The Modulatory Effect of Control on Stress Responding
–
A Translational Perspective with Implications for Resilience Research

Inauguraldissertation
zur Erlangung des Akademischen Grades
eines Dr. phil.,

vorgelegt dem Fachbereich 02 – Sozialwissenschaften, Medien und Sport
der Johannes Gutenberg-Universität Mainz

von

Laura Elisabeth Meine
aus Hannover

Mainz
2021

Referentin: Univ.-Prof. Dr. [redacted]

Korreferent: Prof. Dr. [redacted]

Korreferent: apl. Prof. Dr. [redacted]

Tag des Prüfungskolloquiums: 13. September 2021

For my grandma,
a fun, loving, kick-ass woman.

“Scientific” Principle[1]

Keep wondering.

Life does not add up,
Take its measure
But leave an inch
For whatsoever.

[1] Excerpt from a poem written by the author in November 2017.

Table of Contents

List of Abbreviations

AAL	Automated anatomical labelling
APA	American Psychological Association
BOLD	Blood oxygen level-dependent
BPM	Beats per minute
CC	Control condition
CON	Controllable stress
DFG	German Research Foundation
dPAG	Dorsal periaqueductal grey
DRN	Dorsal raphe nucleus
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Escapable stress condition
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWE	Family-wise error
gPPI	Generalized form of psychophysiological interaction analysis
GRAPPA	Generalized autocalibrating partially parallel acquisitions
HPA	Hypothalamus-pituitary-adrenal
HRF	Haemodynamic response function
ITI	Inter-trial interval
IQR	Interquartile range
LH	Learned helplessness
LMEM	Linear mixed-effects model
MABELLA	Mainz Behavioral and Experimental Laboratory
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-prepared rapid-acquisition gradient echo
MRI	Magnetic resonance imaging
NCATS	National Academy for Advancing Translational Sciences
PANAS	Positive and Negative Affect Schedule
PASTOR	Positive Appraisal Style Theory of Resilience
PTSD	Posttraumatic stress disorder

rmANOVA	Repeated measures analysis of variance
ROI	Region of interest
RT	Reaction time
SAM	Sympathetic-adreno-medullar
SCID	Structured clinical interview for DSM-IV
SD	Standard deviation
SI	Stress immunization
SMA	Supplementary motor area
SPM	Statistical parametric mapping
STADI	State-Trait Anxiety-Depression Inventory
SVC	Small volume correction
TE	Echo time
TR	Repetition time
UNCON	Uncontrollable stress
vmPFC	Ventromedial prefrontal cortex
WEIRD	Western, educated, industrialized, rich, and democratic
YC	Yoked inescapable stress condition

List of Tables

Study 1

Study 2

Supplemental Tables

List of Figures

Introduction

Study 1

Supplemental Figures

Study 2

Supplemental Figure

List of Original Papers

This dissertation is based on the following papers:

1) Meine, L. E.[*], Schüler, K.[*], Richter-Levin, G., Scholz, V., & Wessa, M. (2020). A Translational Paradigm to Study the Effects of Uncontrollable Stress in Humans. *International journal of molecular sciences*, *21*(17), 6010. https://doi.org/10.3390/ijms21176010

   [*]Both authors contributed equally to this work.

2) Meine, L. E., Meier, J., Meyer, B., & Wessa, M. (2021). Don't Stress, It's Under Control: Neural Correlates of Stressor Controllability in Humans. *bioRxiv*. https://doi.org/10.1101/2021.03.30.437657

Abstract

Stress can exert marked and potentially long-lasting effects on an individual's biology, behaviour, cognition, and emotion. Contrary to prevailing views, however, facing a stressor does not necessarily engender negative consequences. There are a number of factors that modulate the stress response. Control is one such factor that has been extensively studied yet merits further examination. Experiments in animals have established divergent effects of stressor controllability: whereas a lack of control over a stressor typically entails symptoms of learned helplessness (i.e., anxiety, passivity), the experience of control appears protective. Translational research has confirmed that this modulation is also evident in humans. However, this research is methodologically heterogeneous and has largely been focused on uncontrollable stress and its relevance for the aetiology of depression (a disorder with symptoms conspicuously resembling those of learned helplessness). The reported benefits of controllable stress, in contrast, have thus far mainly been addressed in animal research that aimed at delineating the underlying neurobiological processes. In this regard, findings highlight changes in brain circuits involving the dorsal raphe nucleus and ventromedial prefrontal cortex.

Although continued endeavours to better understand the aetiology of mental disorders such as depression are certainly needed, there has come a paradigm shift away from disease-oriented approaches. Researchers have increasingly examined factors that keep individuals mentally healthy despite severe stress exposure. Furthermore, the emerging field of resilience research is now working to shed light on the mechanisms that underlie the relationship between protective factors and a good mental health outcome.

Against this backdrop, this dissertation is dedicated to further investigating stressor controllability effects and their neural correlates in humans. In study 1, a translational paradigm was developed that closely resembles the established animal design and tracks the effects of controllable and uncontrollable stress in humans on a behavioural, affective, and cognitive level. In study 2, this paradigm was then modified to study the direct neural correlates of stressor controllability, testing for parallels with findings from animal research.

The results of both studies provide further evidence that control is a powerful modulator of the immediate stress response and subsequent functioning. Study 1 highlights controllability-dependent effects on decision-making and study 2 describes neural activation patterns consistent with the animal literature. Specifically, the ventromedial prefrontal cortex was differentially activated depending on stressor controllability. Furthermore, recruitment of this brain region was associated with the participants' subjective feeling of helplessness.

With reference to the results, special attention is paid in the discussion to the positive effects of experiencing control and its relevance to resilience research. If the experience of control is accompanied by an internalization of a belief in high agency, which in turn has a positive effect on future stress reactions, it could constitute a resilience mechanism. There are already many approaches that capitalize on the role of objective or perceived controllability in the prevention and treatment of mental illness. However, the effectiveness of these approaches seems to depend, among other things, on contextual factors. For example, poverty represents an environment that affords little opportunity for proactive coping, precluding the usefulness of high perceived control. In consideration of these and other relevant factors, future research on stressor controllability should be conducted in more direct collaboration between animal and human researchers, incorporate perspectives from developmental psychology, and pay attention to more diversity in samples.

