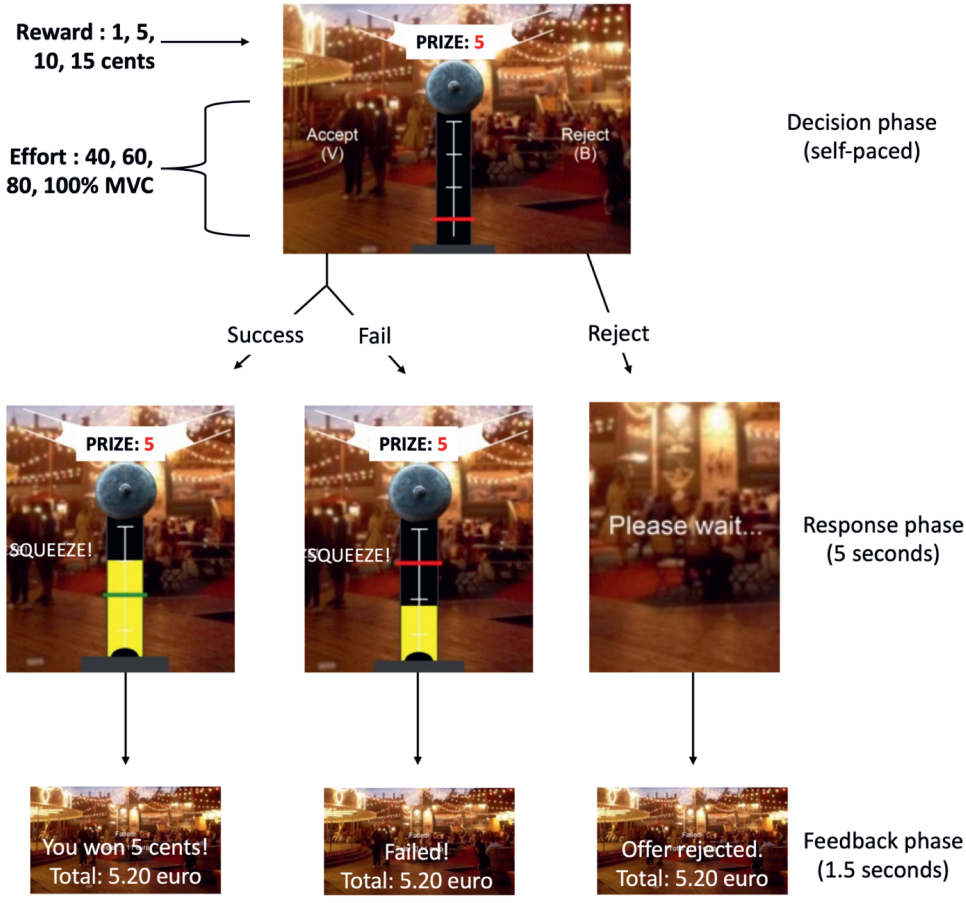

Figure 1 | Schematic overview of the cost-benefit task.
Prizes (rewards) were displayed by the banner number above the high striker (1, 5, 10, 15 eurocents) and the associated effort levels were displayed by the height of the red bar on the high striker (40, 60, 80, 100 % MVC). On each trial,

participants, decided whether they were willing to exert the indicated effort for the specified reward, if they deemed a particular combination was worth the effort. In case they accepted the offer (by pressing the V button), they had to squeeze a dynamometer until they reached the red bar -and hold for 1.5 seconds-, in this case the red bar turned green followed by a high tone. Nevertheless, if they failed to reach the bar for the required amount of time, the bar remained red followed by a deep tone. In case they rejected the offer (by pressing the B button), they had to wait for 5 seconds before moving to the next trial. At the end of each trial, participants were given feedback on their total earnings.

Study Procedure

Study participation entailed one session that lasted approximately 4 hours. After passing the medical screening, participants orally received the drug or placebo in tablets. All participants received two tablets according to a 'double dummy" design to ensure identical administration procedures for all drugs. As part of the safety protocol and in order to confirm the physiological effects of propranolol, blood pressure and heart rate were assessed at 6 timepoints (baseline, 30 min, 60 min, 90 min, 120 min, 190 min). A physician was always on site in case of an emergency. Mood states/discomfort were also monitored at 3 time-points using the VAS scale (see above). Immediately after drug administration, participants completed a set of baseline questionnaires (demographics, SPSRQ-RC, SHAPS, ABIS, VAS) and performed the digit span task. Thereafter, calibration of MVC and familiarization with the task followed. Forty-five minutes post drug administration a standard meal was provided (a granola bar and a yoghurt snack) to increase drug's bioavailability and a 2-hour break followed (approximate time maximum -t_{max}- for both drugs). After the break, participants performed the cost-befit decision-making task, which lasted around 20 minutes. At the end of the test day participants were asked to indicate which drug they think they received and were compensated for their time.

Statistical Analyses

All analyses were carried out using R version 3.6.2 (Team, 2013). A series of analyses of variance (ANOVAs) or χ^2 (for categorical variables) was used to compare demographic characteristics and baseline measures between groups. In case of repeated measurements (e.g., VAS, vital signs) we used mixed ANOVAs with time as within-factor and group (placebo/haloperidol/propranolol) as between-factor.

To assess our primary hypotheses, i.e., whether DA and NA have effects on task factors (e.g. reward, effort, time) that influence acceptance rates, a generalized linear model (GLM) was conducted using the glm function from the lme4 package (Bates et al., 2015). Specifically, we use to a two-step procedure to estimate the effects of haloperidol/propranolol for each task factor (Hernaus et al., 2019). First, for every person, the effect of each variable was quantified in a logistic regression where reward, effort cost and block (time) served as independent continuous variables and offer acceptance as dependent variable (coded as binary variable, 0/1). The resulting slopes (i.e., the betas for the independent variables) were compared between groups using an ANOVA (condition as independent, slopes/beta as the dependent variable) (Hernaus et al., 2019; Le Heron et al., 2018; Pfister et al., 2013) as well as against 0 using one-sample *t*-tests. Statistical significance as $p < 0.05$ (two-sided) is reported using Holm–Bonferroni correction, where applicable.

To assess our second hypothesis that DA and NA may affect response vigor, overexertion of participants (average overexertion during 1.5 secs – force threshold) was evaluated with a multilevel linear mixed-effects model (LMM) using the lmer function from the lme4 package (Bates et al., 2015). This model allowed us to assess how vigorously participants squeezed the hand-grip device using group (3 dummy variables), effort (and their interaction) and block (time) as predictors (fixed effects), while accounting for their random-effects within each participant (i.e., participants, block, and effort as random effects).

Results

Demographics, self-report, and physiological measures

Groups did not differ in demographic variables, or self-report measures of trait approach/inhibition motivation, impulsivity and working memory (*see Table 1*). They also did not differ on baseline ratings of repeated-measures items, such as pain [$F(2,136)=1.08$; $p=1$], fatigue [$F(2,136)=0.16$; $p=1$] and the VAS [$F(2,136)=1.93$; $p=0.3$] at t_1. Only 38% of participants correctly guessed which medication they were administered (which we asked at the end of the testing session using a three-option multiple choice question), suggesting successful blinding. Absence of a significant VAS-by-time interaction on all three dimensions (alertness, contentedness, and calmness; all p-values>0.05) revealed no significant drug effects on mood states over time. Measures on vital signs indicate that, as expected, propranolol successfully lowered blood pressure and heart rate (*see Supplemental Results*) via its β adrenoreceptor-blocking effects (Molinoff, 1984).

Table 1 | Sample characteristics.

	PLACEBO (n=45) MEAN (± SD)	HALOPERIDOL (n=46) MEAN (± SD)	PROPRANOLOL (n=48) MEAN (± SD)	ANALYSIS F/X^2 (P-VALUE)
Demographic Variables				
Sex(M/F)	34/11	33/13	35/13	X^2=2.09 (.72)
Age	22.47 (3.1)	23.09 (3.4)	22.9 (3.3)	F=0.46 (.63)
Education(L/M/H)[1]	7/18/20	4/17/25	4/15/28	X^2=9.64 (.65)
Baseline Measures				
ABIS attention	2.08 (0.41)	1.96 (0.39)	2.11 (0.55)	F=1.39 (.25)
ABIS motor	2.1 (0.52)	1.99 (0.54)	2.1 (0.53)	F=0.7 (.50)
ABIS non-planning	2.31 (0.62)	2.02 (0.49)	2.21 (0.65)	F=2.85 (.06)
SHAPS	7.22 (2.31)	7.43 (1.49)	6.96 (1.35)	F=0.87(.42)
SPSRQ reward	27.2 (6.32)	29.20 (6.30)	28.65 (6.02)	F=1.25 (.29)
SPSRQ punishment	26.73 (6.3)	28.67 (7.29)	29.98 (7.89)	F=0.85 (.43)
Digit Span	16.84 (3.6)	17.28 (3.66)	17.4 (4)	F=0.28 (.76)

Note: [1]Educational Degree adapted from The Dutch standard Classification of Education (Statistiek, 2023)

Abbreviations: ABIS, Abbreviated Impulsiveness Scale; SHAPS, Snaith–Hamilton Pleasure Scale; SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SD, standard deviation; M/F, Male/Female; L/M/H, Low/Middle/High

Effects of reward, effort, but not time affect choices to work in exchange for reward

We first investigated if participants were able to complete the accepted offers. Although the given effort levels were challenging (as observed by increasing levels of fatigue over time in the entire sample: t1 vs t3; [t(138)= -3.71; p<0.001]), they were easily achievable and participants succeeded at executing them on M = 98% (SD =0.13) of trials at all effort levels. To further assess whether our task design worked as intended, we evaluated main effects (i.e., in the entire sample) of reward (levels), effort (levels) and block (levels) on the probability of accepting an offer (1=choose to exert effort for given reward, 0=refuse offer and wait). We used a 2-step regression model (Pfister et al., 2013), in which we first quantified the effect of a predictor (i.e., the task variables mentioned above) on acceptance for each individual separately, followed by a comparison (at the group level) against zero to estimate whether the task variable significantly influenced the choice behavior in the task (also see Statistical Analyses).

As expected, reward was significantly higher than 0 [t(93)=21.3, p<0.001], meaning that participants were more likely to accept a given level of effort for an offer with higher reward levels. In contrast, and as expected, effort was significantly lower than 0 [t(104)=-20.61, p<0.001], suggesting that participants were less likely to accept to exert effort for a given level of reward at higher effort levels (see *Figure 2*). It is worth mentioning that, even though participants showed effort-discounting effects, they chose to work on many trials M = 72% (SD =0.45), suggesting that the task was not optimally developed to elicit 50-50% acceptance/rejection offers although, crucially, the main aim of this manuscript was to evaluate group differences in acceptance patterns. For visualization on how participants were discounting reward by effort in each condition *see Supplemental Figure 2*. Importantly, block was not significantly different from 0 [t(124)=-1.32, p=0.19], suggesting that there was no time-trend in acceptance when looking at combined data from all participants (*see Figure 1*).

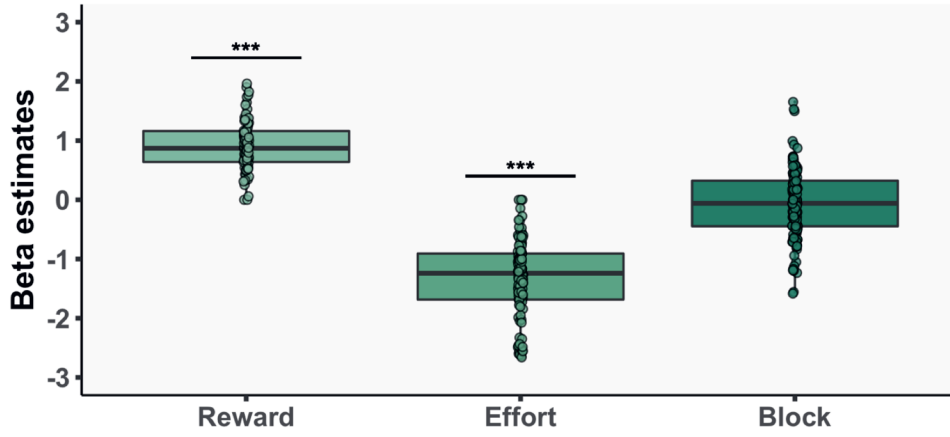

Figure 1 | Reward and effort predict offer acceptance in opposite directions.
Individual-level betas obtained using logistic regression on acceptance for reward, effort, and block in the entire sample. Means ± SD, individual data points, and distribution of the data for each condition are displayed. Significant differences are denoted by asterisks (*: p<0.05, **: p<0.01, ***: p<0.001).

Distinct effects of haloperidol and propranolol during the cost-benefit decision-making task

After confirming that the task worked as intended, we tested our primary hypothesis, i.e., that blockade of DA and NA would exert distinct effects on choice behavior by, for example, modulating the impact of reward, effort, or time on offer acceptance. Surprisingly, we did not observe a main effect of group on reward slopes [$F(2,91)= 2.37$; $p=0.1$]. However, a significant main effect of group on effort slopes [$F(2,88)= 4.22$; $p=0.02$] was observed. Post-hoc comparisons showed that participants on propranolol exhibited a stronger *negative* effect of effort cost on acceptance rates compared to participants on haloperidol [$t(68.4)=-2.83$, $p_{holm}=0.02$]. Comparisons between propranolol and placebo [$t(64.3)= -1.87$, $p_{holm}=0.13$] as well as control and haloperidol [$t(62.6)= -0.1$, $p_{holm}=0.55$] were not significant.

Interestingly, although we observed no effect of block on offer acceptance in the entire sample (see above), we did observe a significant main effect of group on block slopes [$F(2,122)=6.86$; $p=0.002$]. Post-hoc comparisons showed that participants on haloperidol exhibited a stronger negative effect of block (time) on offer acceptance rates compared to placebo [$t(81.9)=-2.83$, $p_{holm}=0.01$] and propranolol [$t(81.8)=-3.46$, $p_{holm}=0.003$]. Moreover, placebo and propranolol groups did not differ significantly [$t(79.5)=-0.51$, $p_{holm}=0.61$] (*Figure 2*). To further explore the effect of block on offer acceptance, we compared whether beta estimates were significantly different from 0 (one-sample *t-test*). The placebo [$t(40)=0.37$, $p=0.71$] and propranolol [$t(40)=1.16$, $p=0.25$] group did not differ significantly from 0, indicating no effect of time on acceptance rate for these two groups. In contrast, the haloperidol group [$t(42)=-3.64$, $p<0.001$] was significantly different from 0 indicating a negative time effect for the haloperidol group only. All in all, these results provide some evidence for an effect of propranolol on effort sensitivity, and an effect of haloperidol that hints towards a reduced willingness to exert effort in exchange for reward over time.

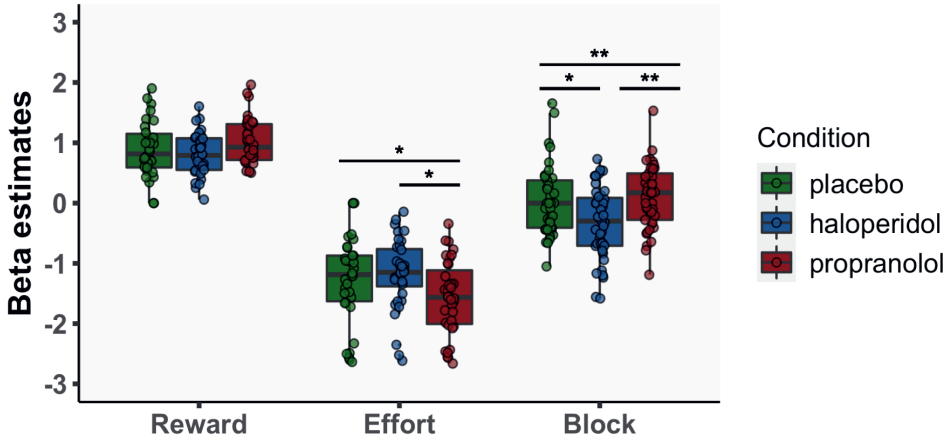

Figure 2 | Drug effects on offer acceptance for reward, effort, and block levels.
Individual-level betas obtained using logistic regression on acceptance for reward, effort, and block per condition. Means ± SD, individual data points, and distribution of the data for each condition are displayed. Significant differences are denoted by asterisks (*: p<0.05, **: p<0.01, ***: p<0.001). The top lines indicate significant main effects.

Haloperidol increased response vigor during the cost-benefit decision-making task

Next, we tested our second hypothesis; whether our pharmacological manipulations affected response vigor, a more implicit measure of motivation that we defined as participants' overexertion relative to the required effort level. Here, multilevel linear regression analyses revealed a significant condition-by-effort interaction, with response vigor being impacted less by increasing effort demands in the haloperidol vs placebo group (*B*=-0.02, 95% CI= [-0.04 – -0.00], *t*=-2.32, *p*=0.02). The interaction was not significant for the haloperidol vs propranolol group (*B*=-0.01, 95% CI= [-0.03 – 0.01], *t*=-1.30, *p*=0.19), nor the placebo vs propranolol group (*B*=0.01, 95% CI= [-0.03 – 0.01], *t*=-1.06, *p*=0.29) (*Figure 3*). These results suggest that only haloperidol exerted an effect on response vigor at time of offer execution.

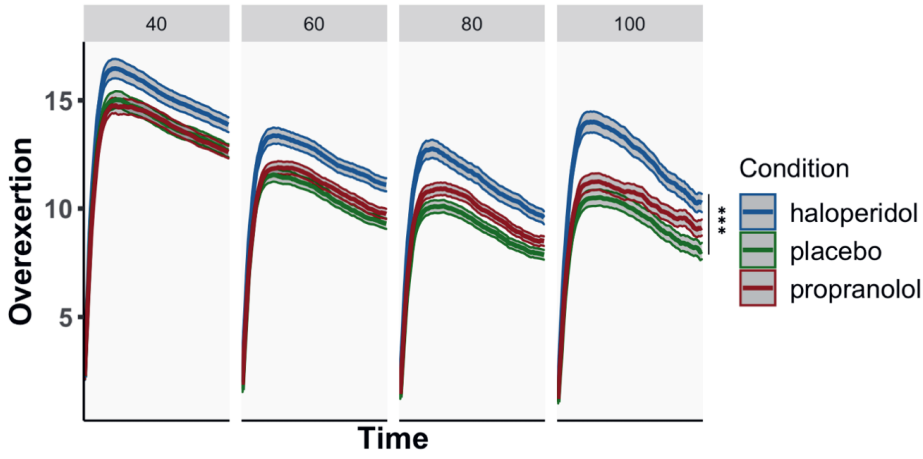

Figure 3 | Response vigor for each condition at each effort level.
Line chart showing how vigorously participants squeezed the dynamometer (effort overexertion comparted to the requested effort level). Time (x-axis) refers to the range of 0 - 1.5 secs that participants had to stay above-threshold. Means ± SD for each condition is displayed.

We next aimed to investigate if drug effects on vigor and offer acceptance were correlated. Importantly, we found a significant positive correlation only in the haloperidol group $\rho_{haloperidol}(44) = 0.36$, $p = 0.001$, suggesting that increased response vigor was associated with increased acceptance rates [$\rho_{placebo}(43) = 0.37$, $p = 0.7$; $\rho_{propranolol}(46) = 0.95$, $p = 0.35$]. Lastly, to evaluate whether increased response vigor in the haloperidol group increased hand discomfort and fatigue, we analyzed the subjective ratings of pain and tiredness, that were asked 3 times during the task. However, no significant condition-by-time interactions were observed for pain [$F(4, 272)=0.73$; $p=0.55$], with equal increases between groups over time, nor for fatigue [$F(4, 272)=0.18$; $p=0.93$], with different within-group trends over time (for visualization *see Supplemental Figure 3*).

Discussion

In this study we investigated the effect of DA (using haloperidol, which primarily targets D_2 receptors), and NA (using propranolol, which non-selectively targets β adrenergic receptors) on a cost and benefit decision-making task, in which participants could choose to exert physical effort in exchange for rewards. The aim was to assess how these two neurotransmitter systems affect explicit cost and benefit valuation, as well as response vigor when executing effortful actions. We found that both neurotransmitter systems were involved in different aspects of cost-benefit decision-making and action execution.

Counterintuitively, we observed that haloperidol increased response vigor compared to placebo. This result suggests that a single low dose of haloperidol may have resulted in enhanced DA transmission, rather than inhibiting its actions. Abundant evidence suggests that low doses of D_2 antagonists can act

in this manner (Devoto et al., 2003; Frank & O'Reilly, 2006; Kuroki et al., 1999). Particularly when given acutely, a low dose of haloperidol has been suggested to augment DA levels due to stronger inhibition of presynaptic D_2 autoreceptors and relatively weak post-synaptic blocking activity (Dias et al., 2012; Lidsky & Banerjee, 1993).

The effect of DA on action vigor aligns well with previous findings suggesting that DA, and particularly tonic DA activity, determines the vigor (magnitude, velocity, duration) used to approach appetitive stimuli (Barter et al., 2015; da Silva et al., 2018; Hughes et al., 2020; Niv et al., 2007; Puryear et al., 2010). In addition, it is important to note that haloperidol, even at low doses, demonstrates high DA D_2 receptor occupancy (Kapur et al., 1996), 25 times higher than D_1 (Bymaster et al., 1999). Postmortem and human studies have shown that D_2 agents predominately modulate striatal relative to prefrontal activity (Camps et al., 1989; Mehta et al., 2003). Striatal DA-mediated dysfunction is known to be involved in many (hypo/hyper kinetic) movement disorders (e.g., PD, Huntington's disease, Tourette syndrome) (Gittis & Kreitzer, 2012). In fact, it has been suggested that DA projections from SNc to the striatum may signal vigor related to speed in PD patients (Mazzoni et al., 2007) which, similar to our study findings, suggests that striatal DA may signal an implicit form of motor motivation. In accordance with this view, mechanistic theories about the role of DA in cognition support that stimulation of D_2 receptors in striatum inhibits No-Go activity (Black et al., 1997; Frank & O'Reilly, 2006).

Surprisingly, our results do not directly link DA with reward sensitivity, as observed in many studies (Burke et al., 2018; Negrelli et al., 2020; Pessiglione et al., 2006; Reuter et al., 2005; Roesch et al., 2007; P. N. Tobler et al., 2005; Tremblay et al., 2011). However, the positive correlation between response vigor and average acceptance rates together with the time effect observed in the haloperidol group could indicate increased reward valuation and willingness to exert effort in exchange of rewards in the beginning of the task, which might have reduced over time with increasing effort expenditure. As such, the reduction in offer acceptance rates over time in the haloperidol group might be attributed to effects of fatigue due to increased response vigor (Müller & Apps, 2019). Fatigue has a gradually increasing trend over time in the haloperidol group compared to the other groups (which show different within-group patterns). Therefore, it is possible that a single question repeated 3 times was not able to capture more subtle yet meaningful group differences in fatigue. As suggested by previous research, DA might have signaled the net value of the choice, which decreased over time possibly due to fatigue (Ang et al., 2015; Varazzani et al., 2015). However, we should highlight, that the task was designed to minimize effects of fatigue, thus future computational modeling analyses could delineate which underlying mechanisms may have mediated this behavior.

With regards to NA, we observed more conservative effort production during choice behavior in the propranolol group compared to the haloperidol group, which might suggest increased sensitivity to effort cost. This result is in agreement with research conducted in non-human primates that has shown pharmacological blockade of NA to enhance the weight of effort on choices that involve reward-effort trade-off, without exerting effects on reward sensitivity (Borderies et al., 2019a). In addition, another study that measured single neuron recordings in LC, which is predominately noradrenergic, showed that around the onset of the action LC activity was modulated by effort significantly more than SNc, which is predominately dopaminergic (Varazzani et al., 2015).

Overall, these results suggest that DA and NA have distinct but complementary effects in effort processing. Based on the above, we suggest that NA may play an important role in signaling how conservative or liberal we can be with effort production given our current energy availability (which is also known to be NA-mediated), but then DA might take over to control the vigor of action used to approach motivationally relevant stimuli, and thus possibly encode the net cost and benefit value of choices. As such, DA and NA may make important contributions to value and energization-related policies that control goal-directed behavior. Future computational modeling can provide further insight into the cognitive mechanisms that may mediate these effects. However, the current findings already provide a step toward understating the interacting role of these two neurotransmitters systems, which are both targets of different pharmacological treatment options, and the dysfunction of which is involved in several neuropsychiatric disorders characterized by motivational impairments.

Strengths, limitations, and future directions

A great advantage of the study is that it directly compared the role of DA and NA in motivated behavior for first time in human participants using a relatively big sample size. With the aim to translate and expand on animal research findings (Varazzani et al., 2015), we used pharmacological agents, such as haloperidol (to preferentially target D_2 receptors), propranolol (to target β adrenoreceptors), and placebo to evaluate the distinct but complementary influence of DA and NA on a cost and benefit decision-making task.

One limitation of the study is that haloperidol did not act as an antagonist, as originally intended, and instead seemed to increase DA levels; a mechanism of action that has been previously reported (see above) (Devoto et al., 2003; Frank & O'Reilly, 2006; Kuroki et al., 1999). Nevertheless, we can still draw important information about the role of DA and NA in motor motivation. Future research using agents with the same drug action (e.g., agonists or antagonists) would be important to validate these findings. In addition, both haloperidol and propranolol exert pharmacological activity on a number of receptors (Davis, 2007). Especially haloperidol acts also on α-adrenergic receptors (Ohta, 1976), therefore we cannot rule out the possibility that haloperidol also exerted weak effects on NA. Hence, it would be advisable for future studies to use agents that target more selectively DA or NA systems. Lastly, propranolol targets mainly β-adrenergic receptors, and its essentially inactive in α-adrenergic receptors (Storch & Hoeger, 2010). It would be interesting for future studies to explore whether manipulating α-adrenergic receptors might yield different results. Despite these limitations, the findings of this study provide further insight into the distinct but interacting role of DA and NA in cost and benefit decision-making and we hope they will inspire future studies to delve deeper into the neurobiological mechanisms of neurotransmitters involved in motivated behavior.

Conclusion

In this study we used pharmacological challenges to investigate the complimentary effects of DA (using haloperidol) and NA (using propranolol) on cost and benefit decision-making in humans. We found that low-dose haloperidol may temporarily increase response vigor at the cost of reduced acceptance over time, while low-dose propranolol might increase sensitivity to effort cost. Further cognitive computational modeling can provide better insight into the precise mechanisms that may mediate these effects. Nevertheless, these findings provide initial evidence on the effects of the two neurotransmitters in (motor) motivation.

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Supplemental Information

Supplemental Methods

Drug Justification and Dosage Levels

Propranolol

Propranolol is a non-selective, β-adrenergic receptor antagonist and competes with catecholamines at β1- and β2 receptors, blocking their sympathetic effects (Black et al., 1964). Propranolol is used as a treatment for many conditions including hypertension, arrythmias, anxiety and migraines. It is a lipid soluble drug that crosses the blood-brain barrier freely and acts both inside and outside the central nervous system (Black et al., 1964; Cahill et al., 2000).

To our knowledge only 3 studies have tested the effect of propranolol in the context of decision-making. The first study utilized a memory task and found that treatment with propranolol resulted in a conservative bias during uncertain conditions (Corwin et al., 1990). The other study used a gambling task and found that treatment resulted in decreased sensitivity to monetary loses (Rogers et al., 2004). While the third study used also a gambling task and found that propranolol reduced loss aversion especially in subjects with higher initial levels of loss aversion (Sokol-Hessner et al., 2015). A dose of 40mg has previously been administered orally to block noradrenergic response in numerous studies (Hermans et al., 2011; Kroes et al., 2016; Schwabe & Wolf, 2011) demonstrating a strong safety profile.

Haloperidol

Haloperidol is a high potency typical antipsychotic (O'Carroll et al., 1999). It exerts its antipsychotic effect through its strong antagonism to post-synaptic DA receptors (it preferentially binds to D_2 receptors although it has low affinity for numerous receptors, e.g., D_1), particularly in the mesolimbic system of the brain (Dold et al., 2015).

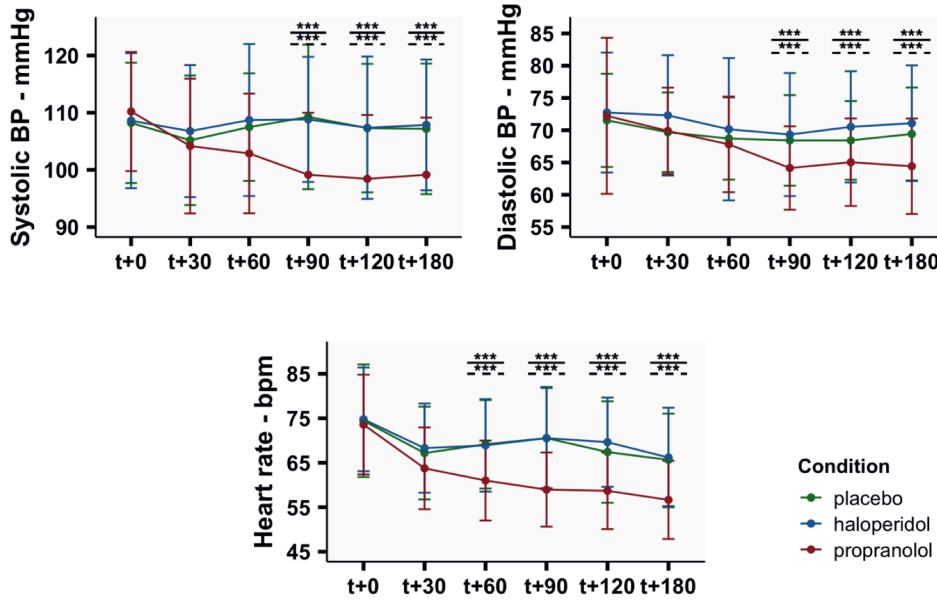
Numerous studies have used haloperidol to exploit its mechanism of action. Studies evaluating the effect of haloperidol in the context of decision making suggest that administration of haloperidol decreases sensitivity to reward (Reuter et al., 2005; Tremblay et al., 2011). Interestingly, similar patterns towards reward sensitivity have been observed between Parkinson's disease patients and healthy volunteers after receiving 2mg haloperidol (Pessiglione et al., 2006). Converging evidence suggests that chronic high-dose use of haloperidol could lead to unwanted adverse events, however acute treatment even at high doses is well-tolerated, and has a safety profile that is similar to other antipsychotics (Chen et al., 2020; Dossenbach et al., 2008; Schrijver et al., 2016; Yoon et al., 2013).

Supplemental Results

Vital signs

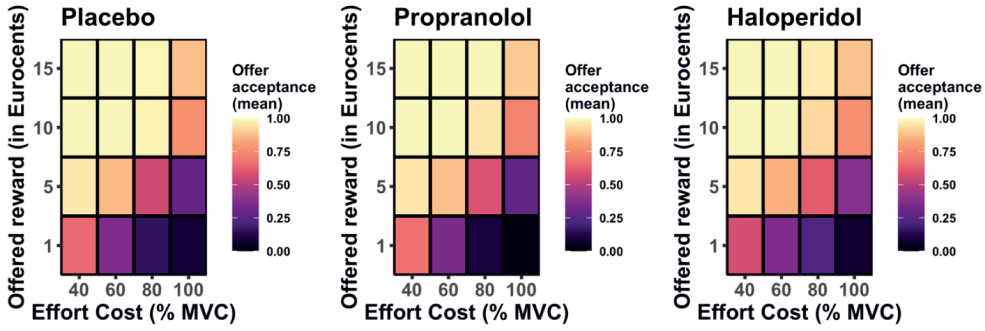
To evaluate whether propranolol successfully blocked β- adrenoreceptor, we checked at the vital signs. A condition-by-time interaction was observed for vital sign measures [systolic blood pressure (SBP): $F(10, 680)=10.01$, $p<0.001$, $n^2_G= 0.03$; diastolic blood pressure (DBP): $F(10, 680)=3.25$, $p<0.001$, $n^2_G= 0.02$; heart rate: $F(10, 68)=9.48$, $p<0.001$, $n^2_G= 0.03$]. Simple main effect analyses

revealed that only the propranolol group exhibited reduction in blood pressure and heart rate over time compared to the other groups with statistical differences starting from *t+60* until *t+180* (the end of the session), thus being present throughout the duration of the task (which started at ~ *t+140*). More analytically, for SBP: *t+90* placebo vs propranolol $t(86.9)= 4.13$, $p<0.001$, *t+90* haloperidol vs propranolol $t(91.8)= 4.31$, $p<0.001$, *t+120* placebo vs propranolol $t(90.5)= 3.82$, $p<0.001$, t+*120* haloperidol vs propranolol $t(90)= 3.66$, $p<0.001$, *t+180* placebo vs propranolol $t(87.6)= 3.60$, $p=0.001$, *t+180* haloperidol vs propranolol $t(89.2)= 3.93$, $p<0.001$. For DBP*: t+90* placebo vs propranolol $t(89.1)= 3.05$, $p=0.01$, *t+90* haloperidol vs propranolol $t(78.7)= 3.07$, $p=0.01$, *t+120* placebo vs propranolol $t(90.9)= 2.53$, $p=0.03$, *t+120* haloperidol vs propranolol $t(85.4)= 3.42$, $p=0.003$, *t+180* placebo vs propranolol $t(90.9)= 3.31$, $p=0.003$, *t+180* haloperidol vs propranolol $t(87.3)= 3.93$, $p<0.001$. For heart rate: *t+60* placebo vs propranolol $t(88.5)= 4.14$, $p<0.001$], *t+60* haloperidol vs propranolol $t(88.9)= 3.94$, $p<0.001$, *t+90* placebo vs propranolol $t(79.9)= 5.52$, $p<0.00$, *t+90* haloperidol vs propranolol $t(82.9)= 5.65$, $p<0.001$, *t+120* placebo vs propranolol $t(81.8)= 4.14$, $p<0.001$, *t+120* haloperidol vs propranolol $t(88.7)= 5.66$, $p<0.001$, *t+180* placebo vs propranolol $t(86.4)= 4.49$, $p<0.00$, *t+180* haloperidol vs propranolol $t(85.3)= 4.58$, $p<0.001$]. For comparisons between haloperidol and placebo all *p-values > 0.05 (see Supplemental Figure 1).*

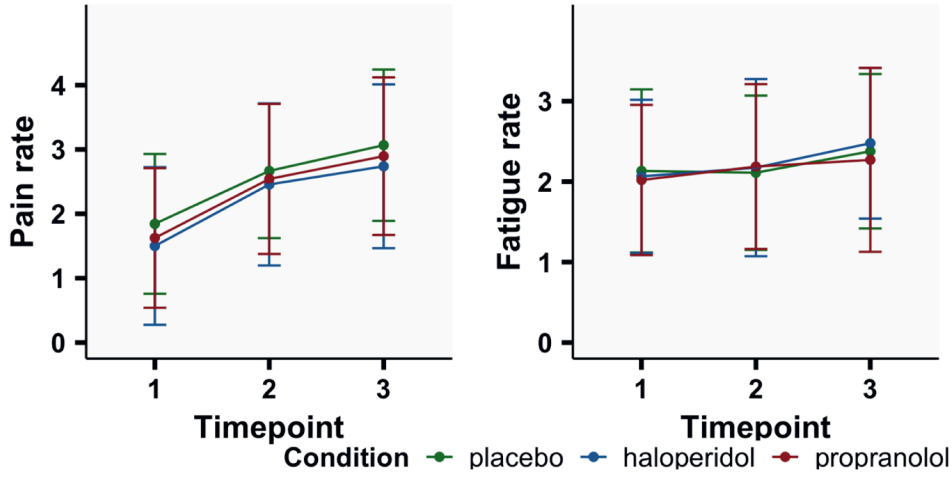


Supplemental Figure 1 | Vital sign measurements.

Upper row displays systolic and diastolic blood pressure (mmHg: millimeters of mercury). Lower row displays heart rate (bpm: beats per minute). Means ± SD are displayed for each condition at each timepoint. Significant differences are denoted by asterisks (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$). Solid line denotes control vs propranolol and dashed line denotes haloperidol vs propranolol simple main effects.



Supplemental Figure 2 | Effort discounting during the task.
Proportion (mean) of acceptance to work per group (placebo, propranolol, haloperidol). Participants at all groups were more likely to accept to work at higher reward and lower effort level, indicating that participants were discounting rewards by effort.



Supplemental Figure 3 | Subjective ratings on momentary pain and fatigue.
No significant condition-by-time interactions observed. Both hand pain and fatigue ratings increase over time in all groups. Somewhat different trends within conditions are observed for fatigue ratings. Means ± SD for each condition at each timepoint are displayed.

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CHAPTER 5

Worries about the COVID-19 pandemic and the dynamic regulation of emotions in the general population: A network analysis study

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Abstract

The impact of the COVID-19 pandemic on mental health has been widely reported. Yet, little remains known about the psychological mechanisms associated with changes in mental well-being during the currently ongoing pandemic. Here, we use a network analysis to unravel complex relationships between COVID-19 related stressors and emotional states during the initial phase of the COVID-19 (April 2020). Adults living in the Netherlands and Belgium (N=1145, age 16 and older) (repeatedly) completed an online survey (approximate survey completion rate = 66.2%) about COVID-19 (over a 5-day maximum sampling period). Partial correlations and contemporaneous networks illustrated that worries about the impact of the COVID-19 pandemic were primarily associated with distress and mood ratings, which were subsequently associated with other indicators of well-being. Temporal network analysis revealed that COVID-19 worries were selectively associated with the reciprocal interplay between high distress and low positive mood (https://osf.io/vtdkr/). These results may point to potential mechanisms by which initial worries about the COVID-19 pandemic might have impacted psychological well-being.

Keywords: COVID-19, distress, mood, emotional states, network analyses

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, and its associated socioeconomic consequences, can be considered a stressor of unprecedented, global scale. Although still ongoing, experts have expressed concerns about the potential adverse effects of pandemic-related stressors on well-being and mental health (Cénat et al., 2021; Leach et al., 2021). These worries stem from various aspects related to the COVID-19 pandemic.

For instance, the implementation of nationwide lockdowns and curfews, aimed at mitigating the spread of the virus, have profoundly disrupted social activities, thereby aggravating feelings of loneliness (O'Sullivan et al., 2021; Tull et al., 2020). Recent evidence suggests that social isolation and feelings of loneliness during the COVID-19 pandemic were associated with depressed mood, heightened anxiety, and poorer sleep quality (Grey et al., 2020; Hwang et al., 2020; Meda et al., 2021; Santini & Koyanagi, 2021): psychological changes that are commonly seen in affective and stress-related disorders. In addition, the unpredictable course of the pandemic has caused unbridled uncertainty (e.g., regarding the impact of the pandemic on a personal, professional, and societal level) (Koffman et al., 2020). Even before the occurrence of COVID-19, it was known that poor coping with uncertainty magnifies worries, anxiety, and avoidance behavior (Hunt et al., 2019; Norr et al., 2013). Such excessive uncertainty and worrying can put a considerable strain on mental health and well-being (Nitschke et al., 2021; Varga et al., 2021).

Past epidemics that share important similarities to the current COVID-19 pandemic in terms of mitigation measures and uncertainty, like Ebola, SARS, and H1N1 Influenza, have been associated with a spike in psychological distress, low mood, and emotional exhaustion (Brooks et al., 2020). Interestingly, studies in UK adults in the initial stage of the COVID-19 outbreak also found elevated levels of anxiety, traumatic stress, depression (Shevlin et al., 2020), and even suicidal ideation (O'Connor et al., 2021). Similarly, studies conducted in Italy, Spain, Germany, and China observed, among others, increased levels of distress and heightened affective symptoms (Losada-Baltar et al., 2021; Mazza et al., 2020; Rauschenberg et al., 2021; Wang et al., 2020). Put together, these results highlight how major health crises can be accompanied by increased distress and altered emotional states.

Given its recency, much remains unknown about the psychological impact of COVID-19 pandemic, for example whether such effects are more specific to emotional states, or changes in mental well-being more generally. Network models (S. Epskamp et al., 2018) can provide important insights into complex relationships among COVID-19 related stressors (e.g., social isolation, worries about the virus, worries about loved ones) and more general indicators of mental well-being (e.g., low mood, distress, loneliness). A great advantage of network analysis is that it allows investigation of direct and indirect interactions among all variables of interest. Importantly, this approach can help identify key variables or clusters of variables that have a strong influence on other variables within a given network. As such, the network approach facilitates understanding of the complex interactions that underlie (changes in) psychological variables, which may provide clues on important variables/clusters that could serve as the target of, for example, interventions

(S. Epskamp et al., 2018). Some initial evidence from COVID-19 network studies in the general population suggests high interconnectivity between COVID-19 related stressors and symptoms of anxiety and depression (Hoffart et al., 2021; Zavlis et al., 2021), pointing to a potentially important role for altered emotional states during the COVID-19 pandemic.

Fewer studies, however, have assessed longitudinal networks. These studies are important because they reveal how changes in emotional states unfold over time. Among the few studies conducted, Fried et al. (2020) observed mixed emotional changes (e.g., increased depression ratings, lower anxiety ratings) over the course of a two-week measurement window early in the COVID-19 pandemic. On the other hand, Martin-Brufay et al. (2020) suggested that the impact of pandemic-related stressors on emotional states was dependent on adaptation strategies using also a two-week measurement window (i.e., negative expectations in the beginning of quarantine lead to better adaption, while positive expectations in the beginning of quarantine lead to poorer adaptation over time). Lastly, Zavlis et al. (2021) observed connectivity between pandemic-related anxiety, and symptoms of generalized anxiety disorder and depression over a one-month interval. These studies once more point to associations between pandemic-related stressors and changes in emotional states, yet much remains inconclusive about their temporal interactions (i.e., whether they predict each other over time).

In an attempt to contribute to and expand on these recent insights, we investigated the psychological state of adults in the Netherlands and Belgium in the earliest phase of COVID-19 pandemic, when social isolation and uncertainty were high. Utilizing cross-sectional and (a maximum of five) repeated measures of psychological variables associated more generally with mental well-being (e.g., low mood, distress, energy, loneliness) and pandemic-specific variables (i.e., worries about the virus, social distancing), in combination with network analyses, we sought to establish the temporal dynamics of emotional states during the initial phase of the COVID-19 pandemic.

Methods

Study outline

To investigate (temporal) associations between COVID-19 related items and psychological indicators of mental well-being during the initial phase of the COVID-19 pandemic, we conducted an online survey among individuals living in the Netherlands and Belgium. The study was active between 2020/03/31 and 2020/04/30, a timeframe during which both countries implemented stringent measures to contain the spread of COVID-19 (*see Figure 1* for an overview of daily infections and examples of regulations implemented by the Dutch government to curtail COVID-19 infections).

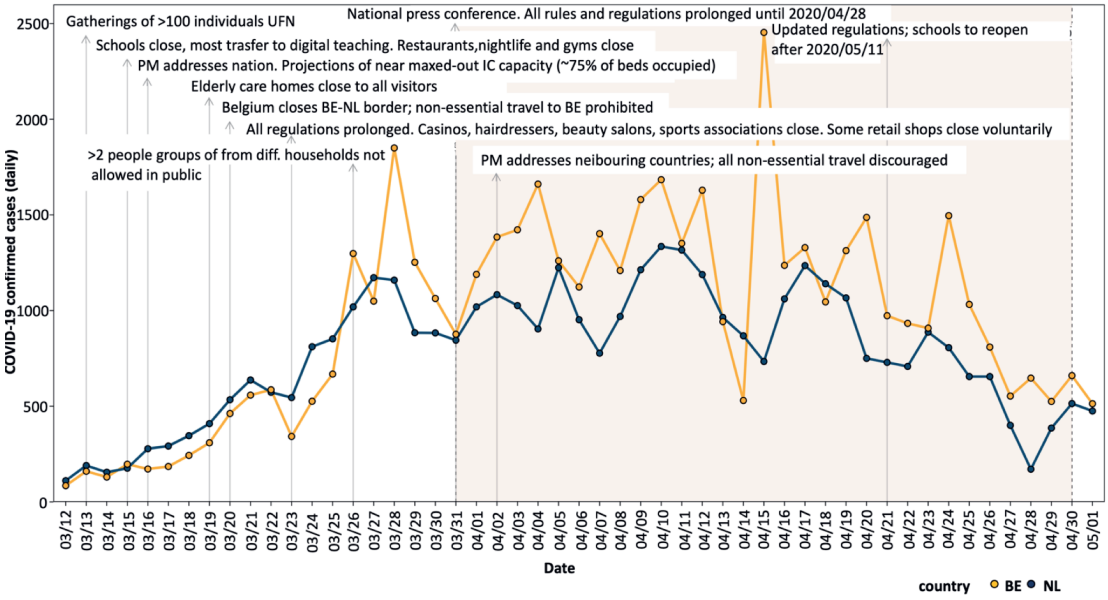

Figure 1 | COVID-19 confirmed cases and measures.
A schematic overview of the daily confirmed COVID-19 cases and the measures taken to mitigate the spread of the virus in the Netherlands and Belgium, displayed in chronological order. All text labels refer to measures that were implemented in the Netherlands.

Participants were recruited via social media (e.g., Facebook, Twitter), university media (website, mailing list), and local news and media (newspaper, television). Dedicated efforts were made to ensure that older adults were also represented in the final sample, including advertisements and availability of tablets for questionnaire completion, and support from staff, in local elderly communities and nursing homes. The study was approved by the Faculty of Psychology and Neuroscience ethical review committee of Maastricht University (protocol number: 221 62 03 2020).

Survey procedure

The survey was hosted on Qualtrics (Qualtrics, Provo, UT) and was accessible to anyone with a digital device with an Internet connection. Participants accessed the survey via an anonymous link and were invited to complete a three-part survey consisting of 1) demographics and COVID-19 status, 2) ratings of psychological indicators of mental well-being (low mood, distress, loneliness, energy, motivation), and 3) ratings of worries about/preoccupation with COVID-19 and adherence to widely disseminated infection-mitigation guidelines that necessitate social distancing.