Zusammenfassung

Stress kann deutliche und potenziell lang anhaltende Auswirkungen auf die Biologie, das Verhalten, die Kognition und die Emotionen einer Person haben. Entgegen der vorherrschenden Meinung führt die Konfrontation mit einem Stressor jedoch nicht zwangsläufig zu negativen Konsequenzen. Es gibt eine Reihe von Faktoren, welche die Stressreaktion modulieren. Kontrolle ist ein solcher Faktor, der bereits viel getestet wurde, aber noch weiter untersucht werden sollte. In Tierexperimenten wurden unterschiedliche Effekte der Stressorkontrollierbarkeit festgestellt: während ein Mangel an Kontrolle über einen Stressor typischerweise Symptome erlernter Hilflosigkeit (d.h. Angst, Passivität) nach sich zieht, scheint die Erfahrung von Kontrolle schützend zu sein. Translationale Forschung konnte bestätigen, dass diese Modulation auch beim Menschen zu beobachten ist. Allerdings ist diese Forschung methodisch heterogen und hat sich weitgehend auf unkontrollierbaren Stress und seine Relevanz für die Ätiologie der Depression (einer psychischen Erkrankung mit Symptomen, die auffällig denen der erlernten Hilflosigkeit ähneln) konzentriert. Der berichtete Nutzen von kontrollierbarem Stress hingegen wurde bisher hauptsächlich in der Tierforschung untersucht, die darauf abzielte, die zugrunde liegenden neurobiologischen Prozesse zu beschreiben. Diesbezügliche Befunde weisen auf Veränderungen in den Hirnschaltkreisen hin, die den dorsalen Raphe-Kern und den ventromedialen präfrontalen Kortex einschließen.

Obwohl fortgesetzte Bemühungen, die Ätiologie psychischer Störungen wie der Depression besser zu verstehen, sicherlich notwendig sind, hat sich ein Paradigmenwechsel weg von krankheitsorientierten Ansätzen vollzogen. Forscher untersuchen zunehmend Faktoren, die Individuen trotz schwerer Stressbelastung psychisch gesund erhalten. Darüber hinaus arbeitet das aufstrebende Feld der Resilienzforschung nun daran, die Mechanismen zu beleuchten, die dem Zusammenhang zwischen Schutzfaktoren und einem guten psychischen Gesundheitszustand zugrunde liegen.

Vor diesem Hintergrund widmet sich diese Dissertation der weiteren Untersuchung von Stressor-Kontrollierbarkeitseffekten und deren neuronalen Korrelaten beim Menschen. In Studie 1 wurde ein translationales Paradigma entwickelt, das dem etablierten Tierdesign möglichst nah kommt und die Auswirkungen von kontrollierbarem und unkontrollierbarem Stress beim Menschen auf verhaltensbezogener, affektiver und kognitiver Ebene untersucht. In Studie 2 wurde dieses Paradigma dann modifiziert, um die direkten neuronalen Korrelate der Kontrollierbarkeit von Stressoren zu untersuchen und auf Parallelen zu Erkenntnissen aus der Tierforschung zu testen.

Die Ergebnisse beider Studien liefern weitere Belege dafür, dass Kontrolle einen starken Modulator der unmittelbaren Stressreaktion und der nachfolgenden Funktionsweise darstellt. Studie 1 hebt kontrollierbarkeitsabhängige Effekte auf die Entscheidungsfindung hervor und Studie 2 beschreibt neuronale Aktivierungsmuster, die mit der Tierliteratur übereinstimmen. Insbesondere wurde der ventromediale präfrontale Kortex in Abhängigkeit von der Kontrollierbarkeit des Stressors differenziell aktiviert. Außerdem war die Rekrutierung dieser Hirnregion mit dem subjektiven Gefühl der Hilflosigkeit der Teilnehmer assoziiert.

Unter Bezugnahme auf die Ergebnisse wird in der Diskussion besonderes Augenmerk auf die positiven Effekte von Kontrollerleben gelegt und die Relevanz für die Resilienzforschung unterstrichen. Wenn die Erfahrung von Kontrolle mit der Verinnerlichung eines Glaubens an eine hohe Handlungsfähigkeit einhergeht, welcher sich wiederum positiv auf zukünftige Stressreaktionen auswirkt, könnte dies einen Resilienzmechanismus darstellen. Es gibt bereits viele Ansätze, die sich die Rolle der objektiven oder wahrgenommenen Kontrollierbarkeit für die Prävention und Behandlung psychischer Erkrankungen zunutze machen. Die Wirksamkeit dieser Ansätze scheint jedoch unter anderem von kontextuellen Faktoren abzuhängen. In Anbetracht dieser und anderer relevanter Faktoren sollte zukünftige Forschung zur Stressorkontrollierbarkeit in direkterer Zusammenarbeit zwischen Tier- und Humanforschern durchgeführt werden, Perspektiven aus der Entwicklungspsychologie einbeziehen und auf mehr Diversität in den Stichproben achten.

"Times of stress are also times that are signals for growth, and
if we use adversity properly, we can grow through adversity."
– Abraham J. Twerski

1. Introduction

Imagine the world is in a pandemic and you are forced to stay at home and work from there. You are trying to finish your dissertation, but property management has set up a noisy construction site and begun the lengthy process of renovating the flat above you. The intermittent drilling and hammering prove quite stressful and you struggle to maintain focus. Now imagine you were one of the construction workers. You do not mind the noise very much, it might even be satisfying to you, an indicator of all the hard work you are getting done: so, the louder the better really. If it starts to get a bit tiring, you simply switch off your drill and take a five-minute break.

This example illustrates how controllability over a stressor can exert divergent effects on the corresponding appraisal and response. On the one hand, the lack of control over an aversive event can induce increased anxiety, passivity, and prove deleterious to cognitive functioning (Datta & Arnsten, 2019; Maier & Seligman, 2016; Overmier & Seligman, 1967). On the other hand, the experience of control is considered protective and may reduce susceptibility to future uncontrollable stressors (Amat et al., 2010; Hartley et al., 2014; Maier & Seligman, 2016). Whereas uncontrollable stress has been discussed extensively as a significant trigger for psychopathology (Fassett-Carman et al., 2019; Pryce et al., 2011; Volpicelli et al., 1999; Wadsworth, 2015), more recently, researchers have shifted focus and begun investigating mechanisms which keep individuals mentally healthy, despite severe stress exposure (Kalisch et al., 2015, 2017; Masten, 2007; Russo et al., 2012). In this context, control represents a promising factor. Indeed, in a series of studies, animal researchers have already made substantial progress in delineating the neurobiological mechanisms which underlie the beneficial effects of control experience (Grizzell et al., 2020; Maier & Seligman, 2016; Worley et al., 2018). The mechanistic knowledge gleaned from their research can be used for interventions aimed at preserving mental health in the face of stress. But efforts to translate animal research on stressor controllability to humans must precede such undertakings. Numerous studies have successfully translated findings on uncontrollable stress (Abramson et al., 1978; Hiroto & Seligman, 1975; Pryce et al., 2011) and, likewise, research on control indicates that the effects hold across species (Amat et al., 2010; Grizzell et al., 2020; Hartley et al., 2014; Henderson et al., 2012). However, studies are rather heterogeneous in their methods and explicit investigations of the neural underpinnings of stressor controllability

effects in humans remain few and far between. Any treatments applied in the clinical context should be firmly based on sound theoretical foundations (Ioannidis, 2004). Hence, further translational research is required and should especially address the neural mechanisms implicated in stressor controllability in humans.

1.1 Stress and Controllability

In order to provide a comprehensive introduction to stressor controllability, this section first outlines the concept of stress before discussing controllability in more detail.