The order of block two and three, as well the item order within each block, was randomized between sessions. We used a structured diary approach (Bolger et al., 2003; Shiffman et al., 2008) to investigate within-person changes in ratings over time, as well as associations among items ratings. Prior to and following completion of the survey, all participants were reminded that the

survey could be completed once per day for a maximum of five days. We opted for a short sampling period due to the high uncertainty at time of conducting the study (i.e., April 2020). At this point it was unclear for how long certain policies and restrictions were going to be implemented. Next, to boost compliance, participants were invited to set an alarm on their phone or computer for the next day, as a reminder to complete the next survey 12-24 hours later. This approach ensured that future prompt times were acceptable to participants, and has been associated with a questionnaire completion rate similar to that of random prompts (Burke et al., 2017). To complete the next report upon being prompted by the alarm, participants accessed the link, filled in a unique participant-generated code (generated during the first session), and completed block two and three again. Demographics were not collected during these follow-up measurements.

The average survey completion time in the entire sample with valid reports (*see section, "3.1 Sample characteristics"*) was 9.40 min (SD=4.40) for the first session and 5.80 min (SD=3.04) for follow-up prompts. Surveys were generally completed within 1-1.5 day intervals (M=1.41, SD=1.04).

Quality control and final sample

We implemented a number of quality control criteria for survey (attempts), which we represent visually in a Sankey chart (*Figure 2*).

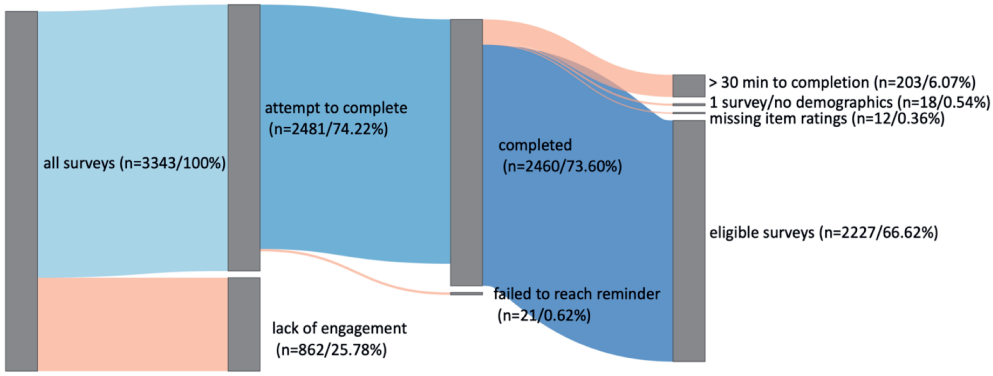

Figure 2 | Sankey diagram showing inclusion/exclusion of participant reports.
The length of each grey link represents the number of included/excluded reports at different times throughout the questionnaire completion process (blue/red colors represent included/excluded reports, respectively). Reported numbers represent unique surveys, and the percentages are relative to the total amount of opened surveys (i.e., 3343**).**

First, survey attempts that were largely incomplete (i.e., ≤50% questions completed) were not considered for analysis (n=862). In most cases, these incomplete reports indicated a lack of engagement: for example, in 90.26% of these 862 survey attempts, participants did not move past

the introduction screen. Remaining survey attempts (i.e., >50% finished) were excluded if the participant did *not* reach the final prompt reminder screen (n=21), leaving a set of 2460 (73.60%) completed surveys.

Completed surveys with a completion time that exceeded 30 min were also excluded (n=203), with 30 min being approximately three times the average completion time. Moreover, a small proportion of completed surveys from participants that only completed the survey once without providing sociodemographic details were excluded from the analysis (n=18). This could have occurred if participants inadvertently indicated during their first survey that they had previously completed the survey. Participants that completed the survey multiple times without providing demographic details, however, were not removed from the dataset, and used in some analyses. Finally, we removed surveys for which at least one of the rating variables of interest, listed in the next section, was missing (n=12).

After removing the ineligible surveys, a final sample of 2227 completed surveys remained (66.62% of opened surveys; 89.76% of surveys that participants engaged with), obtained from 1145 unique participants (1089 with completed demographics), of which 408 participants completed the survey more than once.

Survey items and outcome measures

Survey items focused on psychological indicators more generally associated with mental well-being as well as items that were specific to the COVID-19 pandemic. An overview of all self-rated items is available in Table 1. All items were rated on a 0-100 slider scale with an anchor at both ends describing the intensity of the rating (for subjective ratings 0=completely absent/ not at all, 100=very much so; for COVID-19 related items 0=completely disagree, 100=completely agree). The only exception to this format was the social isolation item, which was rated on a 0-24-hour scale and recoded post hoc to a 0-100 scale for consistency with the other items for the analyses (i.e., hours × 4.167).

Table 1 | An overview of questionnaire items.

Survey Item
Mental well-being ("in the past 24hours, I:")
Positive mood
(felt) cheerful
(felt) carefree
(felt) sad (r)
Distress
(felt) relaxed (r)
(felt) annoyed
(felt) stressed
(felt) anxious
(felt) calm (r)
Motivation
(didn't feel) like doing anything (r)
(wasn't motivated) to do things I typically enjoy (r)
Energy
(felt) well-rested
(had) little energy (r)
Loneliness
(felt) lonely
COVID-19 related items
COVID-19 worries
COVID-19-related news worry me
I can easily think about other things than COVID-19 (r)
I do not leave my home out of fear that I may contract COVID-19
I think COVID-19-related fears are exaggerated (r)
Consider: many COVID-related deaths, many COVID-19 infections, and hospitals with max-out capacities. These are things that won't happen in the country I live in (r)
I am not worried about the repercussions of the COVID-19 pandemic on work, income, or future perspective (r)
Others have a greater chance of contracting COVID-19 than I do (r)
COVID-19 is not worse/more dangerous than the flu (r)
I am scared of contracting COVID-19
I am scared that my colleagues, friends and/or family will contract COVID-19
COVID-19 guideline adherence ("in the past 24 hours, I:")
have followed COVID-19 hygiene guidelines to the best of my ability (1.5 distance, sneezing in elbow, no handshakes, washing hands)
have deliberately not taken the initiative to meet with other people; to minimize the risk of COVID-19 spread [a]
have declined people's invitations (to physically meet) to the best of my ability; to minimize the risk of COVID-19 spread [a]
have not left my home for [XX] consecutive hours [b]

(r) = reverse-scored
[a] Participants were instructed to exclude individuals that they lived with from their answers
[b] Rated on a 0–24-hour scale

Mental well-being items

All internal consistency and factor analyses reported below and under *"Factor Analysis"* were conducted on the eligible 1145 first reports. We used previously-validated items from ecological momentary assessment (EMA) studies (Myin-Germeys et al., 2009) to assess emotional states which we categorized into measures more closely associated with negative/positive mood (three items, Cronbach's α=0.61) and distress (five items, α=0.81). Participants additionally provided subjective momentary ratings of motivation (two items, α=0.79), energy (two items, α=0.50), and loneliness (one item). For each of these five mental well-being domains, item ratings were averaged (see Table 1 for individual items).

COVID-19 items

Participants rated ten COVID-19 related statements about their perceived risk of infection, worries about and preoccupation with (the potential impact of) the virus, and fear of (contracting) the virus (COVID-19 worries; α=0.70). An additional set of four statements was used to assess the degree to which participants adhered to infection-mitigation procedures that involved social distancing, which were disseminated by each country's respective government (COVID-19 guideline adherence; α=0.69). For each of these two COVID-19 domains, item ratings were averaged (see Table 1 for individual items).

Factor analysis

To confirm the existence of a more general mental well-being and COVID-19 domain we conducted an exploratory factor analysis (varimax rotation, here and below) using all rating items listed in Table 1. All 13 mental well-being items loaded more strongly onto factor 1 (0.22 proportion of variance explained) than factor 2, while 12 out of the 14 COVID-19 items loaded more strongly onto factor 2 (0.11 proportion of variance explained) than factor 1 (*see Supplemental Table 1 for factor loadings*). A similar exploratory factor analysis, but this time using all COVID-19 items, revealed that the 4 social distancing guideline adherence items loaded more strongly onto factor 1 (0.17 proportion of variance explained) and 7 out of the 10 worry/preoccupation items loaded more strongly onto factor 2 (0.14 proportion of variance explained). A final exploratory factor analysis using all 13 mental well-being items revealed the existence of two more general psychological constructs, one of which seemingly associated with negative (sad, annoyed, stressed, anxious, lack of undertaking activities/motivation, lower energy, loneliness; 0.27 proportion of variance explained) and the other with positive (cheerful, carefree, relaxed, calm, well-rested; 0.20 proportion of variance explained) psychological states. All in all, these results provide some evidence for the item groupings we discussed above and in Table 1, and for all (network) analyses referenced below we consistently used these item groupings.

Statistical analyses

We first describe sociodemographic characteristics of the final sample using descriptive statistics. Associations (Spearman's ρ for age bracket, χ^2 for categorical predictors) between sample characteristics and survey-related details, such as the number of repeated measurements, and date of first report, were also assessed.

Next, we obtained insights into general, time-related trends in the item ratings. We, therefore, used linear mixed-effects models with surveys nested within participants to investigate associations between average item ratings from the 7 domains (i.e., mood, distress, motivation, energy, loneliness, COVID-19 related worries, COVID-19 guideline adherence) and a) day of first survey (a proxy of more general *between-subjects* changes in ratings during the measurement window, i.e., April 2020) and b) day number relative to day of first survey (a proxy of more general *within-subjects* changes in ratings during the study participation window). These analyses were Bonferroni-corrected for the number of dependent variables tested (α=0.05/7).

Next, we carried out two types of network analyses (Borsboom & Cramer, 2013). The first analysis focused on data from all eligible first surveys ($n_{surveys}$=1145), allowing us to examine cross-sectional associations among all domains of interest. The second analysis focused on longitudinal associations. To limit potential effects of very short or long temporal delays between subsequent surveys, we restricted this longitudinal analysis to surveys with temporal delays of 12 hours to 4 days, leaving a sample of 395 (out of 408) participants with multiple eligible timepoints ($n_{surveys}$=1038).

For the cross-sectional analyses, we computed a) the product-moment correlations and b) the partial correlations between the 7 item domains. Significant correlations at a Bonferroni-corrected α=0.05/21 were visualized in a network graph. For the longitudinal analyses, we fitted a multilevel lag-1 vector-autoregressive model (Bringmann et al., 2013) that provides information on the a) contemporaneous associations at a given time point (7×6/2 = 21 correlations) and b) lagged associations between each variable and the values of all variables from the previous report (7×7 = 49 coefficients). We used a fully multivariate model, in which all variables simultaneously acted as outcomes and all lagged variables were used as predictors. The temporal (lagged) associations were of particular interest given the possible causal insights that might be derived from these analyses (Sacha Epskamp et al., 2018).

Two adjustments were made when fitting this model. First, to account for differences in the lag between adjacent reports, we included the time lag as a predictor in the model and allowed it to interact with the coefficients that represent the temporal associations. The lagged associations we report represent those for a 24-hour time lag. Second, since fitting the model with random effects for each of the lagged coefficients led to convergence problems, we removed these random effects and instead used cluster-robust inference methods (Pustejovsky & Tipton, 2018) to test temporal associations in a model that still included random item intercepts at the subject level. Network graphs for significant contemporaneous (α=0.05/21 correlation pairs) and temporal (α=0.05/49 coefficients) associations were used to visualize these results.

All models were fitted twice; once without including additional covariates and once when controlling for age, gender, education, country, and confirmed daily COVID-19 cases (day prior to measurement). All reported analyses were carried out using R (Team, 2013) using package nlme (Pinheiro & Bates, 2000) for fitting the multilevel vector autoregressive models, package

clubSandwich for the cluster-robust inferences (Pustejovsky, 2020), and package qgraph (Epskamp et al., 2012) for the visualizations of the networks.

Results

Sample characteristics

In the final sample of 1145 participants, 35.66% of participants completed two or more surveys. Demographic variables, available for 1089 participants, are reported in Table 2. In general, participants were more likely to be women (than men) and living in the Netherlands (compared to Belgium). The various education levels and age groups were evenly distributed across the sample, with only some underrepresentation of younger (<20) and older (>70) participants, although participants older than 60 years of age still made up 22.50% of the total sample.

Only a small subgroup of participants self-reported having a formal positive test result for COVID-19 (6.89%), with an additional 1.93% being suspected of having COVID-19 by a physician (see Table 2). Using a rating item that asked about the intensity of influenza-like symptoms, we confirmed that COVID-19 positive and suspected COVID-19 positive participants on average experienced greater flu-like symptoms than COVID-19 negative participants (B_{raw}=33.60, 95% CI=[30.07 – 37.13], t_{1082}=18.69, p<0.001).

Age (Spearman's ρ=0.10, p<0.001) and education level (χ^2=23.68, p=0.02), but not gender (χ^2=10.11, p=0.12), country (χ^2=9.20, p=0.16), or COVID-19 status (χ^2=12.54, p=0.82) were associated with the total number of completed surveys. Participants that completed a greater number of surveys were more likely to participate early in the measurement window (Spearman's ρ for correlation between number of completed surveys and day of first survey=-0.17, p<0.001).

Table 2 | Sample characteristics.

Variables	Percent (%)
Gender	
Female	77.41
Male	22.59
Age	
16-20	1.93
21 -30	21.40
31-40	19.01
41-50	13.96
51-60	21.21
61-70	16.44
>70	6.06
Education	
Intermediate vocational education	35.81
Higher vocational education	30.58
University	33.61
Country	
The Netherlands	76.49
Belgium	23.51
Living situation	
Alone	20.20
With partner	38.57
Children with or without partner	31.13
With parents	7.53
With others	2.57
COVID-19 status[a]	
Negative, no symptoms	90.82
Negative, suspected influenza	0.37
Negative, suspected COVID-19	1.93
COVID-19 positive	6.89
Completed surveys[b]	
1	63.34
2	9.53
3	6.56
4	7.60
≥5	1.97

[a]Suspected or confirmed influenza/COVID-19 by a medical expert and/or PCR test

[b]Based on N=1145 participants

Stability of item ratings during the study and participation window

Mixed-effects model analyses revealed that COVID-19 guideline adherence ratings were associated with day of first survey (B_{raw}=-0.27, 95% CI=[-0.39 – -0.16], t_{1081}=-4.71, p_{bonf}<0.001), corresponding to a difference of 7.83 percentage points (on the 0-100 scale) between participants

that completed their first rating on April 1st versus April 30th. No mental well-being domains nor COVID-19 related worries were associated with day of first survey following a Bonferroni correction.

Positive mood (B_{raw}=0.71, 95% CI=[0.41 – 1.01], t_{934}=4.66, p_{bonf}<0.001), distress (B_{raw}= -0.61, 95% CI=[-0.89 – -0.32], t_{934}= -4.20, p_{bonf}<0.001), and energy (B_{raw}=0.96, 95% CI=[0.59 – 1.33], t_{934}=5.16, p_{bonf}<0.001) ratings were associated with day into the participation/measurement window (relative to first day), suggesting that, over the course of participation, participants rated items slightly more positive (e.g., subtle improvements of 2.44 - 3.84 percentage points over a 5-day sampling period). COVID-19 guideline adherence ratings were also marginally associated with days into the participation window (B_{raw}= -0.32, 95% CI=[-0.54 – -0.09], t_{934}= -2.79, p_{bonf}=0.04).

These results provide some evidence for systematic between- and within-person trends during the study and participation window. We next turn to the network analyses to investigate (temporal) associations among COVID-19 and mental well-being item ratings.

Network analyses

We present a visual representation of the (Bonferroni-corrected) significant Pearson product-moment correlations between item ratings using all eligible first surveys (i.e., cross-sectional network analysis, $n_{surveys}$=1145) in *Figure 3A*. The Bonferroni-corrected *partial* correlations, denoted r_p, revealed small-to-moderate associations among a) mental well-being item ratings (i.e., positive mood, distress, motivation, energy, loneliness), b) COVID-19 item ratings (i.e., COVID-19 related worries and COVID-19 guideline adherence), and c) mental well-being and COVID-19 item ratings (*Figure 3B/Table 3*). Most importantly, greater COVID-19 related worries were associated with *greater* levels of distress (r_p=0.22, p_{bonf}<0.001) and *lower* positive mood (r_p= -0.10, p_{bonf}=0.02), while COVID-19 guideline adherence was associated with *lower* distress (r_p=-0.11, p_{bonf}=0.003).

Table 3 | Associations among item ratings.

	pos.mood	distress	motivation	energy	loneliness	C19 worries	C19 guideline
pos.mood	1	-	-	-	-	-	-
distress	**-0.47**	1	-	-	-	-	-
motivation	**0.13**	**-0.18**	1	-	-	-	-
energy	**0.20**	**-0.17**	**0.31**	1	-	-	-
loneliness	**-0.14**	**0.16**	**-0.23**	-0.03	1	-	-
C19 worries	**-0.10**	**0.22**	0.04	0.07	0.02	1	-
C19 guideline	-0.07	**-0.11**	-0.02	0.01	**-0.09**	**0.37**	1

Values in bold are significant at Bonferroni-corrected threshold (a/number of correlation combinations)

Figure 3C and *3D* provide a visual overview of the contemporaneous and time-lagged associations, respectively, as found in the longitudinal network model using all eligible timepoints from the repeated measures data; $n_{surveys}$=1038. The network of contemporaneous associations was highly consistent with the results from the cross-sectional partial correlation analyses (*Figure 3B* versus *Figure 3C*), with greater COVID-19 related worries being associated with increased distress (r=0.10) and lower positive mood (r=-0.14) ratings. Results from these two analyses, moreover, provide converging evidence that associations among mental well-being items were particularly pronounced in the moment.

Importantly, however, most of the associations among mental well-being items were no longer significant when examining the temporal relationships between these items (*Figure 3D*). Time-lagged associations were primarily observed between COVID-19 related worries and mental well-being items. Specifically, greater worries related to the COVID-19 pandemic at timepoint t were associated with greater distress (B_{raw}=0.17, 95% CI=[0.10 – 0.25], t_{125}=4.48, p_{bonf}<0.001) and lower positive mood (B_{raw}= -0.17, 95% CI=[-0.25 – -0.09], t_{138}=-4.36, p_{bonf}=0.001) at timepoint t+1. Moreover, distress and positive mood were among the few mental well-being items that were temporally associated (B_{raw}=-0.25, 95% CI=[-0.35 – -0.16], t_{139}=-5.26, p_{bonf}<0.001 for distress → positive mood; B_{raw}= -0.16, 95% CI=[-0.23 – -0.08], t_{145}=-4.01, p_{bonf}=0.005 for positive mood → distress). Although temporal associations were mostly small-to-modest, these results suggest that COVID-19 related worries may strengthen the reciprocal (negative) interplay between positive mood and distress. When repeating the analyses while controlling for several demographic covariates ($n_{surveys}$=898, *Supplemental Figure 1*), we observed a highly similar network of time-lagged associations, emphasizing the selective temporal dynamics involving positive mood, distress, and COVID-19 related worries.

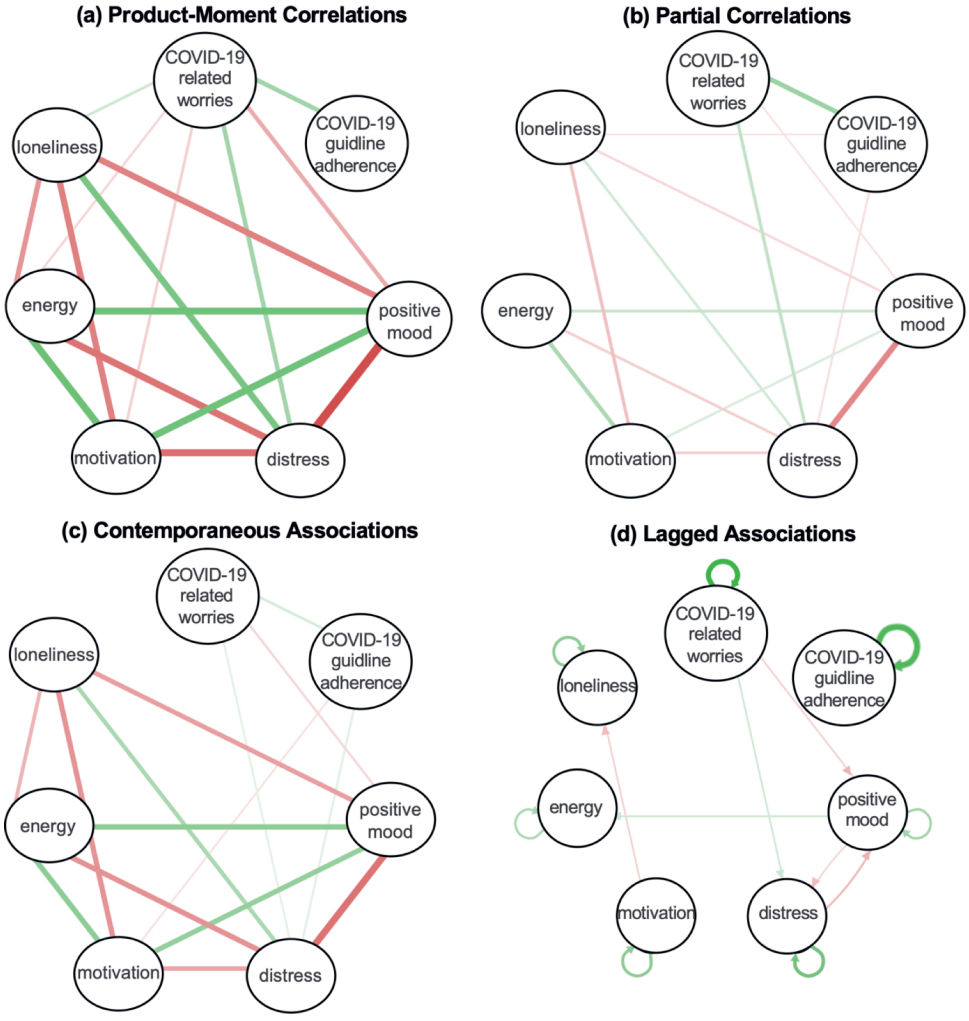

Figure 3 | Network analyses.

Top: Cross-sectional correlation analyses using all eligible first surveys ($n_{surveys}$=1145). Bottom: Associations obtained from a vector-autoregressive model using all eligible repeated measures ($n_{surveys}$=1038). Associations visualized in 3A-B represent Pearson product-moment and partial correlation coefficients, respectively. Associations visualized in 3C represent the estimated contemporaneous correlations among variables. Associations visualized in 3D represent slopes/B_{raw} coefficients and are directional; they indicate how ratings of variable X at timepoint *t* are associated with ratings of variable Y at timepoint *t*+1. Temporal autocorrelations in 3D are visualized as curved/circular arrows. Green = positive association; red = negative association. Line thickness and color intensity corresponds to the association strength. Only significant associations are shown (based on Bonferroni corrections for 21 unique correlation pairs in 3A-B-C and for 49 time-lagged associations in 3D).

Discussion

Here we investigated the psychological state of adults in the Netherlands and Belgium during the initial phase of the COVID-19 pandemic, a time of drastic changes in daily life routines due to uncertainty surrounding the COVID-19 pandemic and preventive measures taken to curtail the spread of the virus. Using network analyses, we found evidence for selective dynamic temporal interplay between worries about the COVID-19 pandemic and negative emotional states characterized by higher distress and lower positive mood.

Our cross-sectional results involving Pearson product-moment correlations revealed associations between COVID-19 related worries – e.g., about infection risk, future repercussions, and impact on loved ones – with all mental well-being items. However, cross-sectional associations after controlling for correlations among rating items and contemporaneous associations (using longitudinal data) revealed a more nuanced pattern of results. In these analyses, COVID-19 related worries were consistently associated with *higher* ratings of distress and *lower* positive mood ratings. In turn, positive mood and distress ratings were associated with other indicators of mental well-being, such as loneliness, motivation, and energy.

Previous work has reported associations between COVID-19 stressors and a range of mental health proxies, including loneliness/social behavior, anxiety, and energy (Fried et al., 2020; O'Sullivan et al., 2021; Ryu et al., 2021). Interestingly, in studies employing network methodology – even when using heterogenous samples in terms of participant characteristics and/or (subclinical) psychopathology – low positive mood and distress exhibit high centrality within depression-anxiety symptom networks, followed by other symptoms such as anhedonia, low energy, worthlessness, and nervousness (Bai et al., 2021; Beard et al., 2016). These observations are consistent with the notion that stress reactivity and low positive mood are paramount to the regulation of mental well-being (Flores-Kanter et al., 2021; Olff et al., 2021). For example, affective states are strong predictors of social behavior, daily-life activities and routines, and subsequent stress coping (Flores-Kanter et al., 2021; Quoidbach et al., 2019). Collectively, our cross-sectional and contemporaneous findings point to the presence of a relationship between COVID-19 stressors and heightened negative emotional states, which may exert secondary influences on other components of well-being, such as energy, motivation, and loneliness.

Importantly, associations among indicators of mental well-being were primarily observed in the same measurement window. Our time-lagged network analysis – which illustrates how variables predict each other in subsequent measurement windows (S. Epskamp et al., 2018) – revealed temporal associations within a selective cluster of items including COVID-19 related worries, distress, and positive mood. These ratings were not only (positively) autocorrelated, indicating a degree of similarity for ratings of a given item across time, but they also fueled each other over time. Specifically, COVID-19 related worries at timepoint *t* (e.g., day 1) were linked to lower positive mood and increased distress at *t+1* (e.g., day 2). These results could indicate that increased COVID-19 related worries may impact the dynamic regulation of emotional states over longer temporal windows. In addition, low positive mood and increased distress reciprocally interacted,

resulting in a vicious cycle (i.e., high distress ⇄ low positive mood; *Figure 3D*). Previous studies have postulated the existence of a bidirectional relationship between stress and (negative) affect, which can express itself in a downward spiral characterized by low positive mood and high distress (Langens & Stucke, 2005; Martinowich & Lu, 2008; Wichers et al., 2009; Wolk et al., 2016). Such interactions between low positive mood and distress can also be observed in the flow of daily life (Bos et al., 2018). Moreover, enhanced stress reactivity is associated with more severe depression and anxiety levels (van Winkel et al., 2015). Thus, our results suggest that worries about the current COVID-19 pandemic have the potential to selectively accentuate the negative interplay between low positive mood and distress. It would, therefore, be interesting for future studies to evaluate whether low positive mood and distress could keep reinforcing each other, even when initial worries about the pandemic start to fade away.

Despite the impact of COVID-19 worries on positive mood and distress, ratings of some mental well-being items (e.g., positive mood, distress, and energy) slightly improved throughout the measurement window. These findings are in agreement with previous studies reporting that after an initial increase in negative emotional states, the intensity of self-ratings may subside over time (Bendau et al., 2021; Fried et al., 2020). These relative improvements in emotional states could suggest the presence of an initial elevation bias in negative psychological states, which is often observed in self-report studies (Shrout et al., 2018). Alternatively, improvements could be indicative of successful adaptation or resilience (Veer et al., 2021).

Interestingly, adherence to hygiene and social distancing measures slightly decreased during the measurement window. This is in agreement with a gradual decline in adherence to protective measures reported in previous studies (Petherick et al., 2021; Scandurra et al., 2021), and may have been associated with a drop in cases and/or good news reports (e.g., planned reopening of public institutions announced later in the measurement window). Given the moderate decrease in distress over time, this finding corroborates the observed positive association between distress and COVID-19 guideline adherence in the contemporaneous network. That is, lower distress may lead to reduced guideline adherence – either directly or indirectly via the COVID-related worries node.

All in all, our data collected in the initial stages of the COVID-19 pandemic suggest that increased pandemic-related worries are associated with heightened negative emotional states. Temporal associations among COVID-19 related worries, distress, and positive mood may constitute a mechanism by which the ongoing pandemic could impact mental well-being, although studies with longer measurement intervals and knowledge of underlying resilience determinants would be necessary to support such conclusions. If confirmed, this mechanism may provide one explanation for the increased prevalence of affective/stress-related disorders reported during the COVID-19 pandemic (Qi et al., 2021; Salari et al., 2020).

Strengths and limitations

An advantage of the network approach used in this study is that it highlights the complex associations that collectively influence mental well-being. Our results provide initial insights into

the psychological mechanisms that may be impacted by the currently on-going COVID-19 pandemic, and, as such, provides clues on potential risk or resilience mechanisms during major health crises.

However, whether and under which circumstances these emotional changes will meaningfully contribute to psychopathology remains elusive and speculative. One caveat of this study is its short duration, which resulted in short intervals between subsequent measurements in conjunction with a relatively small sample size for online research. Although in this study we observed short-term temporal stability of the network, it would have been helpful to evaluate associations among mental well-being and COVID-19 specific items over longer intervals. Longer-term measurement windows with larger sample size could reveal whether COVID-19 worries, distress, and positive mood dynamics, uncovered here, persist over the course of the pandemic. Furthermore, caution is warranted regarding the generalizability of findings due to potential attrition bias, as observed when comparing cross-sectional and longitudinal data (35.63% of the total sample completed the survey more than once). Past research has shown that people with mental health problems are more likely to discontinue participation in follow-up measures (da Graca et al., 2023). Thus, lack of information regarding participants mental health history and/or use of psychotropic medication is another limitation that should be acknowledged.

Although we controlled for several sociodemographic variables, our design was not optimized for stratified analyses, for example based on gender, age, psychiatric history, geographical location, ethnicity, or education, which could explain the low effect sizes observed. Several studies have identified potential sociodemographic risk factors that predict worse mental health outcomes during the COVID-19 pandemic, including being female, younger in age, having pre-existing mental health problems, lack of social support, previous trauma, and experiencing additional stressful events in the past month (Li & Wang, 2020; O'Connor et al., 2021; O'Sullivan et al., 2021; Olff et al., 2021; Varga et al., 2021). Given the age distribution of this sample, future work could look at the association of age with measured variables, such a social isolation, impact on loved ones, etc. (Minahan et al., 2021; Sojli et al., 2021). A final limitation is that our sample is self-selected, meaning that it may not be representative of the entire population. Thus, reported findings should be extrapolated with caution.

Conclusion

To conclude, this network-based study evaluated the potential psychological repercussions of the COVID-19 pandemic in the Netherlands and Belgium. We identified worries about COVID-19 to be temporally associated with the reciprocal interplay between distress and low positive mood. Increased distress and low positive mood, in particular, seem to be important factors that may possibly, in the long run, be associated with adverse mental health outcomes in the current health crisis.

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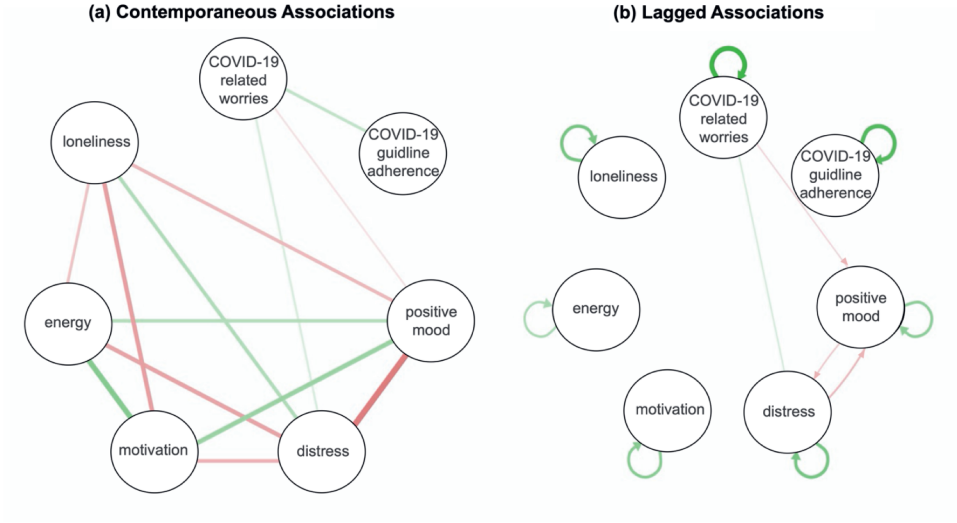
Supplemental Information

Supplemental Table 1

Item	Factor1	Factor2
cheerful	-0.68	-
carefree	-0.37	-0.19
sad*	-0.73	-
relaxed*	0.70	-
annoyed	0.63	-0.18
stressed	0.74	-
anxious	0.70	0.25
calm*	0.54	0.11
lose interest*	-0.71	-
lack motivation*	-0.63	-
well-rested	-0.48	-
low energy*	-0.61	-
lonely	0.63	-
WorryNews	0.36	0.41
EasyThinkOther*	0.53	0.20
FearOutside	0.21	0.55
FearExag*	-	0.52
NotHere*	-	0.20
NoFearFuture*	0.20	-
OthersMoreLikely*	-	0.19
CovIsFlu*	-	0.40
FearContract	0.25	0.61
FearOtherContr	0.25	0.56
CovidAdvice	-0.16	0.57
SocOthers	-	0.64
IgnoreInvites	-	0.66
Leave24	-	0.22

Factor loadings for exploratory factor analysis using all 15 mental well-being items and 14 COVID-19 related items.



Supplemental Figure 1 | Network analyses.
Association networks obtained from the vector-autoregressive model that included age, gender, education, country, and confirmed daily COVID-19 cases as covariates. **Note.** Networks were visualized using procedures described in the main text and *Figure 3*.

CHAPTER 6

The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies

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Brain Research, 2019, 1725, 146476

Abstract

Alzheimer's disease constitutes a growing cause of cognitive impairment in aging population. Given that current treatments do not produce the desired therapeutic effects, the need for finding alternative biological and pharmacological approaches is critical. Accumulating evidence suggests inflammatory and oxidative stress responses as potential causal factors of cognitive impairments in Alzheimer's disease and healthy aging. Curcumin has received increased interest due to its unique molecular structure that targets inflammatory and antioxidant pathways as well as (directly) amyloid aggregation; one of the major hallmarks of Alzheimer's disease. Therefore, this review summarizes preclinical and clinical findings on curcumin as a potential cognitive enhancer in Alzheimer's disease and normal aging. Databases used for literature searches include PubMed, EMBASE and Web of Science; in addition, clinicaltrials.gov was used to search for clinical studies. Overall, animal research has shown very promising results in potentiating cognition, both physiologically and behaviourally. However, human studies are limited and results are less consistent, complicating their interpretation. These inconsistencies may be related to differences in methodology and the included population. Taking into account measurements of important inflammatory and antioxidant biomarkers, optimal dosages of curcumin, food interactions, and duration of treatment would increase our understanding on curcumin's promising effects on cognition. In addition, increasing curcumin's bioavailability could benefit future research.

Keywords: Alzheimer's disease, aging, curcumin (curcuma longa), cognition, preclinical studies, clinical trials

Introduction

Neurodegeneration is a hallmark feature of many age-related devastating diseases. The most frequent neurodegenerative disease is Alzheimer's disease (AD), which accounts for 60-70% of cases with dementia (Duthey, 2013; Erkkinen et al., 2018). The symptoms of AD are characterized by faltering cognitive abilities followed by impaired social and behavioural functioning. The main histopathological features of AD are amyloid-β (Aβ) plaques, caused by changes in proteolytic processing of amyloid precursor protein (APP), and neurofibrillary tangles (NFTs) caused by hyper-phosphorylation of the tau protein (Hardy & Selkoe, 2002). According to World Health Organization's (WHO) report, 35.6 million people worldwide suffer from this disease and as the lifespan of elderly population increases it is estimated that the frequency will be doubled by 2030 and tripled by 2050 (Duthey, 2013). At present, pharmacological treatments to prevent or cure the cognitive decline are lacking. Even though the existing cognitive enhancers approved for AD, such as donepezil and galantamine, may postpone cognitive deterioration, many patients do not respond to the treatment, the beneficial effect is temporal and accompanied by a number of adverse effects (Husain & Mehta, 2011).

The lack of effective pharmacotherapy has led researchers to seek alternative approaches in order to treat or prevent AD and more neurobiological underpinnings are being discovered. Accumulating evidence suggests neuroinflammation, oxidative stress, mitochondrial dysfunction or autophagy as potential etiologies for AD (Amor et al., 2014; Amor et al., 2010; Guo et al., 2018; Kim et al., 2015). For example, it has been reported that in populations with chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), the risk for developing AD is significantly lower (Breitner et al., 1995; Stewart et al, 1997). Although recent studies regarding the effect of NSAIDs on AD have yielded both negative and beneficial results (Zhang et al., 2018; Miguel-Alvarez et al., 2015), one major limitation for the use of NSAIDs is the gastrointestinal toxicity caused by inhibition of cyclooxygenase (Lim et al., 2001). Therefore, the urgency of finding new, safer, (more) effective pharmacological strategies is commonly accepted. Epidemiological studies indicate that natural antioxidant agents, such as polyphenols, fatty-acids or vitamin-rich aliments, may delay the occurrence of neurodegenerative diseases, however, randomized controlled clinical trials are absent to confirm the protective or therapeutic efficacy of such molecules (Bastianetto & Quirion, 2004; Stab et al., 2012).

Curcumin is an active hydrophobic polyphenol extracted from the rhizomes of herb *Curcuma Longa* Linn, also known as turmeric, which belongs to the family of zingiberaceae. Traditionally, curcumin has been used as a remedy for many ailments in India and China (Ghosh et al., 2015). Modern medicine has shown that curcumin exhibits a wide variety of biological and pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, chemoprotective properties, due to its ability to modulate numerous signaling molecules (Gupta et al., 2012; Hewlings & Kalman, 2017). Its anti-inflammatory activity can be attributed to the suppression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) enzymes via down-regulation of nuclear factor kappa B (NF-κB) as well as inhibition of several inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a) or interleukin (IL) -1, -2, -6, -8, and -12 (Jurenka,

2009). Curcumin's ability to scavenge free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), provides its antioxidant capacity (Alisi et al., 2018). Multiple studies in rodents and humans have shown that curcumin crosses the blood brain barrier (BBB) (Dende et al., 2017; Mishra & Palanivelu, 2008; Reddy et al., 2018). However, its main drawback is the low bioavailability due to poor solubility, low absorption, rapid metabolism, and rapid excretion (Gupta et al., 2012). Much effort has been made attempting to overcome this issue and new formulations have been developed, including liposomal encapsulation, nanoparticles, powder form, micellar form, emulsions, co-administration with other substances, or separate administration of its constituents. Curcumin is considered to be a safe compound, thus suitable for daily dietary use as established by the Joint Nations and World Health Organization Expert Committee on Food Additives (JECFA) (JECFA, 1996). Therefore, many curcumin-based products are currently freely available (Jamwal, 2018).

Both the pleiotropic and favorable safety profile of curcumin make it a promising compound for use in complex diseases, such as AD and associated cognitive decline. Novel approaches advocate that these cognitive deficits may be caused by abnormalities in multiple signaling pathways; especially inflammatory and oxidative stress mediated pathways. Thus, multi-target compounds could effectively combat cognitive deficits. Since curcumin interacts with numerous molecules involved in these pathways, it may be a promising compound for treatment / prevention of cognitive decline. Therefore, the aim of this systematic review is to provide an overview of pre-clinical and clinical studies that have examined how curcumin affects cognitive performance in AD and non-pathological aging.

Methods

This systematic review was conducted according to the established PRISMA guidelines (Liberati et al., 2009). A literature search was conducted in PubMed, EMBASE and Web of Science to obtain both preclinical and clinical trials. In addition, ClinicalTrials.gov was searched for human studies. The following keywords were used: ((((((curcuma [MeSH Terms]) OR curcumin [MeSH Terms]) OR curcuma) OR curcumin)) AND (((((((cognitive) OR cognition) OR cognitive disorders [MeSH Terms]) OR "cognition disorders") OR "Alzheimer's disease") OR "aging") OR neurodegenerative diseases [MeSH Terms])). Separate searches were applied for clinical and pre-clinical studies using the respective filters. Retrieved articles were imported to EndNoteX8. All articles were independently screened for, duplicity, eligibility by author SV and checked by author CV.

Inclusion criteria were: I) original research, II) published in English, III) use of any form of curcumin as the main pharmacological challenge or treatment (including cases in which a compound was added in order to increase curcumin's bioavailability), IV) use of validated cognitive tests (either for animals or humans) and V) published before June 2018. Articles were excluded if I) the study did not evaluate AD or aging, II) no cognitive or behavioral tests were used III) curcumin was used as a positive control or as adjunctive therapy IV) only abstract was available V) the article was a review, a case report, an *in-vitro*, *in-silico* or a non-randomized clinical study.

In total the search yielded 819 articles of which 38 met inclusion criteria (*Figure 1*). Six hundred forty-five preclinical articles were retrieved of which 32 were included after full text screening. One hundred seventy-four human studies were identified of which 5 articles were deemed for inclusion after the final screening. In total, 21 preclinical studies evaluating AD and 11 studies examining healthy aging were included. Aging was included since not only is aging the prime risk factor for the development of AD but also the majority of clinical trials has been conducted in a healthy or mildly cognitive impaired geriatric population. Therefore, it was considered essential to include studies examining aging due to their high translational value. Study characteristics are depicted in *Table 1*. Concerning the clinical trials, three of the studies evaluated curcumin on a healthy geriatric population, while the remaining two studies used patients with mild to moderate Alzheimer's disease to test curcumin's efficacy on cognition.

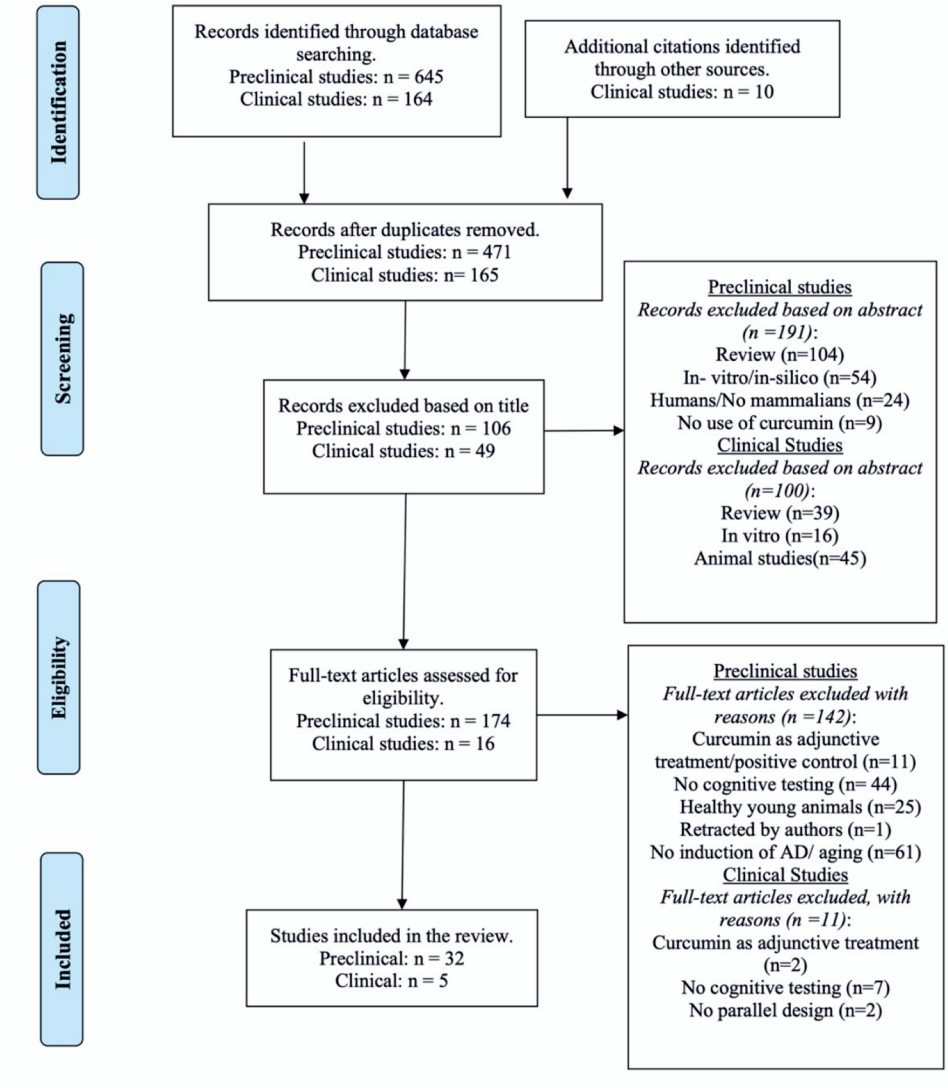

Figure 1 | Flow diagram of the systematic review process.

Results

Preclinical studies

Alzheimer's disease (AD)

AD is characterized by the presence of intraneuronal NFTs and extracellular Aβ plaques, leading to neuronal loss and brain atrophy (Hardy & Selkoe, 2002). Cognitive decline, caused by the accumulation of Aβ plaques and NFTs, is evident in an anterior-posterior manner, from memory and executive functioning to learning deficits. However, the underlying mechanism inducing these protein aggregates remains elusive. Currently, no pharmacological treatment is available to ameliorate the symptoms of the disease. Curcumin binds to Aβ plaques, reducing their

neurotoxicity and initiating their degradation (Lim et al., 2001). Therefore, it is considered a promising therapeutic agent for altering the cognitive symptoms of AD, as evident by the excess of preclinical studies examining its efficacy.