1.1.1 Stress and its Effects

Stress permeates many different research disciplines and has increasingly become a popular subject (McEwen & Akil, 2020; Robinson, 2018). Hans Selye, considered the father of stress research, is often reported to have said: "Stress in health and disease is medically, sociologically, and philosophically the most meaningful subject for humanity that I can think of" (Robinson, 2018, p. 334; Szabo et al., 2012, p. 472). Despite an abundance of publications, or perhaps precisely because of this, no consensus has yet been reached on how to define stress (American Psychological Association; APA; 2017). Already in 1984, Lazarus and Folkman suggested conceptualizing stress as "a rubric for many variables and processes" (p. 12). Levine (2005) also considered it a "composite, multidimensional concept" (p. 940) and identified three subclasses, of which, he argued, existing definitions covered but a part. Specifically, he listed the stressor, its processing by designated systems, and the resulting response, which work together interactively. In line with this, Cohen et al. (2016) more recently made the following suggestion:

> We propose that stress be viewed broadly as a set of constructs representing stages in a process by which environmental demands that tax or exceed the adaptive capacity of an organism occasion psychological, behavioral, and biological responses that may place persons at risk for disease. (p. 456)

On a neurobiological level, stress involuntarily sets in motion a series of processes that trigger the fast-acting sympathetic-adreno-medullar (SAM) axis and also mobilize the slower hypothalamus-pituitary-adrenal (HPA) axis (Godoy et al., 2018; Wadsworth et al., 2019). While the SAM system quickly prompts the release of catecholamines, such as noradrenaline, the HPA axis culminates in the secretion of glucocorticoids, such as cortisol (Chrousos, 2009; Godoy et al., 2018). The organism is immediately put into a state of preparedness for adaptive

action. This state is reflected, e.g., in adjusted hormone levels, an accelerated heart rate, elevated blood pressure (Chrousos, 2009), and dilated pupils (Pedrotti et al., 2014) – all of which therefore serve as indicators of stress reactivity. Through highly coordinated interaction and designated feedback loops, the two systems achieve an adaptive regulation of the biological stress response (Joëls & Baram, 2009). More precisely, the organism is called to action quickly but once the stress abates, a recovery to baseline levels is initiated equally swiftly to preserve resources. By contrast, a sustained stress response observed under chronic stress conditions is commonly associated with pathophysiological processes and pervasive disorders (McEwen, 2008).

The described neurobiological processes compel the organism to show a particular behaviour. Specifically, an acute stressor generally induces a fight, flight, or freeze response (Cannon, 1929; Ly et al., 2017; Wadsworth et al., 2019). Broadly speaking, the organism enters a state of heightened awareness which may go along with increases in certain cognitive functions such as attention and memory (Beste et al., 2013; Degroote et al., 2020; Goldfarb et al., 2019; Yuen et al., 2009) and decreases in others (Shields et al., 2016). In fact, human research is rarely concerned solely with the behavioural consequences of stress exposure (see Ly et al., 2017 for an exception), but rather studies these in conjunction with assessments of cognitive functions (Lupien et al., 2007; Shields et al., 2016), which tend to be in focus. Animal researchers, however, operate under certain constraints (their subjects generally do not supply self-report data) and have made it their business to derive highly detailed behavioural data. To delineate the stress response in terms of behaviour, cross-species indices that are frequently investigated comprise reaction time (RT; Shields et al., 2019), startle responses (Deuter et al., 2012; Herten et al., 2016), passivity (Ly et al., 2017), escape behaviour (Maier & Seligman, 2016), social interaction, exploration, reward seeking (Gururajan et al., 2019), and navigation (Brown et al., 2020).

Psychologically, acute stress gives rise to changes in mood and affective state (Bolger et al., 1989; Giles et al., 2014). Typically, participants report feeling less positive and more fearful, angry, or depressed in response to an aversive event (Giles et al., 2014; Hammen, 2005; Lieberman et al., 2015). Since the self-report forms the principal measurement, psychological read-outs following stress exposure are exclusively examined in human research. The focus on subjective appraisal is also reflected in the psychological conceptualization of stress. Only an event which the individual perceives both as threatening and as exceeding their resources for adaptive coping is considered stressful (Lazarus & Folkman, 1984). Summarizing the psychological determinants, Lupien et al. (2007) state that a significant (physiological) stress

response is typically induced by situations that are novel, unpredictable, uncontrollable, or include an element of social-evaluative threat (e.g., negative feedback from peers). They distinguish between absolute stressors as real threats that should elicit a significant stress response in everyone (e.g., existential threats), and relative stressors whose stressfulness is implicit and individually interpreted in light of their novelty, unpredictability, uncontrollability, etc. (e.g., a job interview). Relative stressors can be milder in nature and may not always trigger the hard-wired biological reactions that are automatically activated when survival is at stake. The great variability in what individuals perceive as stressful may offer an explanation for sometimes divergent physiological and emotional stress responses (Campbell & Ehlert, 2012). Furthermore, psychological stressors in particular have been associated with considerable inter-individual differences in responding (Kirschbaum & Hellhammer, 1989; Orem et al., 2019; Rohleder et al., 2003).

Indeed, a number of studies have also highlighted the positive effects of stress. For example, Degroote et al. (2020) reported enhanced concentration following exposure to a psychosocial stressor, indicated by greater speed and accuracy in an attention test. Similarly, Beste et al. (2013) could demonstrate stress-related increases in processing efficiency in a dual-task. Yuen et al. (2009) found that acute stress can facilitate working memory via specific neurobiological processes. There is also evidence that stress boosts associative and item memory, provided that the aversive stimulation occurs directly before or after encoding, respectively (Goldfarb et al., 2019). Researchers have tried to integrate findings on stress-induced memory-enhancement by reconceptualizing stressful experiences as teaching signals for the brain that promote learning (Trapp et al., 2018). Finally, a recent study was able to show improvements in emotion regulation following stress exposure, albeit only in men (Langer et al., 2020).

However, the vast majority of studies has linked stress with rather negative outcomes. For example, in the context of learning and decision-making, stress is generally associated with diminished flexibility and, in turn, the use of suboptimal strategies (Leder et al., 2013; Otto et al., 2013; Schwabe & Wolf, 2013; Smeets et al., 2019). Schwabe and Wolf (2009) demonstrated that exposure to an acute stressor prompted habitual action selection over a more deliberate approach in a subsequent decision-making task. In a recent study, participants were asked to run on a treadmill either wearing light clothing or heavy firefighter gear. The heat stress induced in the latter group led them to commit significantly more errors in a learning task, highlighting the implications for real-life decision-making under high stakes (Coehoorn et al., 2020). In general, severe or traumatic stress is commonly discussed as a trigger for

psychopathology (Hammen, 2005; McLaughlin et al., 2020). Furthermore, even exposure to milder stressors, so-called daily hassles, was shown to be a significant predictor of affective disorders such as anxiety, obsessive-compulsive disorder, and depression (Asselmann et al., 2017). Shields et al. (2017) also reported a negative relationship between the frequency of relatively common stressful life events and memory performance. In today's increasingly fast-paced, interconnected world, the negative consequences of stressor exposure are recognized as a matter of societal concern (APA, 2020; Houtman et al., 2007; Techniker Krankenkasse, 2016).