Natural Curcumin

Natural curcumin, the substance obtained without chemical modification, has been studied extensively. Ishrat et al. (2009) explored the effects of natural curcumin (80 mg/kg) on cognitive performance using intracerebroventricular–streptozotocin (ICV–STZ) infused rats. Streptozotocin (STZ) is a diabetogenic substance that inhibits the neuronal insulin receptor and leads to cholinergic deficiency exerting cognitive impairments along with oxidative stress. Therefore, ICV–STZ is used as a model for sporadic dementia of the Alzheimer's type (SDAT). Three weeks of oral curcumin treatment after STZ induction significantly improved spatial learning and memory compared to the vehicle treated group. However, both STZ infused groups showed poorer performance compared to the sham controls. Furthermore, no difference was observed between sham groups receiving curcumin or vehicle, indicating that curcumin is effective in obstructing STZ induced cognitive impairment but does not affect cognition in healthy rodents.

Using a comparable model, Agrawal et al. (2010) evaluated the preventive and the therapeutic effect of 200 mg curcumin on SDAT. Curcumin was administered orally 14 days prior to disease induction or 6 days after its induction. Administration of curcumin enhanced memory performance in Morris Water Maze (MWM) over time in both conditions. Additionally, levels of oxidative stress, acetylcholine and insulin were restored after administration of curcumin.

Similarly, Awasthi et al. (2010) evaluated the preventive role of curcumin at oral doses of 10, 20 and 50mg/kg, starting the same day as the induction of SDAT. To evaluate the therapeutic potential, curcumin was also administered at 25 and 50 mg/kg for 7 days after the induction of the disease. Curcumin prevented memory deficits at dosages of 20 and 50 mg/kg, while administration of 25 and 50mg/kg of curcumin reversed memory impairments in a dose dependent manner with the higher dose exerting more beneficial effect. Furthermore, curcumin restored cerebral blood flow, oxidative stress and acetylcholinesterase activity. Another research group assessed the protective role of curcumin at a dose of 300 mg kg/day, i.p. (Isik et al., 2009). Additionally, the level of insulin-like growth factor-1 (IGF-1), a growth factor that promotes phosphorylation of tau protein was upregulated and neuronal loss was mitigated after treatment with curcumin.

More recently, Samy et al. (2016) studied the role of curcumin as well as erythropoietin in an ICV-STZ rat model. Animals were injected with saline or STZ. The latter group was treated subsequently with vehicle, curcumin (80 mg/kg/day, p.o.), erythropoietin (500 IU/kg every other day, i.p.) or with a combination of curcumin and erythropoietin for three months. Administration of curcumin and/or erythropoietin restored behavioral, histological and biochemical ICV-STZ induced alterations. However, curcumin was considered preferable due to its less severe long-term adverse effects compared to erythropoietin.

Contrary, a study evaluating prolonged administration of oral curcumin at doses of 25, 50 and 100 mg/kg, found no beneficial effect in short-term spatial memory of ICV-STZ infused rats (Bassani et al., 2017). However, an improvement was detected in short term recognition memory. Additionally, even though curcumin did not increase neurogenesis, a reduction of neuroinflammatory biomarkers was observed, which according to authors could possibly contribute to the frequently observed therapeutic effects of curcumin.

The familial form of AD (FAD) was studied by Zhang et al. (2015), who evaluated the protective effect of curcumin at 50, 100, and 200 mg/kg, i.p. on intraventricularly injected $A\beta_{1-42}$ animals. Acute treatment with curcumin did not exert positive results. However, cognitive deficits, shown at the Y-maze and MWM, improved after chronic treatment (7-day administration) with 200 mg/kg curcumin compared to placebo. The results were comparable to the sham group. Similarly**,** Wang et al. (2013) and Yin et al. (2014) tested the effect of curcumin (300 mg/kg, i.p.) on a $A\beta_{1-40}$ AD model and found that curcumin reversed spatial learning and memory impairments concomitantly promoting hippocampal regeneration.

Frautschy et al. (2001) tested whether dietary curcumin has a protective effect on Aβ-induced neurotoxicity when administered for 2 months prior to $A\beta_{1-42}$ and Aβ/HDL injection. A dose of 500 ppm of curcumin reversed spatial memory impairments as compared to the untreated Aβ-infused rats. Additionally, curcumin protected against Aβ deposits to a greater extent than ibuprofen. Another group evaluated curcumin (300 mg/kg, i.p.) on a $A\beta_{1-40}$ model (Wang et al., 2011). Curcumin improved spatial memory to levels comparable to the sham group and suppressed neuronal apoptosis in the hippocampus by balancing the expression of the two apoptotic genes, Bax and Bcl-2.

The effect of different doses of curcumin was explored by Wang et al. (2014)**.** This group utilized an APP/PS1 double transgenic AD model to examine the effect of low (160ppm) and high (1000ppm) dose of curcumin after administration for 6 months in diet. The researchers detected a significant cognitive improvement at both doses compared to the untreated group, while a significant dose-response effect was found throughout time with higher doses of curcumin producing greater cognitive improvement. In addition, data suggest that curcumin reduced Aβ deposits potentially by promoting autophagy.

Formulated Curcumin

Despite the positive effects of curcumin on cognition, its main disadvantages when administered to a human organism are the low bioavailability, the rapid gastrointestinal metabolism and the poor blood brain barrier (BBB) penetration. Therefore, many formulations aiming to improve the bioavailability and stability of curcumin have been developed. One of these formulations includes polymersomes (POs) loaded with curcumin, accompanied by transferrin (Tf) and Tet-1 peptide (Tf/Tet-1-POs) (Jia et al., 2016). POs are artificial vesicles in which the drug is loaded to control permeability and increase stability. In addition, Tf is used to increase BBB permeability via endocytosis and Tet to facilitate the delivery to neurons due to its affinity with the ganglioside GT1B receptor on neurons. In the study by Jia et al. (2016), $A\beta_{1-42}$ AD mice were treated with curcumin

(15mg/kg, i.v.) for 14 consecutive days to test different combinations of the abovementioned constituents. Results illustrated a significant improvement of Aβ-induced spatial and learning memory in mice treated with curcumin-Tf/Tet-1-PO and curcumin-Tf-PO compared with the untreated controls. The fact that animals treated with the empty Tf/Tet-1-PO did not display improvement in their performance suggests that curcumin is the compound contributing to the beneficial outcome.

Another formulation of curcumin was evaluated by Hoppe et al, who tested the differential effects of free curcumin and curcumin-loaded lipid-core nanocapsules (Cur-LNC) for 10 days in an $A\beta_{1-42}$-induced model (Hoppe et al., 2013). The results showed significant improvement in cognitive tests for both formulations of curcumin. Interestingly, a 20-fold lower dose of Cur-LNC (2.5 mg/kg/day, i.p.) demonstrated similar neuroprotective effects as the high dose free curcumin (50 mg/kg/day). Furthermore, downregulated levels of the proinflammatory cytokines TNF-α and IL-1β in the hippocampus were observed only after administration of Cur-NLC, indicating higher bio-distribution of curcumin under nanoparticle formulation.

Tiwari et al. (2013) reported comparable results. Curcumin-loaded biodegradable poly (lactic-*co*-glycolic acid) (PLGA) nanoparticles (Cur-PLGA-NPs) were found to be effective in reversing cognitive impairment and increasing neurogenesis in an AD rat model at a lower dose than uncoated natural curcumin after a three-week treatment. Specifically, after intraperitoneal injections at dosages of 10 and 20 mg/kg of Cur-PLGA-NPs, a 2.1- and 2.8-fold respective increase was reported in brain curcumin levels compared to the same doses of natural curcumin, indicating increased bioavailability of this formulation.

Ahmed et al. (2010) compared the effects of the parent curcuminoid mixture with its three separate constituents, specifically curcumin, bisdemethoxycurcumin and demethoxycurcumin in Aβ-infused rats. All components showed a memory-enhancing effect at 3 mg/kg, i.p., whereas the curcuminoid mixture had no effect on memory at the same dose. At 30mg/kg, i.p. all treated groups showed a significant beneficial effect on memory, but the three separate components showed additional improvement over time, suggesting that the parent curcuminoid mixture might not be as effective as its separate components. On a molecular level, after short term treatment the curcuminoid mixture and the bisdemethoxycurcumin improved post-synaptic density protein (PSD-95) in the hippocampus, a marker of postsynaptic plasticity, with the lower dose (3mg/kg) being more effective. However, after prolonged administration the other two components show similar outcome. Interestingly, after long term treatment a high dose of demethoxycurcumin (30mg/kg) seemed to be more effective in augmenting synaptophysin and calcium/calmodulin dependent protein kinase type IV (camkIV) expression - biomarkers of synaptic plasticity - compared to the other compounds. The authors suggested that these results probably indicate that different compound compositions could result in different beneficial outcomes depending on the model or the type of the disease.

Yanagisawa et al. (2015) utilized the double transgenic APP/PS1 model to compare three forms of dietary curcumin; natural curcumin, FMeC1 and FMeC2. FMeC1 is a derivative of curcumin

substituted at the C-4 position, which previously has shown to bind to Aβ deposits, while leaving Aβ monomers untouched (D. Yanagisawa et al., 2010). FMeC2 is a product of FMeC1 hydrolysis. Improved spatial memory comparable to the sham group, was evident in the group treated with FMeC1; however, no memory improvement was observed in the group treated with free curcumin or FMeC2. Likewise, treatment with FMeC1 reduced the accruement of $A\beta_{40}$ and $A\beta_{42}$, while this trend was not observed after treatment with natural curcumin or FMeC2. Additionally, Okuda et al. (2017) evaluated a new derivative of curcumin, called PE859 (1 and 3 mg/kg/day, i.g.), on a SAMP8/TaSlc mouse strain. No significant differences were displayed on spatial learning and memory. However, PE859 seemed to diminish insoluble $A\beta_{1-40}$ but not $A\beta_{1-42}$ deposits.

Besides Aβ deposits NFT's accumulation is a hallmark of AD. For that reason, Ma et al. (2013) explored the effect of dietary solid lipid nanoparticle *Longvida*® (500ppm) on a Tau mice model with intraventricular injections of tau dimers. Their findings suggest that curcumin supplementation may improve memory and result in a number of biochemical alternations leading to suppressed tau aggregation. To examine abnormal deposition of both Aβ and NFT's, Sundaram et al. (2017) chose to use a p25 transgenic mice model to evaluate the same dietary form of curcumin. Both features of AD were reduced presumably due to suppressed levels neuroinflammatory cytokines MIP-1α, TNF-α and IL-1β. Additionally, *Longvida*® improved spatial and working memory as observed in the 8-arm radial maze.

More recently, McClure and his team (2017) introduced an inhaled formulation of curcumin to increase BBB permeability and tested its efficacy in preventing AD. They have shown that treating young 5XFAD mice with intranasal curcumin prevented memory deficits and Aβ plaque burden in adulthood as compared to the untreated mice. In addition, no side effects or incidents of toxicity were reported in the respiratory and the circulatory system of the animals as expected to due to the nebulized form of curcumin.

Overall, the vast majority of AD animal models indicates that curcumin has both preventive and therapeutic effects on cognition. Beneficial effects are observed not only on molecular but also on behavioral level. Formulated curcumin seems to result in increased bioavailability compared to the natural compound.

Non-pathological ageing

Aging is a physiological process associated with functional, morphological and biochemical alternations in the central and peripheral nervous system. The biological underpinnings of aging remain unclear; however, oxidative stress, inflammation and mitochondrial dysfunction have been suggested to play an important role in age-related cognitive impairments, causing individuals to become vulnerable for developing neurodegenerative diseases (Troen, 2003). Given its potential positive effects on oxidative stress and inflammation, curcumin could be of interest in ameliorating aging-associated cognitive impairments and/or reducing the risk for development of neurodegenerative diseases, such as AD.

Kumar et al. (2011) studied the neuroprotective effects of orally administered curcumin at 15 and 30 mg/kg using galantamine (5mg/kg) -an acetylcholinesterase inhibitor prescribed for the treatment of cognitive decline in AD- as a positive control group in a D-galactose (D-gal) animal model. D-gal is a decreasing sugar that can accelerate senescence and induce cognitive dysfunction to experimental animals in a way that resembles human aging. Groups treated either with curcumin or galantamine performed better on cognitive tasks compared to the untreated D-gal group, even though locomotor activity remained the same in all groups. In addition, both curcumin and galantamine diminished levels of oxidative stress and mitochondrial dysfunction. The results thus indicate that CUR could be an alternative treatment for aging-induced cognitive deficits with a higher dose showing more beneficial results.

Equally, Nam et al. (2014) studied the effects of orally administered curcumin at 300 mg/kg in D-gal induced mice. A beneficial trend of curcumin on learning and spatial memory was observed in D-gal mice treated with curcumin as compared to the vehicle treated D-gal mice. No significant difference was found in cognitive performance between curcumin and vehicle treated healthy animals. Results demonstrated increased neuronal proliferation in the hippocampus after administration of curcumin, as evident by the elevated brain-derived neurotrophic factor (BDNF) protein expression and increased phosphorylation of the transcription factor CREB in the respective brain region.

The same model was applied to compare the synergistic effect of curcumin and piperine versus curcumin and piperine monotherapy when administered orally at doses of 20mg/kg or 40 mg/kg for curcumin and 6mg/kg or 12mg/kg for piperine by the group of Banji et al. (2013). Combined curcumin and piperine showed superiority, in a dose dependent manner, compared to separate administration in ameliorating memory and normalizing oxidative burden, biochemical levels and hippocampal morphology. Moreover, using a similar study design they compared the same compound synergism but this time using higher doses of piperine (Banji et al., 2013). As in the previous study, co-administration of curcumin and piperine ameliorated movement and cognitive deficits caused by D-gal administration, while also reducing oxidative stress in a dose dependent manner. One year later the same group evaluated the effects of combined curcumin and hesperidin (glycoside). Likewise, both separate and co-administration augmented behavioral performance with higher doses of the mixture demonstrating better overall profile in reducing mitochondrial and oxidative damage as well as apoptosis (Banji et al., 2014).

Sun et al. (2013) studied the effects of 20 and 50 mg/kg curcumin when administered intragastrically using senescence-accelerated mouse prone 8 (SAMP8 mice). SAMP8 is a line that closely mimics human's phenotype of senescence; therefore, it was compared with a normal aging SAMR1 strain. They found an improvement in spatial memory at both doses of curcumin compared to the untreated SAMP8 mice as well as enhanced antioxidant capacity and synaptic plasticity. Again, stronger effects were found on the high dose of curcumin (50 mg/kg).

A different approach was followed by Dong et al., who instead of modeling senescence in young animals, evaluated the effect of curcumin in normal aging rats (Dong et al., 2012). Non-spatial and

spatial memory were tested after 6 and 12 weeks of curcumin treatment (480 mg/kg in chow). After 12-weeks curcumin treatment, spatial memory significantly improved in the aged rats, whereas no effect was found after a 6-week administration. A subtle improvement in non-spatial memory was detected in the curcumin group after both treatment durations. Interestingly, increased neurogenesis was observed in the hippocampus of the rats after prolonged administration of curcumin.

Another study found small beneficial effects of curcumin (300mg/kg/day, p.o.) in aged rats (Belviranlı et al., 2013). Performance on learning and spatial memory improved in curcumin treated compared to vehicle treated rats. However, except from a downregulated marker of oxidative stress (malondialdeyde) in the group treated with curcumin the other markers remain unchanged (protein carbonyl and glutathione). Yu et al. also examined the effect of prolonged administration of curcumin on aged rats (Yu et al., 2013). Curcumin ameliorated cognitive deficits induced by aging. The underlying mechanism of curcumin's action could be attributed to the activation of the neuronal nitric oxide synthase/nitric oxide (nNOS/NO) pathway.

In a more recent study, Vidal et al. (2017) similarly examined the effect of oral curcumin on aged rodents. Animals treated with curcumin exhibited better performance on recognition memory as compared to the vehicle treated group. Additionally, curcumin improved dendritic spike density and dendritic length in the hippocampus and the prefrontal cortex, however, with regards to the amygdala the results were not consistent across measurements.

The only study examining non-human primates was the study of Moore et al. (2017). In this study middle aged rhesus monkeys received curcumin or placebo in their diet to assess its effect on age related cognitive deficits. Results revealed amelioration of spatial memory in the curcumin treated animals, however, no improvement was observed concerning the visual recognition memory. According to the authors, this deviation could probably be explained by the fact that in middle aged monkeys recognition memory has not begun to decline yet, whereas spatial memory is typically deteriorated at this age-range.

In general, results indicate that curcumin may benefit age-related cognitive impairments. Higher doses of curcumin seem to be more effective compared to the lower doses regardless the route of administration and co-administration with piperine seems to enhance further curcumin's effect.

Table 1 | Summary of the included pre-clinical studies.

Study	*Duration of treatment*	*Study design, Dose & Route of administration*	*Species (N)*	*Cognitive Measurements*	*Primary Objective*	*Main results*
Alzheimer's disease						
Ishrat et al. (2009)	3 weeks	(1) $Sham_1$: operation+ vehicle; (2) $sham_2$: operation+ CUR (80 mg/kg, p.o.); (3) STZ +vehicle, p.o.; (4) STZ +CUR (80 mg/kg, p.o.)	Male Wistar rats (N= 40; n=10/group)	MWM, PA	The effect of curcumin on cognitive impairments and oxidative damage in ICV-STZ infused rats.	CUR counteracted ICV-STZ-induced alterations in cognitive and behavioral parameters and in markers of oxidative stress.
Agrawal et al. (2010)	1-14 days (pre-treatment) 14-20 days (post-treatment)	(1) Untreated group; (2) swimming control (no training); (3) vehicle treated group, p.o.; (4) Sham group; (5) STZ group; (6) pre-treated CUR (200mg, p.o.) + STZ; (7) post-treated CUR 200mg, p.o. + STZ	Adult male Sprague–Dawley rats (N=35; n= 5 per group)	MWM	The effect of curcumin on memory and insulin receptors in the brain.	Curcumin improved memory and restored insulin, cholinergic and oxidative stress markers.
Awasthi et al. (2010)	1-21 days (pre-treatment) 19-25 (post-treatment_	Pre-treatment: (1) Control group; (2) Sham group; (3) STZ group; (4) STZ+ 10mg/kg CUR; (5) STZ+ 20mg/kg CUR; (6) 50mg/kg CUR, p.o. post-treatment (1) STZ+ vehicle; (2) STZ+ 25 mg/kg CUR; (3) STZ+50 mg/kg CUR, p.o.	Adult male Swiss albino mice (n = 6-8 per group)	MWM, PA	The preventive and therapeutic effect of curcumin on memory, cerebral blood flow, oxidative stress, and cholinergic levels.	Curcumin prevented and reversed spatial memory deficits in a dose dependent manner. Additionally, it improved cerebral blood flow, oxidative and cholinergic levels in the brain.
Isik et al. (2009)	10 days	(1) Sham group; (2) STZ+ vehicle (0.5 ml, i.p.); (3) STZ+ CUR (300 mg/kg daily in vehicle, i.p.)	Male Wistar rats (N = 24; n_1 = 8, n_2= 7, n_3= 8)	PA, MWM	The neuroprotective effect of CUR compared to ICV-STZ induced cognitive impairments.	Curcumin significantly improved behavioral and histological alterations resulting from ICV-STZ induction. Additionally, IGF-1 levels were elevated after administration of curcumin.
Samy et al. (2016)	3 months	(1) Sham group; (2) ICV-STZ +vehicle; (3) ICV-STZ + curcumin (80 mg/kg/day,	Male Wistar rats (N=40; n= 8/group)	MWM, PA	The comparison of combined CUR and erythropoietin treatment against	Both combined and monotherapy reversed cognitive, biochemical, and

		p.o.); (4) ICV-STZ+ erythropoietin (500 IU/kg q.o.d, i.p.); (5) ICV-STZ + curcumin (80 mg/kg/day, p.o.) & erythropoietin erythropoietin (500 IU/kg q.o.d, i.p.)			monotherapy in cognition.	histological changes. However, curcumin demonstrated a better safety profile.
Bassani et al. (2017)	30 days	(1) Sham group; (2) STZ infused group; (3) STZ+ CUR (25mg/kg, p.o).; (4) STZ+ CUR (50mg/kg, p.o.); (5) STZ+ CUR (100 mg/kg, p.o.)	Male Wistar rats (N=35; n_1=7, n_2= 7, n_3=6, n_4=8, n_5=7)	OFT, OLT, ORT, EPM, Y-Maze	To examine the possibility that chronic administration of CUR may favor cognition of STZ induced rats and increase neuronal proliferation.	At high dosages curcumin might be able to prevent short term recognition but not spatial memory. No signs of neurogenesis were evident, but reduced neuroinflammation was observed.
Zhang et al. (2015)	7 days	(1) Sham group; (2) Aβ1-42 + saline; (3) Aβ1-42+ 50, (4) 100, and (5) 200 mg/kg, i.p. of curcumin respectively	Male Sprague Dawley rats (N=40; n=8 in each group)	Y-Maze, OFT, MWM	The modulating impact of curcumin on cognitive deficits after ventricular injection of amyloid-β1-42 (Aβ1-42).	Chronic CUR supplementation attenuated Aβ1-42 induced cognitive impairments and increased BDNF levels in the hippocampus.
Wang et al. (2013)	7 days	(1) Sham group; (2) $Aβ_{1–40}$ (10 μl) + vehicle (300 mg, i.p.); (3) $Aβ_{1–40}$ + CUR (300 mg, i.p.)	Male Sprague-Dawley rats (N= 48; n= 16/group)	MWM	To examine the protective effect of CUR on $Aβ_{1–40}$-induced cognitive deficits and explore whether CUR acts on collapsing response mediator protein-2 (CRMP-2).	Treatment with CUR significantly ameliorated cognitive impairments and moderated phosphorylation of CRMP-2 leading to hippocampal regeneration.
Yin et al. (2014)	7 days	(1) Sham group; (2) $Aβ_{1–40}$ + vehicle (300 mg/kg, i.p.); (3) $Aβ_{1–40}$ + CUR (300 mg/kg, i.p.)	Male Sprague-Dawley rats (N= 48; n= 16/group)	MWM	To explore the underlying mechanisms of curcumin for the treatment of AD.	CUR significantly improved spatial memory performance. CUR's mechanism of action could be related with suppressing hippocampal Nogo receptor expression and subsequently increasing axonal regeneration.

Frautsch y et al. (2001)	2 months	(1) Control group, vehicle; (2) Aβ infused+vehicle (chow); (3) Aβ infused+ CUR (500 ppm, chow)	Female Sprague-Dawley rats (N=30; n=10/ group)	MWM	Protective activity of dietary curcumin against Aβ-induced neurotoxicity and cognitive deficits.	CUR prevented memory deficits and attenuated Aβ deposits as well as post-synaptic density (PSD)-95 loss.
Wang et al. (2011)	7days	(1) Sham group +saline; (2)$A\beta_{1-40}$ + saline; (3) $A\beta_{1-40}$ + CUR (300mg/kg/day, i.p.)	Male Sprague-Dawley rats (N=48; n= 16/group)	MWM	The effect of CUR on AD related cognitive deficits and cell apoptosis.	CUR significantly improved cognitive impairments and protected against neuronal apoptosis.
Wang et al. (2014)	6 months	(1) APP/PS1 control group; (2) APP/PS1+CUR (160 ppm); (3) APP/PS1+CUR (1000 ppm) in diet, chow	Male mice (N=33; n=11/group)	MWM	To evaluate whether CUR can induce autophagy and attenuate cognitive impairments induced in APP/PS1 double transgenic mice model.	CUR improved memory in a dose depended manner and induce autophagy.
Jia et al. (2016)	14 days	(1) CUR solution; (2) CUR-Pos; (3) CUR-Tf/-Pos (15mg, i.v.); (4) CUR-Tet-1-Pos (15mg, i.v.); (5) CUR-Tf/Tet-1-Pos (15mg, i.v.); (6) $A\beta1_{-42}$ induced control group + saline i.v.; (7) sham control group	Male C57BL/6 mice (n=8 per group)	MWM	The effect of different formulations of CUR on cognition in Aβ1-42 induced mice.	CUR-Tf/Tet-1-Pos and CUR-Tf-PO formulations demonstrated significant improvement after Aβ-induced memory and cognitive impairment. *In vivo* and *in vitro* results supported better bioavailability of Tf/Tet-1-Pos formulation.
Hoppe et al. (2013)	10 days	(1) Sham group; (2) sham +free CUR; (3) sham + CUR-loaded lipid-core nanocapsules (Cur-LNC group); (4) $A\beta_{1-42}$ infused group; (5) $A\beta_{1-42}$ infused+ vehicle (6) $A\beta_{1-42}$ infused + blank lipid-core nanocapsules (B-LNC group), (7) i.c.v. infused + free CUR; (8) Cur-LNC group) →50 mg/kg/day CUR and	Male Wistar rats (n=10-16/ group)	Y-Maze, NORT	To compare efficacy and bioavailability of free CUR versus Cur-LNC and identify potential mechanisms underlying curcumin's protection against $A\beta_{(1-42)}$ induced cognitive impairment.	Administration of curcumin in both formulations prevented behavioral impairments, neuroinflammation and cell synaptic malfunctions triggered by Aβ induction. Nanoencapsuled curcumin demonstrated higher potency compared to free CUR.

		2.5 mg/kg/day Cur-LNC, i.p.				
Tiwari et al. (2013)	3 weeks	(1) Sham group; (2) Aβ untreated (2) Aβ+ empty PLGA-NP-; (3), (4) Aβ+bulk Curcumin-Treated Group (0.5 and 20mg/kg, i.p.) mg/kg); (5), (6) CUR-PLGA-NPs-Treated Group (0.5 and 20 mg/kg, i.p.)	Male Wistar rats (n=6/ group)	PA	Comparison between bulk CUR and CUR nanoparticles in hippocampal neurogenesis and cognition.	CUR-loaded nanoparticles at both doses and high doses of bulk curcumin ameliorate cognitive impairments and potentially increases neurogenesis in an Aβ rat model.
Ahmed et al. (2010)	5 days →short term & 20 days→ long term	(1) Control group; (2) Ab induced group; (3), (4) curcuminoids 3 mg/kg and 30 mg/kg, i.p.; (5), (6) curcumin, 3 mg/kg and 30mg/kg, i.p.; (7), (8) bisdemethoxycurcumin 3 mg/kg and 30 mg/kg, i.p; (9), (10) desmethoxycurcumin 3 mg/kg and 30 mg/kg, i.p.	Male, Sprague–Dawley rats (n=8/group)	MWM	The effects of curcuminoid mixture and its individual constituents on spatial learning and memory in an amyloid-beta (Aβ) peptide-infused rat model of AD.	Individual curcuminoid components demonstrate more effective profile than the parent mixture on memory performance.
Ma et al. (2013)	4 months	(1) Wild-type animals; (2) Control hTau mice; (3) hTau + CUR -Longvida (500 ppm in chow)	Male & female C57Bl/6J mice (N=24; n_1=9, n_2= 7, n_3=8)	MWM, Y-Maze, NORT	The effect of dietary curcumin on NFTs accumulation and memory.	CUR supplementation enhanced cognitive performance in mice and reduced soluble tau aggregates.
Sundaram et al. (2017)	12 weeks	(1) WT normally fed; (2) WT Longvida 4g/kg (0.8g CUR/kg) in chow; (3) p25Tg normally fed; (4) p25Tg CUR Longvida 4g/kg (0.8g CUR/kg) in chow	Male & female C57BL/6 mice (N=22; n_1=5, n_2=6, n_3=5, n_4=6)	8-arm radial maze	To investigate fundamental and behavioral effects of Longvida® on AD mice model.	Dietary Longvida improved cognitive functions and mitigated neuroinflammation as well as features of AD.
Daijiro Yanagisawa et al. (2015)	6 months	(1) WT group; (2) Control group, APPswe/PS1dE9; (3) APPswe/ PS1dE9+free CUR; (4) APPswe/PS1dE9 + FmeC1; (5)	Male & female C57BL/6 mice (N=48; n_1=12, n_2=12, n_3=6, n_4=12, n_5= 6)	MWM, Y-Maze	To compare free CUR, FmeC1 and FmeC2 for the treatment of AD.	FmeC1 showed superior efficacy in reducing cognitive deficits and Aβ aggregates compared to the

		APPswe/PS1dE9 + FmeC2 → 500ppm in chow				other two formulations.
Okuda et al. (2017)	9 weeks	(1) SAMP8/TaSlc + vehicle; (2) SAMP8/TaSlc + PE859 (1mg/kg/day, i.g.); (3) SAMP8/TaSlc + PE859 (3mg/kg/day, i.g.)	Male SAMP8/TaSlc mice (N=25; n_1=9, n_2=n_3=8)	MWM, Y-Maze, Rotarod, Grip strength	To examine the efficacy of a new CUR derivative, named PE859 on an AD model.	Even though no significant differences were observed in behavioral testing, PE859 reduced Aβ1-40 aggregates.
McClure et al. (2017)	18 Weeks	(1) WT group; (2) 5XFAD, control; (3) 5XFAD + 5mg/kg CUR, i.n.	Male & female C57BL/6 mice (N=30; n= 10/group)	Y-maze	To evaluate intranasal formulation of CUR for the prevention of AD.	Nebulized CUR prevented memory deficits and reduced formation of Aβ plaques.
Ageing						
Kumar et al. (2011)	6 weeks	(1) Vehicle control group; (2) D-gal (100 mg/kg, s.c.); (3) Galantamine (5 mg/kg, p.o.) +d-gal (100mg/kg); (4) CUR (15 mg/kg, p.o.) +d-gal (100 mg/kg); (5) CUR (30 mg/kg, p.o.) +d-gal (100 mg/kg, s.c.); (6) CUR alone (30mg/kg, p.o.)	Male Laca mice (n=12 per group)	MWM, EPM	To explore the possible protective role of curcumin against D-galactose-induced cognitive dysfunction, oxidative damage, and mitochondrial dysfunction in ageing mice.	All treatment groups showed improvement in cognitive and neurobiochemical markers. Locomotor ability remained unchanged.
Nam et al. (2014)	10 weeks	(1) Control group + vehicle; (2) D-gal (100 mg/kg, s.c.); (3) CUR (300 mg/kg, p.o.) (4) D-gal (100 mg/kg, s.c.) + CUR (300 mg/kg, p.o.)	Male C57BL/6 mice (n=10 per group)	MWM	The effects of CUR on learning and spatial memory in healthy and D-galactose-induced aged mice.	Curcumin protected against memory impairment induced by D-gal and increased neurogenesis in the hippocampus.
D. Banji et al. (2013)	49 days	(1) Young rats + vehicle, p.o.; (2) Aged rats +vehicle, p.o.; (3) Young rats + D-gal (60mg/kg, i.p.); (4) Young rats + D-gal+ CUR (20mg/kg, p.o.); (5) Young rats + D-gal+ piperine (6mg/kg, p.o.); (6) Young rats + D-gal + CUR (20mg/kg, p.o.) + piperine (6mg/kg, p.o.); (7) Young rats + D-gal + CUR (40mg/kg, p.o.) +	Male Wistar rats (N= 36; n=6 per group)	MWM	To compare effects of single and combined administration of CUR and piperine on aging.	Superior effect of combined compared to separate administration of CUR and piperine in cognitive and neurobiochemical changes related to aging.

		piperine (12mg/kg, p.o.)				
Banji et al. (2013)	56 days	(1) Young rats + vehicle, p.o.; (2) Aged rats +vehicle, p.o.; (3) Young rats + D-gal (150mg/kg, s.c.); (4) Young rats + D-gal+ CUR (40mg/kg, p.o.); (5) Young rats + D-gal+ piperine (7.5 mg/kg, p.o.); (6) Young rats + D-gal + CUR (20mg/kg, p.o.) + piperine (7.5 mg/kg, p.o.); (7) Young rats + D-gal + CUR (40mg/kg, p.o.) + piperine (15mg/kg, p.o.)	Male Wistar rats (N= 36; n=6 per group)	EPM, Rotarod	To delineate the synergistic effect of curcumin and piperine in treating aging symptoms and to compare it with monotherapy.	Co-administration of CUR and piperine improved cognitive and motor D-gal induced impairment and reduced oxidative stress.
Banji et al. (2014)	63 days	(1) Control group + vehicle; (2) D-gal (150mg/kg, s.c.) + vehicle; (3) D-gal+ CUR (50 mg/kg, p.o.); (4) D-gal +hesperidin (10 mg/kg, p.o.); (5) D-gal + CUR (50 mg/kg, p.o.) + hesperidin (10 mg/kg, p.o.); (6) D-gal+ CUR (100 mg/kg, p.o.) + hesperidin (25 mg/kg, p.o.)	Wistar rats (Not mentioned)	MWM	To delineate the combination of CUR and hesperidin as compared to their individual administration for the treatment of D-gal induced cognitive impairments.	The mixture of CUR and hesperidin as well as individual administration minimized the behavioral impairments. The higher doses of the mixture reversed apoptosis, mitochondrial and oxidative damage.
Sun et al. (2013)	25 Days	(1) SAMR1 mice, as control (normal aging); (2) SAMP8 mice; (3) SAMP8 + CUR (20 mg/kg, i.g.); (4) SAMP8 + CUR (50 mg/kg, i.g.)	Male SAMP8 and SAMR1 mice (n=22/group)	MWM	The effect of CUR on learning and memory in aging and its possible mechanisms.	Both dosages of CUR significantly improved cognition, normalized oxidative damage and enhanced synaptic plasticity. The higher dose displayed stronger effects.
Dong et al. (2012)	6 &12 weeks	(1) Control group; (2) CUR (480 mg/kg, in chow) → six weeks; (3) CUR (480 mg/kg, in chow) → twelve weeks	Male Sprague-Dawley rats (N=45; n=15/group)	OFT, Rotarod, social recognition test, MWM	To assess behavioral performance and hippocampal cell proliferation in aged rats after 6- and 12-week curcumin-fortified diets.	Non spatial memory improved at both durations, whereas spatial memory was improved after long-term treatment but not after short-term.

						Increased neurogenesis after 12-week treatment.
Belviranlı et al. (2013)	12 days	(1) Aged control group + vehicle; (2) Aged Cur group (300mg/kg/day, p.o.)	Female Wistar rats (N=20; n=10/group)	MWM	The effect of CUR on cognitive impairments and oxidative stress induced by age.	Administration of CUR significantly improved spatial learning and memory, whereas some markers of oxidative stress were decreased.
Yu et al. (2013)	21 days	(1) Young control group + vehicle; (2) Aged control group + vehicle; (3) Aged CUR group (50mg/kg, i.p.); (4) Aged CUR (50mg/kg, i.p.) + 7-NI (150 mg/kg, i.p.); (5) Aged 7-NI (150 mg/kg, i.p.)	Male Kunming mice (N= 48; n=12/group)	NORT, PA	To investigate the effect of CUR on cognitive decline caused by aging and to explore its mechanism of action.	CUR alleviated memory impairment in aged mice.
Vidal et al. (2017)	60 days	(1) Aged control group + vehicle; (2) Aged CUR treated group (100mg/kg/day, p.o.)	Male Sprague-Dawley rats (N=20; n=20 per group)	NORT	To investigate the effects of curcumin treatment in aged rats and its relationship with neurogenesis.	CUR improved memory and elevated dendritic spine density and length in certain brain regions.
Moore et al. (2017)	8 months	(1) Middle aged control group +vehicle; (2) Middle aged CUR treated group (500 mg in diet)	Male & female rhesus monkeys, *Macaca mulatta*, (N=17; n_1=9, n_2=8)	DNMS, DRST	The effect of CUR on aging related memory deficits.	CUR improved spatial but not recognition memory in middle aged monkeys.

CUR =curcumin, i.p.=intraperitoneal, p.o.=per os (orally), i.g.=intragastrical, s.c.=subcutaneous injection, i.v.=intravenous, i.n.=intranasal, ICV=intracerebroventricular, WT=wild type, MWM=Morris Water Maze, PA=passive avoidance task, OFT=open field test, OLT=Object location test, ORT=object recognition test, NORT=Novel Object Recognition task, EPM=elevated plus maze, DNMS=delayed non-matching to sample task, DRST=delayed recognition span task, SAMP8=senescence-accelerated mouse prone 8, SAMR1=senescence-accelerated-resistant, q.o.d=every alternate day, KI=knock-in, 3NP=3-nitropropionic acid, C-SLN=curcumin solid lipid nanoparticle

Clinical Trials

With regards to human data, a few randomized clinical trials (RCTs) have been conducted measuring cognitive functioning after curcuminoid administration. The majority of these trials included an elderly population, with or without AD. In total five articles met the inclusion criteria. Study specifics are displayed in *Table 2.*

Rainey-Smith et al. (Rainey-Smith et al., 2016) conducted a randomized study in which participants between 40 and 90 years old without cognitive impairment were tested on a battery of clinical and cognitive testing after 12 months of 1500mg *Biocurcumax*^{TM} or placebo administration. The results showed cognitive decline after 6 months in the placebo group on the Montreal cognitive assessment, that is used to assess general cognitive functioning; however, cognitive performance in the curcumin group remained stable. This difference on Montreal cognitive assessment was not observed after the 12-month follow-up. Other cognitive and clinical measures revealed no differences between groups across time. The authors concluded that curcumin does not enhance cognition, but rather attenuates its decline over time. It must be noted that out of 160 participants that underwent baseline assessment, 23 subjects, two of which belonged in the placebo group, were excluded from the analysis due to reported gastrointestinal complains, suggesting that the high dose of *Biocurcumax*^{TM} used in the study has probably impacted tolerability of the compound.

A comparable population was assessed by Cox et al. (2015). Sixty healthy adults, between 65 and 80 years of age, were tested using an acute (1 and 3 hours after a single dose), chronic (four weeks) and acute-on-chronic (1 and 3 hours after single dose following 4-week treatment) administration of 400mg dose of *Longvida*® Optimized Curcumin. This compound is a solid lipid formulation that contains approximately 80mg of curcumin. One-hour post-dose, curcumin administration had a beneficial effect on working memory and sustained attention measurements. A similar pattern was observed after chronic administration; however, no significant results were found 3 hours' post-acute administration. Moreover, mood was improved; increased calmness and a reduction in fatigue were observed in the chronic curcumin group.

Examining the effect of curcumin on cognition, Baum et al. (2008) conducted a pilot trial in a Chinese adult population, over 50 years of age with progressive cognitive impairment (probable or possible AD). Curcumin was administered at 1 or 4 g either in capsules or as powder for 6 months and was compared to placebo. No differences in Mini-Mental state examination (MMSE) scores were detected throughout time or among treatments. Additionally, there was no significant difference in serum $A\beta_{1\text{-}40}$ levels among treatments, however $A\beta_{1\text{-}40}$ levels tended to increase on curcumin, indicating reduced Aβ aggregation in the brain after treatment with curcumin. Additionally, curcumin increased vitamin E, reflecting a potential antioxidant activity. Interestingly, capsules exhibited better bioavailability compared to the powder formulation, whereas no differences in curcumin's metabolites was observed between 1 and 4 g. Furthermore, no severe side effects were reported after curcumin's administration.

Ringman et al. (2012) evaluated the efficacy of a different curcumin formulation; the Curcumin 3 Complex®, which is the parent curcuminoid mixture comprising the three different constituents (curcumin, bisdemethoxycurcumin and demethoxycurcumin). The compound was administered for 24 weeks in a population with mild to moderate AD. Participants were randomized into 3 groups (placebo, 2g/day and 4g/day curcumin). The experiment extended for 24 weeks, during which the placebo group was randomly divided into the 2 or 4g/day groups. No evidence of Curcumin C3 Complex® efficacy at cognition or at Aβ and tau levels in plasma and CSF were found, while low

bioavailability in plasma was reported. Moreover, three participants of the curcumin group dropped out due to gastrointestinal complains.

More recently, Small et al. (2018) evaluated the effect of Theracurmin®, a compound that contains 90 mg of curcumin. Forty non-demented adults between 51 and 84 years of age were randomized to either Theracurmin® or placebo twice a day for 18 months. Visual and verbal, short-term memory as well as attention improved in the Theracurmin® group in comparison to the placebo group. Additionally, data derived from FDDNP-PET scans indicate reduction in amyloid and tau accumulation in the amygdala and stable levels in the hypothalamus of the curcumin treated group compared to respective elevated levels in the placebo group.

Results of human studies are mixed with regards to curcumin's use on cognitive impairments. Besides *Biocurcumax™* that was administered in a high dose, the other compounds have demonstrated a safe profile. Due to the limited number of published RCTs, the findings remain inconclusive.

Table 2 | Summary of the included human studies.

Study	*Study Design*	*Drug & Dose*	*Duration*	*Disorder Age (N)*	*Cognitive Measure-ments*	*Primary Objective*	*Main results*	*AE*
Rainey-Smith et al. (2016)	R, DB, PC, PG	(1) Placebo (2) 1500 mg/day Biocurcu maxTM	12 months	Healthy elderly 40-90 y (N=96; n1= 57, n2= 39)	(1) RAVLT (2) COWAT; (3) WAIS-R; (4) Computeriz ed CogState battery; (5) MoCA	Ability of curcumin to prevent cognitive decline	Cognitive decline after 6 months in placebo but not in curcumin. Effect on mood	23 gastrointesti nal complains (2 on placebo)
Cox et al. (2015)	R, DB, PC, PG	(1) Placebo; (2) 400 mg Longvida ® (assess ment: 1 and 3h and 4-week treatmen t)	4 weeks	Healthy elderly 60-85 y (N= 60; n_1= 30, n_2= 30)	(1) COMPASS; (2) DASS21; (3) CFS; (4) BL-VAS; (5) STAI	Effect of acute and chronic administrat ion of curcumin on cognition, mood and biochemic al. measures	Single-dose improved performance on working memory and sustained attention. Four-week treatment improved WM and reduced fatigue. Downregulat ion in total and LDL cholesterol.	NO
Baum et al. (2008)	R, DB, PC, PG	(1) Placebo; (2) CUR (1g); (3) CUR (4g) → CUR was given	6 months	Cognitive decline/ possible AD >50 (N=27; n_1= 8, n_2= 8, n_3= 11)	MMSE	Safety, biochemic al and cognitive changes in AD	No differences on cognitive decline were observed. Similar bioavailabilit y between 1 and 4g CUR,	4 gastrointesti nal (2 on placebo, 2 on 1 g, 1 on 4 g), 3 respiratory tract infections (2

		either as powder or in capsules					but better bioavailability when CUR administered in capsules	on placebo, 1 on 1 g), 3 dizziness (1 on placebo, 1 on 1 g, 1 on 4 g), 2 delusions (1 on 1 g, 1 on 4 g), 2 edema (1 on placebo, 1 on 1 g), 1 hearing impairment (on placebo)
Ringman et al., (2012)	R, DB, PC, PG (Open label extension)	(1) Placebo; (2) Curcumin C3 Complex® (2g/day); (3) Curcumin C3 Complex® (4g/day)	24 weeks (48 weeks-open label extension)	Mild-to-moderate AD >49 (N= 30; n_1= 10, n_2= 10, n_3= 10)	(1) (ADAS-Cog); (2) NPI; (3) ADCS-ADL	Safety and tolerability of Curcumin C3 Complex®. Efficacy in cognition	Non-significant change on MMSE results after Curcumin C3 Complex® administration. Low bioavailability of the compound and no alternations of AD biomarkers	Three gastrointestinal symptoms
Small et al., (2018)	R, DB, PC, PG	(1) Placebo; (2) Theracurmin® (90 mg CUR) orally, b.i.d.	18 months	Non-demented 51-84 y (N= 40; n_1= 19, n_2= 21)	(1) SRT; (2) BVMT-R; (3) Trail Making Test	The effect of curcumin on memory performance and on deposition of amyloid plaques and tau tangles	Theracurmin® improved memory and attention performance and prevented neuropathological deposition in amygdala and hypothalamus	Gastrointestinal complain (4 in the curcumin and 2 in the placebo group)

R=randomized, DB=double blind, PC=placebo control, PG=parallel groups, WM=working memory, RAVLT=Rey Auditory Verbal Learning Test, COWAT=Controlled Oral Word Association Test, WAIS-R=Wechsler Digit Symbol Scale from the Wechsler Adult Intelligence Scale revised, MoCA=Montreal cognitive assessment, COMPASS=Computerized Mental Performance Assessment System, DASS21=21-item version of the Depression, Anxiety and Stress Scales, CSF=Chalder Fatigue Scale, BL- VAS=Bond-Lader Visual Analogue Scales, STAI=State-Trait Anxiety Inventory, MMSE=Mini- Mental State Examination, ADAS- Cog=Alzheimer's Disease Assessment Scale - Cognitive Subscale, NPI=Neuropsychiatric Inventory, ADCS-ADL=Alzheimer's Disease Cooperative Study - Activities of Daily Living, NPI-Q=Neuropsychiatric inventory-brief questionnaire, b.i.d=bis in die, SRT=Buschke Selective Reminding Test, BVMT-R= Brief Visual Memory Test-Revised.

Discussion

Curcumin's diverse array of molecular targets, that offers anti-inflammatory and antioxidant properties, have made it an interesting compound for the enhancement of cognitive function. Therefore, the aim of the current review was to provide an overview of both preclinical and clinical studies examining the effectiveness of curcumin for cognitive enhancement both in Alzheimer's disease and healthy aging.

Summary of findings

Pre-clinical studies

Preclinical models have predominately demonstrated a positive effect of curcumin on cognitive functioning. Common practice in animal research is the inclusion of two control groups; a sham group that undergoes the same operational procedures as the experimental group without the induction of cognitive and biochemical alternations, and/or a control group with induced cognitive impairments treated with vehicle. Some preclinical studies have reported improvement of the curcumin treated group in cognitive testing comparable to the sham group, suggesting complete recovery of cognitive functions (Wang et al., 2011; Yanagisawa et al., 2015; Zhang et al., 2015). However, the majority of studies have reported superiority of curcumin compared to the control group. Interestingly, in healthy or sham animal groups treated with curcumin cognitive performance was not altered (Ishrat et al., 2009; Nam et al., 2014). This suggests that curcumin is able to reverse or prevent disease induced cognitive decline rather than enhance further 'normal' cognitive functioning. This is probably related to the ability of curcumin to act directly on Aβ plaques as well as to its anti-inflammatory and antioxidant properties.