1.1.2 Modulating the Stress Response

Overall, stress has been discussed both as a detriment to normal functioning as well as a promoter in certain contexts. Several factors have been identified which appear to modulate the stress response and the short and long-term effects of stress. A widely accepted notion is that stressors can represent useful signals which ready the organism for adaptive action, but can be harmful if very severe, highly frequent, prolonged (McEwen, 2000, 2008), or when occurring during a sensitive phase in development (Lupien et al., 2009). Improvements in cognitive functions have generally been observed under conditions of mild stress, but, however, not under extreme exposure (Sandi, 2013). This differential effect is best captured in an inverted U-shape relationship, i.e., stress-related arousal enhances beneficial processes, but only up to a certain point. Beyond this point, levels of stress become too high and are instead associated with deleterious effects (Sapolsky, 2015). Mild stressors imply that the individual has ample resources to overcome the "challenge", whereas severe stress is taxing to such a degree that it effectively shuts down the system, leaving little room for active coping. Nevertheless, recurrent exposure to mild stressors can bring about dire consequences comparable to a single severe stressor (Asselmann et al., 2017; Kanner et al., 1981). Considering the amount of energy required to prepare the organism for adaptive stress responding, it becomes clear that repeated stress encounters can prove extremely draining. Furthermore, without sufficient time to recuperate, stress reactions may become chronic. Bruce McEwen coined the term "allostatic load" to describe the amount of physiological "wear and tear" that results from dealing with repetitive or prolonged stress and predisposes the organism to disease (McEwen, 2000; McEwen & Stellar, 1993, p. 2094). To sum it up, stress can be both good and bad and the goal should not be to prevent its occurrence altogether, but rather to tune it to optimal levels (Sapolsky, 2015).

In this dissertation, control is discussed as the lever with which stress may be adjusted in order to prevent psychopathology and to promote resilience. Control represents a modulating factor which has been extensively studied in both animal and human stress research. Studies have shown that individuals react in markedly different ways to a stressor, depending on whether they have control over it or not (Bhanji et al., 2016; Bollini et al., 2004; Henderson et al., 2012). Control is commonly thought to mitigate the negative effects of stress, whereas a lack of control appears to exacerbate them (Maier & Seligman, 2016). There are, however, many intricacies in the literature on stressor controllability, not least concerning the question of how control can and should be operationalized.

1.1.3 The Many Forms of Control

Control has evolved as a central construct in stress research; however, it comes in many guises which should be clearly distinguished. Steptoe and Poole (2016) helpfully differentiate behavioural control, perceived control, cognitive control, and self-control.

If an individual effectively prevents, reduces, or terminates aversive stimulation through direct action, this is generally termed behavioural or instrumental control (Haggard, 2017). Behavioural control is most readily manipulated in experiments and represents a more objective form of control. Researchers have typically compared different subject groups, one of which could learn an action which modified the stressor, while another had no such action at its disposal (Maier & Seligman, 2016; Wanke & Schwabe, 2019). In most cases, the instrumental response affected the stressor in a deterministic manner. However, studies in the field of decision-making have also employed probabilistic designs in which the likelihood of action-outcome contingencies differs across stimuli or experimental blocks (Dorfman & Gershman, 2019).

Perceived control describes the "belief in one's ability to exert control over situations or events in order to gain rewards and avoid punishments" (Ly et al., 2019, p. 2) which, arguably, should align with the objectively given possibilities for control but has been shown to deviate (Ajzen, 2002; Wanke & Schwabe, 2019; Yon et al., 2020). Individual variation in perceived control may arise from differences in generalized control beliefs. In this context, the literature discusses the concepts of "perceived self-efficacy" (Bandura, 1977) and "locus of control" (Rotter, 1966; Lefcourt, 1982). They describe two trait-like qualities of an individual: the belief in one's capacity to carry out behaviours necessary to meet current situational demands and the degree to which an individual ascribes control over their life outcomes to

themselves (internal) versus to external circumstances, respectively. Both concepts are used to explain differences in how individuals deal with stressful events (Bandura et al., 1988; Roddenberry & Renk, 2010; Schönfeld et al., 2017), with high perceived self-efficacy and a more internal locus of control generally found to be favourable (Brown et al., 2016; Náfrádi et al., 2017; Zlomuzica et al., 2015).

Beyond the objective and subjective controllability of events, cognitive control is a construct which frequently crops up, especially in studies investigating stress effects on cognitive functions. Steptoe and Poole (2016) discuss it mainly as an individual's capacity to control their reactions in an effort to cope, but cognitive control more commonly refers broadly to executive functions such as attention, inhibition and memory, which facilitate information processing and adaptive behaviour (Botvinick & Braver, 2015). More precisely, cognitive control processes operate in a top-down framework, overriding reflexive behaviour in favour of more goal-directed action. However, such higher-order cognition is computationally demanding (Kool et al., 2017) and harder to maintain under stress. Accordingly, many researchers could show that acute stress induces a switch from goal-directed strategies to habitual learning (Otto et al., 2013; Radenbach et al., 2015; Schwabe & Wolf, 2009).

Self-control describes a construct akin to cognitive control. The term generally encompasses processes such as self-regulation, self-discipline, willpower, suppression of impulses, and delay of gratification (Duckworth, 2011). More so than cognitive control, it is often related to emotion regulation (Paschke et al., 2016; Tice & Bratslavsky, 2000). Across studies, greater self-control has been tied to more favourable long-term life outcomes, e.g., health and financial prosperity (Moffitt et al., 2011). Steptoe and Poole (2016) suggest that self-control enables certain stress coping mechanisms whereby fewer stressors are encountered, potential threats rendered less likely to manifest, and more beneficial appraisal responses facilitated.

Crucially, these different aspects of control are not independent from one another. According to models from reinforcement learning (Ly et al., 2019; Moscarello & Hartley, 2017), control beliefs can be understood to arise from the cumulative prior experiences of the individual. More precisely, judgments about the controllability of a situation are inferred through the experience of contingency. If an action reliably leads to a particular outcome, the individual can reasonably assume that their action is instrumental in bringing about the outcome. In other words, they perceive themselves to be actively exerting control and feel a "sense of agency" (Haggard, 2017). This experience will in turn inform how the individual handles similar situations in the future. If they consistently experience that their actions are

consequential, they will come to estimate their agency as generally high, irrespective of the specific situation. Moscarello and Hartley (2017) posit that a recurrent experience of control consequently leads to more proactive behaviour, whereas repeatedly experiencing a lack of control produces reactive behaviour. Ly et al. (2019) discuss the role of disturbed controllability perceptions in psychopathology. They emphasize that perceived control does not always correspond perfectly to the possibilities of instrumental control that a particular environment actually affords. For instance, depression is characterized by reduced perceived control and feelings of helplessness (Liu et al., 2015), while pathological gambling is associated with unrealistically high and therefore problematic levels of perceived control (Orgaz et al., 2013). It follows that perceived control specifically presents a potential target for treatments.