Indeed, a number of preclinical studies have reported downregulation of biomarkers of inflammation (e.g. TNF-α, IL-1β) and oxidative stress (e.g. lipid peroxidation, ROS, nitrite and glutathione) believed to be involved in cognitive impairments, confirming the anti-inflammatory and antioxidant properties of curcumin (Agrawal et al., 2010; Banji, Banji, Dasaroju, & Annamalai, 2013; Banji, Banji, Dasaroju, & Kumar Ch, 2013; Banji et al., 2014; Bassani et al., 2017; Hoppe et al., 2013; Ishrat et al., 2009; Kumar et al., 2011; Sandhir et al., 2014; Singh & Kumar, 2017; Sundaram et al., 2017). Increased neurogenesis observed after treatment with curcumin or initiation of autophagy suggest other possible actions of this compound in potentiating cognition (Dong et al., 2012; Nam et al., 2014; Tiwari et al., 2013; Wang et al., 2014; Wang et al., 2013). These outcomes highlight the wide array of molecular mechanisms of curcumin compared to the existing mechanistic target of cognitive enhancers.

Clinical studies

Contrary to animal studies, only a limited number of clinical studies has examined curcumin's effect on human cognitive functioning. The results of these studies are inconsistent; some studies report no cognitive enhancing effects of curcumin (Baum et al., 2008; Ringman et al., 2012) whereas other studies suggest a beneficial effect of curcumin on cognition (Cox et al., 2015; Rainey-Smith et al., 2016; Small et al., 2018). Similar to animal research some studies suggest protective mechanisms of curcumin against cognitive decline (Baum et al., 2008; Small et al., 2018). Findings

concerning Aβ reduction are ambiguous, since most of the peripheral measurements, such as plasma, serum and CSF levels have not detected significant changes in Aβ or tau levels between curcumin and placebo (Baum et al., 2008; Ringman et al., 2012); however, neuroimaging supports that curcumin reduces Aβ deposits in the brain (Small et al., 2018). Unfortunately, only one study has reported measurements on oxidative stress biomarkers (Baum et al., 2008), while none of the studies have reported measurements on inflammatory biomarkers, although these are the main targets of curcumin and have shown great improvement in animal research.

Translational and Methodological Limitations

Results of animal and human studies are not completely aligned. In animal research, curcumin predominantly yields promising outcomes for the treatment of cognitive functions in AD and aging, which is not observed in all human trials and is possibly related to the different types of memory studied in animals and humans. Preclinical research has mainly evaluated spatial working memory and learning. Nevertheless, in patients suffering from AD episodic and working memory are the first to be affected at the onset of the disease (Gold & Budson, 2008; Jahn, 2013). Perhaps the use of tests measuring episodic memory along with the standard measurements of spatial working memory could increase the translational value of the animal studies; however the reliability of those tests is still debatable (Griffiths & Clayton, 2001; Roberts, 2006). In addition, this difference in types of impaired memory between humans and animals poses the question of whether underlying biological differences might lead to impairment of different aspects of memory across species.

It is known that none of the animal models authentically reproduces the full constellation of symptoms observed in human pathology (Jackson-Lewis et al., 2012; LaFerla & Green). In both cases, a wide variety of models has been utilized to reproduce the separate disease-like symptoms. However, different models affect different aspects of disease-related mechanism and pathology. For instance, in AD some animal models do not develop NFTs, some models develop Aβ-40 while others Aβ-42 accumulation. The same applies to non-pathological aging. In addition, even though the existing animal models are valuable for revealing key inflammatory or oxidative biomarkers involved in downstream pathologies of both conditions, none of these models reproduces the exact inflammatory or oxidative response due to differences in the nature of inflammation / oxidative stress between humans and rodents (LaFerla & Green).

An important issue, that could contribute to the difference in results between animals and human studies, is the heterogeneous methodology used in preclinical and clinical studies. For example, in preclinical studies different formulations of curcumin in different strains were used as well as different doses in different routes of administration e.g. orally, intraperitoneal, intravenously, etc. In addition, the use of different behavioral tests that evaluated different aspects of memory and learning affects generalizability of results, especially considering that in some cases distinction between motor and cognitive components may be difficult (Sterniczuk et al., 2010). All these factors complicate a reliable transition from preclinical to clinical studies.

Furthermore, similar to animal studies, different formulations and different doses of curcumin were used in human studies. Also, different tests were used to assess cognitive performance. The

majority of studies included a relatively small number of participants resulting in limited power (Baum et al., 2008; Ringman et al., 2012; Small et al., 2018). Additionally, the differences in ethnicity, namely Caucasian and Asian, further complicates interpretation of the different results, since certain drugs can differently affect people according to their race/ethnicity (Burroughs et al., 2002). For instance, genetic factors, such as polymorphisms or cultural differences, e.g. increased use of curcumin in many Asian cuisines, can be major determinants of curcumin's effects. So far, none of the studies have reached Phase III in clinical trials, suggesting that curcumin has not fully met expectations. However, for reasons outlined above and because of the restricted number of clinical studies performed to date, it is not possible to directly compare clinical studies and draw concrete conclusions about the effectiveness of curcumin yet.

Future directions

Bioavailability of Curcumin

The major drawback of curcumin supplementation for therapeutic purposes is the low bioavailability of the compound. Many equivalents of curcumin have been developed to improve this. As mentioned previously, administration of any of the three constituents (curcumin, bisdemethoxycurcumin and demethoxycurcumin) separately instead of the parent curcuminoid mixture was recommended as a more efficient way of treatment (Ahmed et al., 2010). Furthermore, a synergistic effect of curcumin with other dietary supplements, such as piperine, α-lipoic acid, N-acetylcysteine, B vitamins, vitamin C, and folate, has been suggested to enhance its effects (Parachikova et al., 2010; Rinwa & Kumar, 2012). However, at present nanoparticles are mainly used, since they demonstrate better BBB penetration and provoke deeper biochemical changes than free curcumin (Hoppe et al., 2013; Kundu et al., 2016; Ma et al., 2013; Sandhir et al., 2014; Tiwari et al., 2013). Nevertheless, there is still room for improvement and future research should focus on ways to further increase curcumin's systemic bioavailability, in particular by improving BBB permeability and reducing first pass metabolism of the compound.

A dose-response relationship should also be taken into account. The optimal dose would have maximum cognitive enhancing effects with the safest pharmacokinetic profile. It is important to mention that the vast majority of animal studies illustrates beneficial effects of curcumin on cognition in a dose dependent manner with the higher dosages generally being more effective compared to lower dosages used in animals (Reeta et al., 2009; Sun et al., 2013; Tiwari et al., 2013; Tiwari & Chopra, 2013; Wang et al., 2014; Zhang et al., 2015). However, there are animal studies that report an inverted U-shape effect in Aβ plaques reduction but behavioral data are not available (Lim et al., 2001). At the same time, human studies suggest a ceiling effect concerning the dose of curcumin (Baum et al., 2008). Subsequently, a medium dose range might be preferable at clinical settings. The existing studies have evaluated disperse formulations of curcumin impeding any comparison between compounds. Therefore, it is of substantial importance to conduct reliable pharmacokinetic/ pharmacodynamics (PK/PD) and comparative studies in order to determine a standard dose using the analogue that would be able to reach brain targets in the most efficacious way.

An interesting subject for future research would be the impact of nutritional status on curcumin's therapeutic effects. Curcumin is a highly lipophilic molecule. One animal study showed aggravated cognitive performance in rats consuming high-fat diet in conjunction with curcumin administration (Wu et al., 2006). In contrast, clinical studies suggest that consuming a meal rich in fat prior to curcumin's administration slows down gastric elimination and allows maximum absorption of the compound (Lao et al., 2006; Ringman et al., 2012; Vareed et al., 2008). Nevertheless, a number of pharmacokinetic clinical studies has been performed in fasted subjects (Bertolino et al., 1998; Gota et al., 2010; Kanai et al., 2012; Kocher et al., 2015; Schiborr et al., 2014). The clinical trials discussed here used different dietary patterns prior administration of curcumin.

Another issue for future consideration is the targeted population in human studies. Clinical studies have mainly used participants without established cognitive dysfunction. However, in preclinical studies, amelioration of cognitive deficits was evident in cognitive impaired rodents. Curcumin did not exert beneficial effects on cognition of healthy or sham control animals, suggesting that curcumin enhances cognitive deficits rather than boosts normal cognitive functioning (Ishrat et al., 2009; Nam et al., 2014). Clinical findings have also supported that this compound does not significantly improve cognitive functioning in healthy or mildly cognitive impaired population, but probably prevents or stabilizes cognitive decline (Cox et al., 2015; Rainey-Smith et al., 2016; Ringman et al., 2012; Small et al., 2018). Therefore, evaluation of patients with established cognitive deficits might yield different results.

Lastly, an important factor that could benefit future trials, is an extended duration of treatment. Curcumin exerts its therapeutic effect through anti-inflammatory and antioxidant pathways. However, regulation of inflammation, oxidative stress or neurogenesis are lengthy processes. In human trials, the maximum duration of curcumin's administration was 18 months and yielded the most positive results compared to the rest of the studies that lasted one year or less (Small et al., 2018). Considering the low bioavailability of the compound, prolonged periods of treatment may be required to detect essential improvement in cognition.

Conclusion

In conclusion, numerous preclinical studies have demonstrated beneficial effects of curcumin on cognition in AD and non-pathological aging. However, a limited number of human studies was identified, and these results are less consistent than results of preclinical work. Preliminary evidence from human studies supports preclinical findings that curcumin may stabilizes / prevents cognitive decline rather than improves it in healthy population. Since, curcumin is an interesting compound with potential capability of preventing cognitive decline, it is crucial to find ways to bridge this translational gap. An important advantage of curcumin is that constitutes a natural, widely available compound. Thus, it does not involve a great economic burden for the patients that might benefit from its use. Additionally, even though studies have reported mild side effects in the elderly patients at a high dose, curcumin demonstrates a safer profile compared to the current compounds. Thus, as current treatments for cognitive impairments remain insufficient and are accompanied by severe side-effects, curcumin may be a promising alternative. However, further

research to improve curcumin's bioavailability is crucial and more human trials examining curcumin's cognitive enhancing effect are necessary.

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CHAPTER 7

General Discussion

Purpose of this dissertation

The central aim of this thesis was to explore the diverse effects of multiple forms of stress on cognition at various levels of analysis, including behavioral (**chapter 2, 3, 4**), cognitive (**chapter 2, 4, 5**), neurochemical (**chapter 4, 6**), and self-report (**chapter 3, 5**) measures. A summary of the results for the separate chapters is provided in the Appendix. This chapter will attempt to discuss and integrate the main findings of previous chapters. Additionally, several methodological considerations and future directions will be discussed.

The changing conceptual landscape: stress as one of the core transdiagnostic regulators

In the introduction of this thesis (**chapter 1**), it was outlined that stress is a risk factor for many neuropsychiatric disorders (Hammen, 2005; Lupien et al., 2009; Revollo et al., 2011; Wilson et al., 2005), with a particular emphasis on the impact of stress on (subthreshold) motivational and cognitive dysfunctions (Lupien et al., 2009; Salamone et al., 2015; Salamone et al., 2016).

Results from this thesis add to this growing body of work. In **chapter 3**, the relationship between altered cost-benefit reinforcement learning and constructs strongly linked to a transdiagnostic risk of psychopathology were evaluated, namely perceived chronic stress, anhedonia, energy/fatigue, impulsivity, using self-report measures in the general population, which also included a smaller sample of people with a diagnosis of depression and anxiety. Key results from this chapter suggest that perceived chronic stress and impulsivity were associated with a more general reduction in reinforcement learning regarding the costs and benefits of actions. Surprisingly, neither anhedonia nor energy/fatigue were associated with task performance, even though these constructs have received increased scientific attention as transdiagnostic components of psychopathology (Huys et al., 2013; Müller et al., 2021; Waltz & Gold, 2016). One potential explanation for these findings could be the use of a naturalistic sample including heterogenous groups of patients, which in the past has shown to result in different outcomes compared to using strictly selected patient groups (Brolsma et al., 2021). Another explanation could be that chronic stress has been found to be a predisposing factor to symptoms like anhedonia and fatigue, hence these symptoms were not correlated with task performance in the general population.

In **chapter 5**, network analyses were used to evaluate how worries and stress about the COVID-19 pandemic, and adherence to mitigation guidelines, were associated with several self-reported indicators of mental well-being, namely mood, distress, energy, loneliness, and motivation in adults living in the Netherlands and Belgium. The results showed that worries about COVID-19 were mainly linked with increased subjectively reported distress and lower mood, which in turn exerted secondary influences on the other indicators of mental well-being, i.e., energy, loneliness, and motivation. Interestingly, temporal network analysis showed that worries related to COVID-19 at a given time point were associated with increased distress and lower mood at the following time point. Moreover, these two factors (i.e., distress and mood) reciprocally interacted over time in a downward spiral manner. These results could provide a mechanistic explanation of how (di)stress may be a predisposing factor but also consequence of other mental health problems. For example,

stress related to COVID-19 may contribute to the onset or exacerbation of symptoms associated with affective/stress-related disorders (as increased prevalence was observed during COVID-19) by increasing distress and worsening mood which, in turn, could also intensify each other, resulting in increased stress and, potentially, a vicious cycle.

Interestingly, the Hierarchical Taxonomy of Psychopathology (HiTOP) model (Krueger et al., 2018), a relatively novel theoretical framework which summarizes transdiagnostic dimensions in a hierarchical manner, views (di)stress as a high-order factor. Results from **chapter 3** and **chapter 5** are in agreement with the HiTOP model. Specifically, they suggest that stress is an important transdiagnostic regulator, followed by other factors ranked lower in the HiTOP hierarchy, in our studies anhedonia, fatigue, or loneliness. Thus, these results underscore the notion that stress (like other high-order factors, e.g., impulsivity) may influence a wider range of behaviors compared to lower-order factors (e.g., anhedonia), and therefore warrants extensive attention. To deepen our understanding about stress, we further explored different stress dimensions aiming to unravel how they impact cognition and behavior.

Cost and benefit learning under acute and chronic stress

As previously mentioned, stress can affect cognition and motivation in various ways. The combination of graded dimensions related to both stress (e.g., acute - chronic duration; low - high intensity) and the cognitive processes (e.g., habitual - goal directed) under investigation can determine the outcome of their interaction (i.e., beneficial or impairing) (Sandi, 2013). The importance of investigating the full range of variation of such factors (or constructs) to move towards a dimensional conceptualization of psychopathology is highlighted in the Research Domain Criteria (RDoC) framework (Insel et al., 2010). In line with this approach, the first chapters of this thesis, **chapter 2** and **chapter 3,** have focused on investigating the effect of acute and chronic stress respectively on a specific aspect of cognition, namely the (cost and benefit) reinforcement learning (included in the Positive Valence System of RDoC's framework). Measurements of cost and benefit learning evaluate whether participants are incentivized more by (monetary) benefits or (physical/cognitive) effort costs when (learning to) carry(ing) out goal directed actions. By teasing apart the impact of costs and benefits on goal-directed behavior, and by making explicit distinctions between acute and chronic stress, **chapter 2** and **3** aimed to better understand how various aspects of the stress response may influence specific motivational processes involved in goal-directed behavior.

In **chapter 2** we found that, following acute stress induction, participants improved learning to maximize rewards relative to learning to minimize effort cost, which may have been driven by an increased sensitivity to reward versus effort cost. On the contrary, no-stress control participants showed similar performance on learning to maximize rewards and minimize effort, as well as similar sensitivity to both reward and effort cost. These results align well with previous work that has found increased sensitivity for positive but not negative outcomes after acute stress induction (Lighthall et al., 2013; Mather & Lighthall, 2012; Petzold et al., 2010). Using cognitive computational modeling we demonstrated how the asymmetric impact of acute stress on cost-benefit learning might be attributed to changes in reward and effort learning rates. In other words,

these analyses revealed how acute stress might prompt individuals to employ cognitive strategies that direct motivation towards obtaining pleasurable outcomes (i.e., reward) at the cost of avoiding negative outcomes (i.e., expending effort).

On the other hand, in **chapter 3** we observed that higher levels of perceived chronic stress were associated with a general learning reduction, independent of whether participants were learning to maximize rewards or minimize effort. In addition, perceived chronic stress was associated with reduced sensitivity to both positive and negative reinforcers, but not positive/negative punishments. These observations are in agreement with previous studies showing that stress-related disorders are characterized by reduced reward sensitivity and reduced influence of previous outcomes on subsequent actions (Ironside et al., 2018; Olino, 2016; Vidal-Ribas et al., 2019). In addition, these results suggest that chronic stress might be more specific to reinforcement versus punishment learning, rather than valence (i.e., reward versus effort) learning.

Combined, **chapter 2** and **3** underscore how acute and chronic stress exert unique effects on motivation and goal-directed behavior. In **chapter 2,** acute stress was found to facilitate reward maximization and impair effort minimization. In **chapter 3**, perceived chronic stress was associated with impairments in more general learning components. These findings align with past research that has indicated that acute stress enhances reward sensitivity, while chronic stress decreases reward sensitivity, associated with stress-related psychopathology such as loss of motivation and anhedonia (Baik, 2020; Barch et al., 2014; Ironside et al., 2018). So far, many studies that evaluate the effects of stress on motivation have used the term stress to refer to either acute or chronic stress or have used acute stress models to investigate symptoms of chronic stress. Findings from these chapters highlight that future work should acknowledge different types and dimensions of stress, such as acute - chronic stress. In addition, incorporating (cognitive or physical) effort into studies of motivation is essential, as it can provide novel insights regarding cost and benefit computations under acute and chronic stress (Barch et al., 2014; Pessiglione et al., 2017).

As already noted, additional dimensions, such as stress intensity, timing and context can also shape the effect of stress on cognition. For example, an inverted-U-shape relationship between stress intensity and cognition is often described in the literature, suggesting that low or high levels of stress might be impairing, whereas moderate levels might be more beneficial for cognitive functions (Diamond et al., 1992; Kim & Diamond, 2002; Mendl, 1999). This notion is in agreement with findings in **chapter 2,** in which we observed that, following acute stress induction, moderately stressed participants showed greater learning asymmetry in favor of reward maximization. In addition, the time of stressor (e.g., before, during or after the learning process) is an important factor that can lead to differential effects of stress on cognition (Joëls et al., 2006). Lastly, the context can also determine whether acute stress will act adaptively or maladaptively. For instance, the findings reported in **chapter 2** suggest that, depending on the context, the observed cost-benefit asymmetry after acute stress may be adaptive (e.g., reach a desired goal such as safety despite high cost) but may also be maladaptive (e.g., overindulging in rewarding foods or substances, while neglecting energetic costs or even reducing self-control (Maier et al., 2015)).

The role of stress-related neurotransmitters on cost and benefit learning and decision-making

Neurotransmitters including dopamine (DA) and noradrenaline (NA), in addition to the well-studied stress hormone cortisol, are thought to mediate the neural effects of the stress response (Hermans et al., 2014; Jung et al., 2019; Kvetnansky et al., 2009; Vaessen et al., 2015). Both DA and NA are active molecules that belong to the same family known as catecholamines (Gurwitz & Ray, 2022). However, DA has received increased scientific attention, whereas NA is considered a relatively "neglected" neurotransmitter in the context of motivation. Converging evidence suggests that exposure to mild acute stress results in increased levels of dopaminergic and noradrenergic activity in the brain, whilst exposure to severe chronic stress is associated with dopaminergic and noradrenergic downregulation (Bloomfield et al., 2019; Haller et al., 2002; Holly & Miczek, 2016; Koob et al., 1997; Yu et al., 2013), often in a regionally specific manner (Moreines et al., 2017; Roth et al., 1982). Increasing evidence suggests that DA and NA often co-exist and interact on a molecular level, and might exert complex, complementary effects on motivation (Ranjbar-Slamloo & Fazlali, 2020; Xing et al., 2016). Thus, even though comparing their neuromodulatory effects and decoding their behavioral and cognitive outputs can be challenging, it is of imperative importance as these two neurotransmitter systems are implicated in the pathogenesis of several stress-related conditions, such as depression, psychotic disorders, attention deficit hyperactivity disorders, addiction (Nutt et al., 2007; Weinshenker & Schroeder, 2007; Winograd-Gurvich et al., 2006). For these reasons, in **chapter 2** and **chapter 4** of the current thesis, it was investigated how DA and NA may influence motivation, using measurements of cost and benefit learning and decision-making processes respectively.

In **chapter 2**, pupillometry and physiological measures were used in combination with outcomes from cognitive computational modeling to indirectly estimate catecholaminergic activity and its relationship with the strategies employed during a cost-benefit reinforcement learning task. Positive associations were found between RPE (reward learning signals) and pupil size, suggesting a tentative link between catecholamine activation and reward maximization in the stress group. Reward learning rate and RPE-pupil size slopes were inversely correlated with some physiological data and subjective stress ratings suggesting that mainly moderately stressed participants drove the preference for reward maximization (in agreement with the inverted U-shape relationship that has also been described between DA and cognition (Baik, 2020)). Results from EPE (effort learning signals) and pupillometry together with salivary and physiological measures suggested tentative links between increases in NA and reduction in effort cost minimization in the stress group. These findings could suggest that the impact of acute stress on motivation (here, reinforcement learning) may be mediated by DA and NA. However, we should emphasize that indirect measures were used to approximate DA and NA activity in this study.

Therefore, to investigate the effect of DA and NA more directly, in **chapter 4** we used single-dose pharmacological challenges to evaluate the role of these two neurotransmitter systems in motivation (here, cost and benefit decision-making). During the cost and benefit decision-making task, participants could choose to accept or reject an offer if they deemed the reward was worth

the effort exerted on a dynamometer. Preliminary results indicated that low-dose haloperidol (primarily targeting dopamine D_2 receptors) increased response vigor at the cost of reduced acceptance over time, while propranolol (primarily targeting noradrenergic β receptors) may have increased sensitivity to effort cost. These results surprisingly do not directly link DA with reward valuation and provide evidence that DA and NA contribute to effort processing alternations.

It is becoming increasingly evident that there are theoretical and empirical limitations in the traditional DA hypothesis, which has labelled DA as the "reward and motivation" neurotransmitter (Salamone et al., 2009; Weinshenker & Schroeder, 2007). In **chapter 4**, we observed that both DA and NA regulated action-related functions in decision-making processes. Preliminary results suggest that NA may be more specific to mobilization of action and DA more specific to action vigor, in agreement with findings from animal research (Hosking et al., 2015; Schweimer et al., 2005; Varazzani et al., 2015). These findings could contribute to uncovering the neurochemical architecture underlying motivated behavior, as both catecholamines are involved in the development of many (stress-related) neuropsychiatric conditions characterized by motivational deficits and can be dysregulated by different pharmacotherapeutic options.

Interestingly, animal research has attempted to explain how DA might integrate RPE and action-related functions to obtain rewards (measure of motivation). Phasic bursts of DA have been proposed to encode learning signals, whereas tonic or ramping (intermediate in speed) signals have been proposed to encode action/vigor motivation (Jessica et al., 2023; Mohebi et al., 2019; Niv, 2007; Niv et al., 2007). Findings from **chapters 2** and **4**, are consilient with the dual role of DA in cost and benefit learning and decision-making. Human research directly comparing the role of DA and NA in learning versus decision-making would be important to explore how these findings are translated to human subjects.

In search of finding treatments to improve cognition

Studies including clinical and non-clinical cohorts have found that chronic stress is associated with deficits in cognitive skills such as working memory, attention, vigilance etc. (Girotti et al., 2018). Exposure to prolonged or excessive stress has been suggested to accelerate biological aging as well as the onset of functional impairments (Polsky et al., 2022) and age-related diseases, including Alzheimer's disease (AD) (Briones et al., 2012; Wilson et al., 2005). Despite extensive research efforts, there are currently no effective pharmacological treatments to prevent or cure cognitive deficits. Existing cognitive enhancers may postpone the cognitive decline rather than restore cognitive abilities (Husain & Mehta, 2011). **Chapter 6**, evaluates curcumin, a natural compound as a potential cognitive enhancer. Moving away from the amyloid hypothesis, inflammation and oxidative stress have been suggested as potential underpinnings of AD and cognitive decline. Curcumin's anti-inflammatory and antioxidant properties have shown potential for its use as a cognitive enhancer. For this reason, **chapter 6** provides a summary of animal and human research investigating the effect of curcumin on cognition in aging and AD. Animal research has shown promising results in improving cognition. However, results from clinical trials so far have been mixed possibly due to curcumin's low bioavailability and the lack of homogenized clinical

trials. Thus, more research is still needed to enhance curcumin's bioavailability and understand its therapeutic potential.

Methodological considerations

In this thesis different study designs were used ranging from experimental using lab-based set-up, observational using web-based set-up to systematic review of the literature. Consequently, we also used different types of analyses with their own strengths and limitations. As both strengths and limitations are described in the separate chapters, more general points of considerations will be discussed in this section.

First of all, an important strength of the studies described in this thesis is the evaluation of different dimensions of transdiagnostic constructs, namely stress (acute stress in **chapter 2**, perceived chronic stress in **chapter 3**, stress related to COVID-19 in **chapter 5**) and cognition (cost and benefit learning in **chapters 2 and 3**, cost and benefit decision-making in **chapter 4**, emotion regulation in **chapter 5**, and cognitive skills in **chapter 6**). Thus, the current thesis used a diverse set of approaches and samples to study in-depth the effect of the different forms of stress on cognitive abilities including behavioral, cognitive, biological, and self-report measures. In addition, besides the many drawbacks of the COVID-19 pandemic, it provided us with the unique opportunity to measure the effects of stress during an ongoing major stressor (**chapters 3 and 5**) (as opposed to stressors occurred in the past), which may have minimized recall bias and increased ecological validity.

However, besides the strengths presented above, there are several limitations that should be mentioned. Methodological differences across studies included in this thesis make it difficult to compare the results of these studies. For example, we used different study designs, manipulations (e.g., stress versus pharmacology), and proxy measures of motivation (e.g., reinforcement learning versus cost-benefit decision-making), which makes a direct comparison between different chapters challenging. Formal comparisons between the related constructs using standardized measurements could minimize such pitfalls.

Moreover, due to COVID-19 pandemic we had to turn to online studies and rapidly gain new expertise (**chapter 3** and **chapter 5**). Even though this resulted in relatively large sample sizes, it was inevitably accompanied by limitations inherent to the data being gathered through online surveys. For example, self-reports may vary in objectivity when supervision from a researcher is missing. Another concern is that online studies are more likely to be completed by people who are (technologically) literate, as well as by those who might be more interested in the subject under investigation (although this is also possible in other designs). This might have led to selection bias and a convenience sample. Since the motives of the responders are unknown to us, we cannot estimate the extent of these biases and the results should be interpreted with caution. Nonetheless, adopting an online design was the best solution at that time when social distancing measures impeded lab-based data collection. Naturally, other study designs bear limitations as well (e.g., experimental studies might lack ecological validity or observational studies might be more prone to confounding variables).

In most of the studies described in this thesis, females outnumbered male participants; a phenomenon increasingly observed in psychological research. In addition, many chapters focused on young, instead of older, adults, limiting comparisons between sex and age groups. Sex and age are two out of many factors that can cause variability in research findings. Other variables such as weight, personality traits, genetic profile are known to induce variability and substantial individual differences, thus they warrant increased attention and investigation. Lastly, it should be noted that most of the studies used healthy participants which does not allow to draw direct conclusions about psychopathology.

Future directions

All studies described in this thesis have focused on transdiagnostic constructs reflecting either risk factors or subsequent symptoms and used samples ranging from healthy volunteers and the general population to unselected patient groups. In order to define more clear dimensional constructs, it has been proposed that it is advisable for future clinical research to refrain from utilizing case-control designs based on categorical diagnoses (Latzman et al., 2020), because categorical designs may often measure factors that confound between cases and controls on the dimensions of interest. Instead, it has been suggested that researchers should direct their attention towards sampling from heterogeneous patient population and/or the general population, with the possibility of oversampling individuals that fall within the high range on the dimensions of interest (Latzman et al., 2020). Thus, future research using this approach might shed light into several transdiagnostic constructs and facilitate the definition and more optimal use of transdiagnostic dimensions. However, both dimensional and categorical approaches can be valuable under different circumstances (Chmura Kraemer et al., 2004).

Moreover, in the current thesis, we independently evaluated the effects of acute and chronic stress on cost and benefit reinforcement learning (**chapter 2** and **chapter 3** respectively). Nevertheless, further investigation on the interactions between chronic and acute stress on these cognitive computations is needed. For example, it is likely that even though both have an impact on cost and benefit learning (seemingly in different directions) they might not moderate each other's effect (Hammen et al., 2009). However, it is also possible that heightened chronic stress levels may indicate higher likelihood of experiencing acute life events (Turner & Turner, 2005) (e.g. chronic health issues might lead to job loss) and sensitize individuals to have more negative reactions after acute stress (Hammen et al., 2009). On the other hand, another scenario is that chronic stress might decrease negative effects of acute stress acting in a protective way (Cairney et al., 2003; McGonagle & Kessler, 1990). Thus, more research on the relationship between acute and chronic stress and the effect of their interaction on cost and benefit learning and decision-making is needed.

Another point for future consideration relates to exploration of individual differences in the effects of stress on cost and benefit computations. For instance, previous work has revealed gender-dependent effects of stress. Previous findings indicate that after acute stress induction, females show blunted reward responsiveness (making them more prone to anhedonic-like behavior)

(Bogdan & Pizzagalli, 2006), while males show increased reward seeking behavior (making them more prone to substance abuse behaviors) (Lighthall et al., 2012). In addition, acute stress was found to increase risky decision in males compared to females (Mather & Lighthall, 2012). How acute stress affects cost computations, and whether these findings still hold after chronic stress or during reinforcement learning remains to be elucidated. In the majority of our studies under-representation of male subjects did not allow such comparisons (see also methodological considerations).

In **chapter 4** and **chapter 6** we investigated neurochemical agents, used either as drug challenges or therapeutic compounds, in order to explore their effect on cognition. One limitation of such compounds is the lack of target specificity and selectivity, showing affinity for different (sub)types of receptors (Wang et al., 2022). The ability of a drug to distinguish between different targets is important both as a drug challenge, since it can result in more specific physiological effects, but also as a therapeutic agent, since it can be more effective and produce fewer side effects. Another issue of consideration is the degree of drug bioavailability. Low bioavailability is a significant determinant impending successful entry of drug candidates into the market. As described in **chapter 6**, curcumin's low bioavailability is one potential reason why it has not reached phase III of clinical trials yet. Therefore, ways to improve curcumin's bioavailability and blood brain barrier penetration are required. For these reasons, more research is needed to optimize drug delivery, precision, and permeability. Nanoparticle-based formulations have shown potential in this regard, thus improving efficacy and practicability of these formulations might prove to be very beneficial (Mitchell et al., 2021). Lastly, besides catecholamines (**chapter 2, 4**), inflammation is another biological response that underlies stress, motivation, and cognition (as discussed in **chapter 6)**, hence further investigation on their relationship is needed.

Conclusion

Overall, the studies described in this dissertation corroborate with the emerging and fast-developing transdiagnostic approach (promoted by novel models such as RDoC and HiTOP), which aims to provide novel insights into the increased heterogeneity and comorbidity observed among and within mental health problems as well as individual differences in both heathy and patient populations. The ultimate goal was to explore parts of the interaction between the multifaceted aspects of stress and cognition. While the current findings may only represent a fraction of a complex puzzle, they provide important pieces for its gradual completion in the future.

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APPENDIX

General Summary

The overarching aim of this thesis was to explore the interplay between the mutlifaceted aspects of stress and cognition. Over the last decades, research focus has been shifted towards a transdiagnostic, dimensional approach, which investigates constructs (and their dimensions) that are not bound to traditional categorical classifications but cut across different disorders. To gain insight into the dimensionality of mental disorders and health, the primary outlook of **chapters 2, 3, 4, 5** and **6** was to investigate mechanisms underlying the interaction between the various dimensions of stress and cognition.

In **chapter 2**, we investigated the effect of acute stress on a cost (i.e., physical effort) and benefit (i.e., monetary reward) reinforcement learning task testing healthy participants that were allotted to either acute stress or no stress control condition. We found that acute stress reprioritized learning to maximize monetary rewards over learning to minimize the expenditure of physical effort. Using computational modeling, we demonstrated that this learning strategy can arise when reward and effort learning rates are afforded equal importance. Pupillometry analyses showed a link between cost and benefit learning with activity of neuromodulators such as dopamine and noradrenaline. These results provide an initial step in explaining how acute stress could act both beneficially and detrimentally. Specifically, it suggests that prioritizing rewarding over costly things could confer immediate benefits (e.g., reaching a valuable goal despite a high action cost) but, probably depending on the context, might also be detrimental (e.g., substance use relapses under acute stress).

In **chapter 3**, we evaluated how transdiagnostic factors linked to psychopathology (i.e., perceived chronic stress, anhedonia, impulsivity, energy) are associated with alterations in learning about the costs and benefits of actions in the general population, utilizing a simplified version of the task used in chapter 2 for online research purposes. We observed that elevated levels of perceived chronic stress and impulsivity were consistently associated with reduced accuracy in the task, which could be explained by a selective reduction in learning from reinforcement (not punishment). The other factors, namely anhedonia and energy, were not associated with various task performance metrics. These results highlight how interindividual differences related to susceptibility for psychopathology may contribute to cognitive mechanisms that support goal-directed behaviour. In addition, this work illustrates some challenges associated with data collection via online platforms and suggests the use of a single device type when conducting online research.

In **chapter 4**, we investigated the roles of dopamine and noradrenaline - two stress-related catecholamines - on performance in a value-based decision-making task, during which participants could earn monetary rewards in exchange for physical effort. Healthy volunteers were assigned to placebo, propranolol (β-noradrenaline receptor antagonist) or haloperidol (dopamine D2 receptor antagonist) according to a randomized double-blind placebo-controlled design and 150 minutes post-administration (~time max), they completed the cost-benefit decision-making task. Preliminary results indicate that low-dose haloperidol may temporarily increase response at the cost of reduced acceptance over time, while propranolol might increase sensitivity to effort cost.

Future computational modeling can provide further insights into mechanisms that may mediate these effects.

In **chapter 5**, we used network analyses to explore the relationship between COVID-19 related stressors and changes in mental well-being in adults living in the Netherlands and Belgium during the initial phase of the COVID-19 pandemic. Results illustrate that worries about the pandemic were associated with elevated distress and low positive mood, which, in turn were associated with other components of mental well-being, such as energy, motivation, and loneliness. Time-lagged network analysis – which illustrates how variables predict each other in subsequent measurement windows (e.g., from day 1 to day 2), identified worries about COVID-19 to be temporally associated with the reciprocal interplay between heightened distress and low positive mood. The outcome of this study points to psychological mechanisms associated with changes in mental well-being during COVID-19, which, in the long run, could result in poorer mental health outcomes and may provide an explanation for the increased prevalence of affective/stress-related disorders reported during the pandemic.

Chapter 6 presents a summary of preclinical and clinical findings on curcumin as a potential cognitive enhancer. Results demonstrated that animal studies show beneficial effects on improving cognitive functions both on molecular and behavioral level, however, human studies remain mixed regarding curcumin's effects on cognition. This review highlights the difference in findings between preclinical and clinical research regarding curcumin. It suggests that improving curcumin's bioavailability and conducting homogenized clinical trials are required to bridge this translational gap. Because curcumin is a natural, widely available compound with mild side effects, we propose that it warrants further investigation.

Finally, **chapter 7** discusses the main findings, strenghts, limitations and suggestions for future research. Although there is still a long way to go, findings from the current thesis provide some steps for the long term goal of adopting dimensional conceptualizations that could lead to a comprehensive understanding of the full spectrum of mental disorders and health. Future research exploring further both biological and behavioral functioning of the different dimensions as well as their interactions, will help put more pieces together.

Impact Paragraph

Stress is ubiquitous in people's lives, affecting mental well-being and various cognitive functions. Everyone has experienced stress, difficulties concentrating, or reduced motivation at some point in their lives. These symptoms do not necessarily reflect the presence of a mental disorder. However, their prolonged or intense presence is highly associated with a range of mental health problems either as risk factors or as symptoms. Impairments in one of these transdiagnostic constructs (i.e., excessive stress, cognitive deficits, motivational decline) can impact vocational, personal, every-day functioning and can pose a considerable financial burden for society. For instance, past research has estimated that the total costs of stress-related problems worldwide range from $221 million in Australia to $187 billion in the USA (Hassard et al., 2018). In addition, a recent study estimated that in the Netherlands an episode of sick-leave due to stress-related problems amounts to €19,151 on average for Dutch employers (Wolvetang et al., 2022). Thus, increased insight into the different dimensions of these constructs is essential to improve our understanding about transdiagnostic clinical phenomena, which could lead to better treatment options in the future and benefit not only people who experience such problems but also society as a whole.

For this reason, this thesis evaluated the interaction of different dimensions of these transdiagnostic constructs, particularly stress (acute, chronic, COVID-19 related), cognitive aspects of motivational impairments (reward and effort processing during learning and decision-making) as well as cognitive skills (e.g., memory), in accordance with the approach of a unified framework for understanding mental disorder and health as a continuum. Improving transdiagnostic dimensional models could inform interventions in two major ways. The first one is conceptual, since they could provide an explanation on why or which pharmacological agents, as well as psychotherapeutic interventions, are effective for multiple diagnostic groups. The second one is more practical, as they could provide biological targets or psychological dimensions that could be targeted through specialized interventions and have an impact across many conditions (Krueger & Eaton, 2015).

However, implementing transdiagnostic approaches into clinical practice might be challenging as it depends crucially on developing a clear framework as well as assessments and interventions that can replace or supplement their diagnostic counterparts (Fusar-Poli et al., 2019). In this thesis we focused on some sub-components of this complex process. However, complexity should not be equated with vagueness. Therefore, we highlight that we should be very specific when referring to different dimensions (e.g., acute vs chronic stress instead of stress as an umbrella term) because they can result in different biological and behavioral effects as observed in chapters 2 and 3 and discussed in chapter 7.

Another challenge of transdiagnostic approaches is to achieve a more detailed understanding of the circuitries and molecular mechanisms involved in the maladaptive behavioral manifestations in both healthy and dysfunctional states. This would allow identification of systems that are sensitive to dysregulation, and that may be considered candidate targets for future pharmacological and non-pharmacological treatments. For instance, catecholamines, such as dopamine (DA) and noradrenaline (NA), are involved in the pathogenesis of many (mental) disorders and are targets

of multiple pharmacological interventions but they can also be altered in healthy states (chapter 2). Disentangling and/or finding their complementary action could be informative for the development of better, pharmacological treatment strategies (chapter 4). Therefore, continued research on stress and the motivational functions of DA and NA could shed light on the neural circuits underlying some of the motivational symptoms observed in health and psychopathology and could promote the development of novel treatments for these symptoms. In addition, several biological underpinnings are being explored for the treatment of cognitive impairments, which are also present across multiple disorders as well as healthy aging (Abramovitch et al., 2021; Amor et al., 2014; Kim et al., 2015). Particularly, biological pathways such as inflammation and oxidative stress, as discussed in chapter 6, deserve more attention, especially considering that in addition to cognitive deficits they underly a plethora of (mental) disorders.

Next to pharmacological treatments, psychological interventions are equally important. As stated in chapters 2, 3, 4 reward and effort processing dysfunction (in learning and decision-making) is observed in many stress-related disorders. Providing a mechanistic explanation about these processes with the use of computational models could be beneficial for psychotherapeutic interventions. For instance, cognitive-behavioral approaches, such as behavioral activation therapy (Farchione et al., 2017), that encourage effort expenditure/ approach behavior in order to experience rewarding emotions, can be effective on many people that experience decline in motivated behavior (with or without a neuropsychiatric diagnosis). The underlying theory is that re-engagement with various activities, such as work, social interactions, hobbies, which may have been limited due to the clients' condition, will prove to be more enjoyable and less effortful than initially anticipated. As a result, a series of positive prediction errors might gradually adjust clients' expectations regarding the costs and benefits associated with their actions (Zald & Treadway, 2017). For example, exploring how measures of reinforcement learning and RPE signals can be utilized to predict which groups of people might show better prognosis to such treatment can be of high interest. Another relevant intervention for people that experience, for instance, problems with cost benefit decision-making could be motivational interviewing (Miller & Rollnick, 2013). The aim of this approach is to alter subjective costs and benefits associated with behavioral change, allowing the subjective value of a more adaptive behavior to surpass that of maladaptive behaviors (Zald & Treadway, 2017). Moreover, network analyses (chapter 5) can provide key symptoms or clusters of symptoms that could be potential targets for interventions. Exploring how interaction of symptoms contributes to psychopathology could be informative for the development of treatments that target specific symptoms even before psychiatric disorders arise. However, since not everyone who experiences certain symptoms will develop mental disorders, we should highlight that more research is needed to delineate when symptom dynamics might contribute to psychopathology.

Importantly, besides the wide range of patient groups affected by stress exposure, as already mentioned in the thesis (from people with depression and anxiety to Alzheimer's disease), transdiagnostic approaches can also have an important impact in the non-clinical population with subclinical symptoms. Thus, developing tools that could distinguish between different transdiagnostic dimensions could promote further awareness on vulnerable, non-clinical groups and contribute to improving their well-being. Considering the broad target group of this approach,

improving transdiagnostic conceptualization, and exploring related treatment strategies is very important, not only for both clinical and non- clinical population but also for the general health care, economy, and job market worldwide.

Lastly, we have already taken steps to disseminate results of this thesis to the scientific community, so that others can expand on these ideas in the future. This work has been presented in several scientific meetings. In addition, all studies described in this thesis use open science practices. All published papers used open-access publishing, ensuring unrestricted accessibility to a wide range of readers. In addition, research data and source code are publicly available in online repositories with links provided in each paper. This facilitates free access to the data, promoting transparency and enabling reproducibility of results. Additionally, availability of these sources fosters replicability and enhances the ability of researchers to validate the findings.

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Curriculum Vitae & List of Publications

About the Author

Stella Voulgaropoulou was born on August 2nd 1993, in Thessaloniki, Greece. In 2011, she completed her secondary education at 1st Experimental Lyceum “Manolis Andronikos”, Thessaloniki. In 2015, she obtained her bachelor’s degree in Psychology at Aristotle University of Thessaloniki, with major in Experimental and Cognitive Psychology. During this time, she took a Traineeship at the Centre for Prevention of Addictions and Psychosocial Health Promotion - «SIRIOS» in Thessaloniki, Greece. She then moved to the Netherlands to follow a two-year Master of Science in Cognitive and Clinical Neuroscience (with specialization in Drug Development and Neurohealth), which she graduated from in 2018. Continuing the path, she undertook during her master’s research internship, Stella started a PhD program in 2018 at School for Mental Health and Neuroscience in the department of Psychiatry and Neuropsychology at Maastricht University, under the guidance of Prof. Dr. Therese van Amelsvoort, Dr. Dennis Hernaus, and Dr. Claudia Vingerhoets. She will proceed her career working as a post-doc at the same department.

List of Publications

Peer-reviewed manuscripts

Voulgaropoulou, S. D., van Amelsvoort, T. A. M. J., Prickaerts, J., & Vingerhoets, C. (2019). The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Research, 1725*, 146476. https://doi.org/https://doi.org/10.1016/j.brainres.2019.146476

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Manuscripts in preparation or abstract only

Voulgaropoulou, S.D, Vingerhoets, C., Amelsvoort, T., & Hernaus, D., et al. Exploring the Complementary Roles of Dopamine and Norepinephrine in Cost-Benefit Decision-Making. *In preparation.*

Voulgaropoulou, S.D, Vingerhoets, C., Hernaus, D., & van Amelsvoort, T. (2020). Social Cognition in Psychosis: Adapting a Behavioral Task for fMRI Purposes. *Biological Psychiatry,87*(9,Supplement),S223. https://doi.org/https://doi.org/10.1016/j.biopsych.2020.02.579 . *Abstract only*.

Conference activity

Poster presentations

Voulgaropoulou, S.D., Vingerhoets, C., Amelsvoort, T., & Hernaus, D., et al. Exploring the Complementary Roles of Dopamine and Norepinephrine in Cost-Benefit Decision-Making. *Society of Biological Psychiatry (SOBP), 2023.*

Voulgaropoulou, S. D., Viechtbauer, W., Sobczak, S., van Amelsvoort, T., & Hernaus, D. Worries about the COVID-19 pandemic and the dynamic regulation of emotions in the general population: A network analysis study. *European College of Neuropsychopharmacology Congress (ECNP), 2022.*

Voulgaropoulou, S. D., Fauzani, F., Pfirrmann, J., Vingerhoets, C., van Amelsvoort, T., & Hernaus, D. Asymmetric effects of acute stress on cost and benefit learning. *European College of Neuropsychopharmacology Congress (ECNP), 2021.*

Voulgaropoulou, S. D., Fauzani, F., Pfirrmann, J., Vingerhoets, C., van Amelsvoort, T., & Hernaus, D. Asymmetric effects of acute stress on cost and benefit learning. *International Symposium on Biology of Decision Making (SBDM), 2021.*

Voulgaropoulou S.D., Koliastasi M., Lokantidou C., Balaska K., Spanou M., Triantafillaki E. The relationship between sense of coherence and mental health in older adults. *9th Pan-Hellenic Interdisciplinary Conference of Alzheimer's disease and Related Disorders and the 1st Mediterranean Conference of Neurodegenerative Diseases, 2015*

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