1.2 Generalization Processes of Stressor Controllability

Research on reinforcement learning has greatly advanced our understanding of the mechanistic underpinnings of control beliefs. Established frameworks that view perceived self-efficacy and locus of control as stable trait-like characteristics have been expanded to include an account of how they are formed (Ly et al., 2019; Moscarello & Hartley, 2017). According to this perspective, these constructs are inherently experience-dependent and therefore potentially shapeable. In the context of stress processing, animal research has been particularly useful in elucidating the role of control and its neurobiological correlates. The following sections provide an overview of this research, detailing how experiences of controllable and uncontrollable stress may engender fairly stable control beliefs.

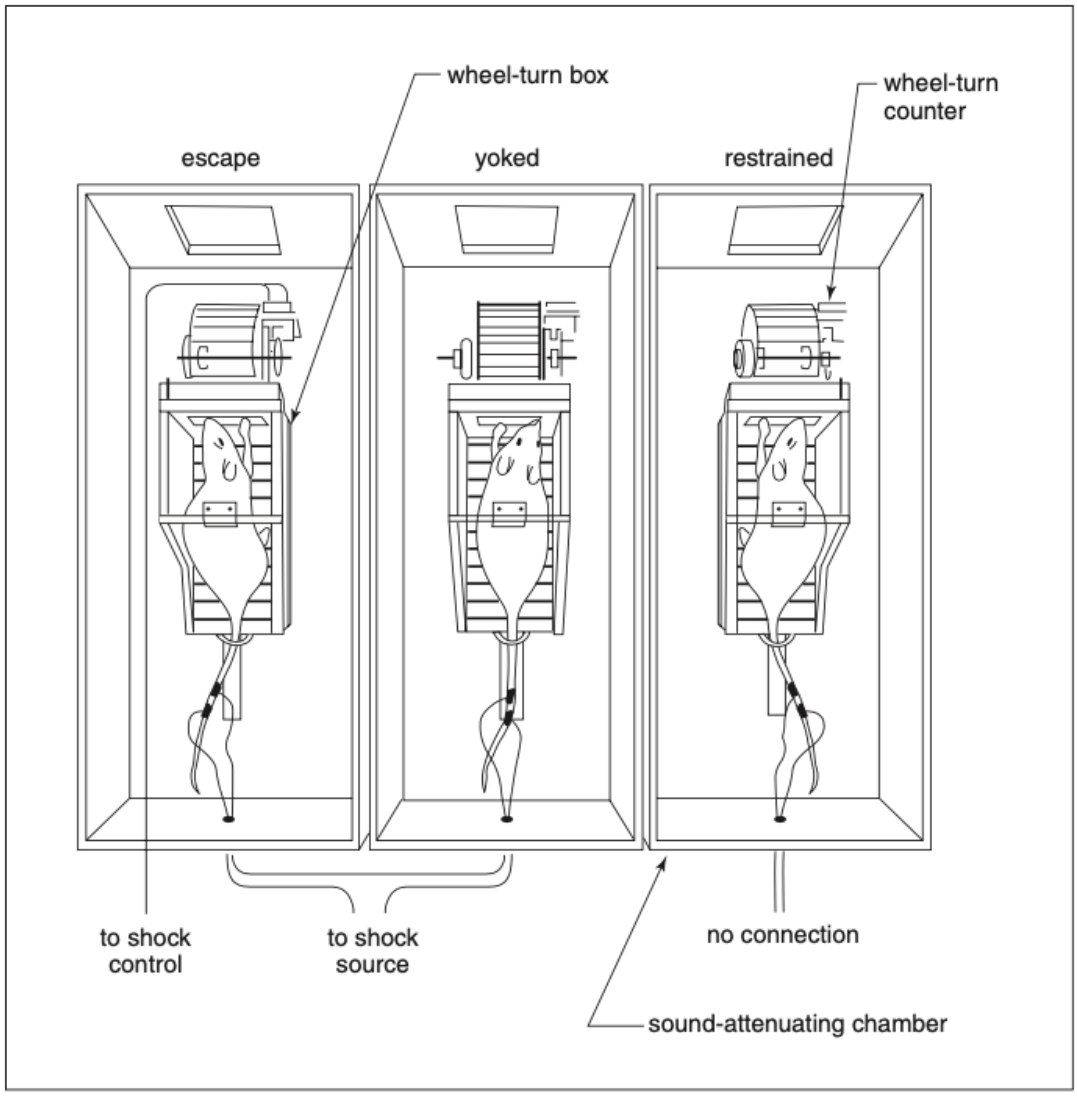
1.2.1 Learned Helplessness and the Aetiology of Depression

Over 50 years ago, Maier and Seligman (1967; 2016) began to study the effects of uncontrollable stress, and their work laid the foundation for what is now one of the dominant animal models of depression (Pryce et al., 2011; Vollmayr & Gass, 2013). They focused on instrumental control which they operationalized as the ability to terminate an aversive stimulus. Although Maier and Seligman were, at least initially, most interested in seeing how a lack of control may manifest itself, they developed an experimental design that allowed the study of both controllable and uncontrollable stress. Their so-called “triadic design” compares three subject groups, one exposed to escapable electric foot shocks (controllable stress), one subjected to inescapable shocks (uncontrollable stress), and a control group not exposed to any

stress (Figure 1). Each of the animals that can terminate the stressor, e.g., by turning a wheel, is yoked to an animal that cannot escape the aversive stimulation. This setup ensures an equal number, duration, and overall pattern of shocks in both groups such that effects of controllability can be cleanly separated from effects of stress.

Figure 1

The Triadic Design



Note. From "Rodent Models of Depression: Learned Helplessness Using a Triadic Design in Rats" by Drugan, 2001, *Current Protocols in Neuroscience*, *14*(1), Supplement 8.10B.4 (https://doi.org/10.1002/0471142301.ns0810bs14). Original graphic from "Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain" by Weiss et al., 1981, *Brain Research Reviews*, *3*(2), p. 173. Copyright 1981 by Elsevier/North-Holland Biomedical Press.

In a series of such experiments, animals showed increased passivity, anxiety and neophobia, along with reduced social interaction and food intake in response to inescapable stress (Maier & Seligman, 2016). Accordingly, lack of control over a stressor appeared to exacerbate its effects. The most striking finding, however, was that in animals that had been exposed to uncontrollable stress this experience appeared to generalize. Following the induction of uncontrollable stress, the animals failed to escape from a stressor they could easily have terminated (Maier & Seligman, 2016; Overmier & Seligman, 1967; Seligman & Maier, 1967). Termed "learned helplessness" (LH), this phenomenon held true across a variety of species, such as dogs (Seligman & Maier, 1967), rats (Drugan, 2001), and fish (Padilla et al., 1970), but also humans (Hiroto & Seligman, 1975). Early translational research revealed that participants were susceptible to developing helplessness even if the subsequent task was of a different modality, e.g., a cognitive problem following an uncontrollable physical stressor (Miller & Seligman, 1975). Whereas subjects appeared to recover with time, the experience of another uncontrollable stressor, shortly after the first, seemed to consolidate the effect and render the subject helpless in the longer term (Lucas et al., 2014; Seligman & Maier, 1967).

Due to the striking resemblance between the symptoms of LH and depression, these findings proved a promising starting point for a better understanding of the aetiology of depression in humans (Henkel et al., 2002; Henn & Vollmayr, 2005; Pryce et al., 2011; Vollmayr & Gass, 2013). Phenomenologically, major depressive disorder is characterized by persistent feelings of sadness, emptiness, hopelessness and/or the loss of interest or pleasure. Additional symptoms may include changes in weight and sleep pattern, agitation or retardation, fatigue, diminished concentration, feelings of worthlessness, guilt, and suicidal ideation (American Psychiatric Association, 2013). Owing to these symptoms, individuals suffering from depression experience severe distress and disruptions in various areas of life, e.g., relationships or work. This is reflected in recent statistics that rank depressive disorders amongst the leading causes for disability (Friedrich, 2017; James et al., 2018). In recognition of the parallels to LH, the view gained traction that experiencing a lack of control may evoke a generalized expectation of low control over the environment, accompanied by feelings of helplessness and hopelessness, which can eventually culminate in full-blown clinical depression (Miller & Seligman, 1975; Pryce et al., 2011; Vollmayer & Gass, 2013). Many researchers reported findings that tie in well with the general idea. A recent example comes from Soral et al. (2021) who observed that the longer participants experienced incontingency between their actions and the outcomes, the less intentional binding (a measure of implicit sense of agency) they subsequently showed. This finding is thus consistent with the notion that

the experience of a lack of control can propagate, leading to changes in control beliefs. In another study, uncontrollability appraisals of recent negative life events were found to be associated with symptoms of depression (Fasset-Carman et al., 2019).

Although other theories have criticized and expanded the LH model of depression (e.g., incorporating inter-individual differences in attributional style; Abramson et al., 1978), it remains prominent and relevant.

1.2.2 Stress Immunization Through the Experience of Control

The past years have seen a steady rise in the prevalence of major depression worldwide, prompting calls to intensify research on treatments and prevention (Steffen et al., 2020). In this regard, studies on LH offer not only insights into the aetiology of the condition, but also starting points for treatments if viewed from a different angle. Whereas a lack of control was associated with highly unfavourable stress responding, the experience of control appeared to mitigate stress effects. In fact, many researchers observed a beneficial effect of control experience over a stressor, e.g., on activity and escape behaviour (Maier & Seligman, 2016), executive control functions (Henderson et al., 2012), fear extinction (Baratta et al., 2007; Hartley et al., 2014), and persistence through setbacks (Bhanji et al., 2016). Lucas et al. (2014) noted that, while it takes only a single experience of controllable stress for rats to show operational controllability (i.e., successful escape from a stressor), further training can additionally lead to "emotional controllability" (i.e., reduced fear responding). They suggest that it is this latter construct which is most predictive of active and successful stress coping. Perhaps emotional controllability in animals can be likened to a consolidated belief in agency as described previously. In general, findings across animal studies indicate that the effects of controllable stress last for at least a period of days, if not months (Amat et al., 2006, 2010; Maier & Watkins, 2010). Hence, researchers concluded that the experience of control conferred a protective effect, akin to a "stress immunization" (SI; Maier & Seligman, 2016).

In order to harness this knowledge for effective interventions, the underlying mechanisms needed to be better understood.

1.2.3 Neurobiological Mechanisms of Stressor Controllability Effects

Taking advantage of the possibilities for high-resolution imaging offered by animal models, Maier and Watkins (2005, 2010) tracked the neurobiological basis of stressor controllability effects. Research had already shown that the fight/flight response appeared to

be mediated by the dorsal periaqueductal grey (dPAG; Amat et al., 1998; Bandler & Depaulis, 1991; Deakin & Graeff, 1991), while the amygdala mediated fear/anxiety (Davis, 1992; Kim & Jung, 2006). In response to inescapable stress, subjects subsequently displayed inhibited dPAG function and enhanced amygdala activation (Graeff et al., 1996). Based on these findings, the researchers uncovered a key role of the dorsal raphe nucleus (DRN), a relatively small structure located on the midline of the brainstem (Maier & Watkins, 2005). The DRN is strongly connected with both cortical and subcortical regions as it supports serotonergic innervation (Ishimura et al., 1988; Ren et al., 2018). More specifically, it has inhibitory projections to the dPAG and provides excitatory input to the amygdala (Graeff et al., 1996; Figure 2a) and therefore presented a candidate most likely involved in LH and SI circuits.

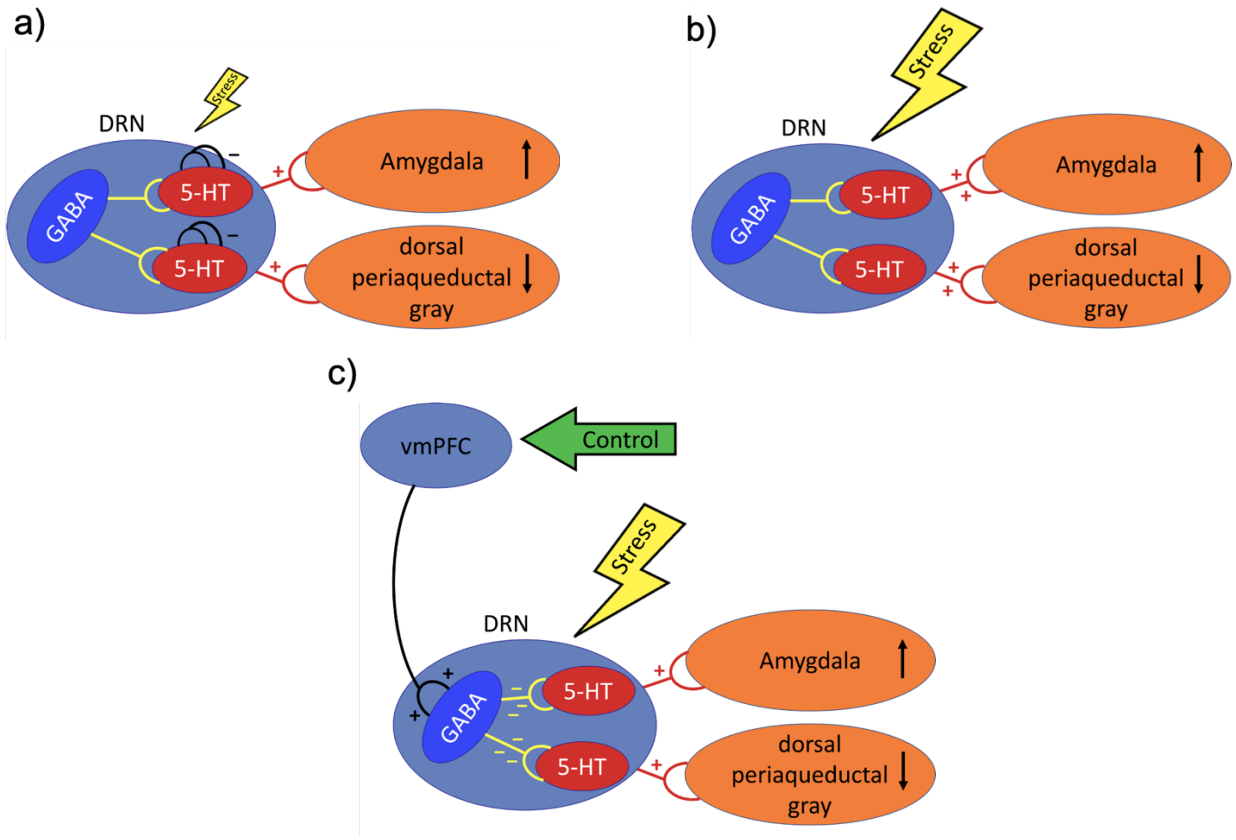
Grahn et al. (1999) employed in vivo microdialysis to study serotonin levels in the DRN in live animals subjected to escapable and inescapable stress. They observed a general increase in serotonin levels upon stress onset, but while levels dropped in the escapable condition once the animal had detected control, they remained elevated after inescapable stress. Although the DRN has inhibitory autoreceptors that function in a self-regulatory capacity to limit serotonergic activity, these appear desensitized and effectively disabled under very high levels of serotonin (Maier & Seligman, 2016). Exposure to inescapable stress evidently produces such a large increase in serotonin that the autoreceptors are down-regulated, leading to a sensitization of the DRN serotonergic neurons, which can last for several days (Maier & Seligman, 2016; Rozeske et al., 2011; Figure 2b). In line with this, studies on LH had found previously that symptoms proved quite long-lasting (Lucas et al., 2014).

In search of the mechanism that caused serotonin levels to drop rapidly upon detection of control, Maier and colleagues reasoned that cortical regions must be involved. After all, these receive somatomotor and somatosensory input and can perform the complex computational processes necessary for registering instrumental control (Fuster, 2015; Maier & Seligman, 2016). Since the DRN mainly receives cortical projections from the ventromedial prefrontal cortex (vmPFC; Peyron et al., 1997), this brain region was therefore targeted. More specifically, glutamatergic neurons from the prelimbic region of the vmPFC synapse on GABAergic interneurons in the DRN (Maier & Seligman, 2016). The vmPFC thus inhibits serotonergic neurons in the DRN (Figure 2c). To confirm the hypothesis that the vmPFC is selectively activated under escapable stress, exerts top-down control over the DRN and thus attenuates the stress response, Baratta et al. (2009) conducted an experiment using retrograde tracers. They injected these into the DRN and watched them trace back, eventually labelling all cell bodies in the vmPFC that project to the DRN. With the labels in place, the group

assessed the neuronal activation of the projecting neurons in response to escapable shock, inescapable shock, or no shock. As expected, only escapable shock activated projections from the vmPFC to the DRN. Critically, this signalling pathway was shown to be necessary for the protective effect of control to manifest (Amat et al., 2005). Taking it further, experiments could demonstrate that direct activation of this pathway via a pharmacological agent, prevented the animal from showing the typical passivity otherwise displayed under inescapable stress (Amat et al., 2008, 2016).

Figure 2

Neurobiological Underpinnings of Stressor Controllability



Note. a) Stress triggers serotonergic projections from the DRN to the amygdala and dPAG, exciting the former and inhibiting the latter. Negative feedback loops constrain the magnitude of serotonergic output from the DRN. b) Inescapable stress shuts down the autoreceptors within the DRN, resulting in increased serotonergic output and correspondingly enhanced stress responding in the amygdala and dPAG. c) Upon detection of control, the vmPFC sends excitatory input via glutamatergic projections to GABAergic interneurons within the DRN. In turn, these inhibit serotonergic cells and thereby constrain the stress response. DRN = dorsal raphe nucleus; dPAG = dorsal periaqueductal grey; vmPFC = ventromedial prefrontal cortex; 5-HT = Serotonin. Adapted from "Learned helplessness at fifty: Insights from neuroscience" by Maier & Seligman, 2016, *Psychological Review, 123*(4), p. 356 (https://doi.org/10.1037/rev0000033). Copyright 2016 by American Psychological Association.

To summarize, these discoveries represent major steps in charting the mechanisms of LH and SI. A number of studies have successfully translated findings on stressor controllability to humans on a cognitive-behavioural level (Hartley et al., 2014; Henderson et al., 2012) and there is emerging evidence for the involvement of the vmPFC and amygdala also in humans (Kerr et al., 2012; Salomons et al., 2015; Wang & Delgado, 2021). Despite this, human research on the neurobiological underpinnings still lags behind – especially with regard to SI.

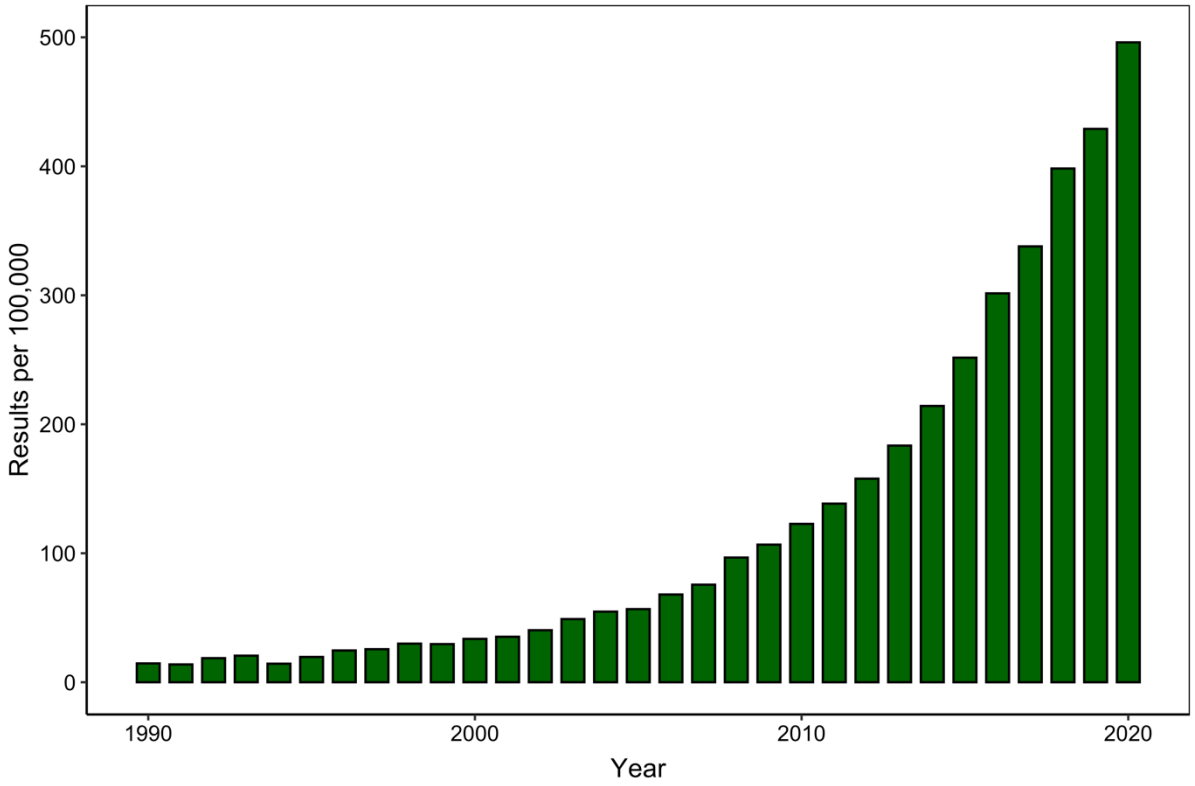
Given that stressor controllability has been shown to be critically implicated in the development of depression and other mental disorders (Fassett-Carman et al., 2019; Pryce et al., 2011; Wadsworth, 2015), a better understanding of the mechanisms involved can substantially aid efforts for treatment and prevention. The latter in particular has received growing attention among researchers in recent years. While for many years studies mainly examined risk factors and the processes by which these translate into disease, research today is increasingly health-oriented as protective factors and resilience mechanisms have moved into focus (Kalisch et al., 2015, 2017; Malhi et al., 2019; Masten, 2018).

1.3 Resilience

The past three decades have witnessed an exponential rise in scientific publications addressing issues around resilience (Figure 3). Nevertheless, discussions on how to define and operationalize this construct are still ongoing.

Figure 3

Results on "Resilience" per 100,000 Citations in PubMed from 1990-2020



Note. The proportion of publications on resilience for each year was obtained through "PubMed by Year" (Sperr, 2016), searching for the keyword "resilience".

Broadly speaking, resilience refers to a good mental health outcome following an encounter with a stressor or adverse life event (Kalisch et al., 2017; Malhi et al., 2019; Masten, 2007). Across several studies that examined responses to adversity, the results showed that a significant proportion of participants remained unaffected by stress (Cohen et al., 2019; Galatzer-Levy et al., 2018). In his seminal work on grief and trauma, Bonanno (2004) concluded that resilience is often the most common response. Indeed, many studies tracking the course of health and dysfunction following events such as a terrorist attack (Bonanno et al., 2006; Durodié & Wainwright, 2019), military deployment (Bonanno et al., 2012; Yurgil et al., 2021), natural catastrophes (Bryant et al., 2014; Lowe et al., 2015; Schwind et al., 2019),

maltreatment in childhood (Miller-Graff & Howell, 2015), or the loss of a loved one (Bonanno et al., 2002) showed stable trajectories or maintained mental health for the majority of participants. That is not to say, of course, that such events do not cause considerable disruption and suffering to a great number of people.

In search of predictors of resilience, research identified different factors including hardiness (Kobasa et al., 1982; Maddi, 2013), optimism (Carver et al., 2010), social support (Cobb, 1976; Ozbay et al., 2007), and grit (Tang et al., 2021). Based on these findings, different self-report scales emerged that essentially summarize the degree to which an individual possesses these relevant components as a measure of resilience (Connor & Davidson, 2003; Wagnild & Young, 1993).

Across studies, resilience has not only been discussed as resistance to adversity, but also in terms of a "bouncing back" (its literal meaning; Merriam-Webster, 2021) or quick recovery of mental health after stress exposure (Smith et al., 2008). Whereas the absence of a response to a stressor seems favourable, many would expect at least a slight temporary deviation from baseline levels (Infurna & Luthar, 2018). The magnitude of change may be influenced by features of the stressor, as previously mentioned, but a resilient response is generally characterized by a rapid return to baseline levels (Kalisch et al., 2017). Furthermore, resilience has been discussed in terms of adaptation (APA, 2012) and even thriving in response to adversity (Carver, 1998). The concepts of both post-traumatic growth (Tedeschi et al., 1998) and psychosocial gains (Mancini, 2019) describe the individual as better off after a stressor, beyond the recovered baseline levels.

Although resilience has often been conceptualized as a stable trait that can be captured by questionnaire (Schultze-Lutter et al., 2016), the terms resistance, recovery, adaptation, and growth all suggest a comparison between pre- and post-stressor levels which a cross-sectional self-report study can hardly afford. Furthermore, questionnaire scores may also confound different constructs that entail distinct contributions to resilience.

In order to establish a framework for future resilience research, an international group of scientists has recently put forward a position paper (Kalisch et al., 2017). They define resilience as "the maintenance or quick recovery of mental health during and after exposure to significant stressors" (p. 786) and they rebuff the claim that it constitutes merely the opposite of vulnerability. After all, resilient and vulnerable phenotypes are not necessarily mutually exclusive, but often co-present within the same disorder (Zannas & West, 2014). Moreover, they highlight that resilience should not be viewed as an innate disposition but rather as the result of a "dynamic process of adaptation to the given stressful life circumstances" (p. 786),

and which may, therefore, be subject to change. It is thus explicitly operationalized as an outcome to be measured by contrasting participant data before and after an adverse event. Previously discovered variables and predispositions that have been shown to be predictive of resilience are grouped under the umbrella term “resilience factors”. In general, this definition advocates for more longitudinal studies to go beyond phenomenological research and to investigate the mechanisms that translate the identified factors into high or low resilience (Kalisch et al., 2015, 2017). Recent forays into the neural and molecular processes of stress resilience provide promising contributions for a more causal understanding of resilience in response to adversity (Feder et al., 2019; Karatsoreos & McEwen, 2013; Osório et al., 2017; Russo et al., 2012).

In this respect, the effects of stressor controllability and especially the associated neurobiological changes merit further investigation. As outlined previously, control (in its many forms) represents a powerful modulator of the stress response (Steptoe & Poole, 2016) and researchers have begun elucidating the mechanisms through which more persistent beliefs in agency (perceived self-efficacy and locus of control) manifest (Moscarello & Hartley, 2017) and affect mental health (Ly et al., 2019). Research on the neurobiological level strongly implicates the vmPFC, DRN, as well as stress-related brain regions such as the amygdala and their interactions (Maier & Seligman, 2016). However, these findings are largely constrained to the animal domain and human research has thus far mainly focused on the negative consequences of experiencing a lack of control, not the beneficial effects of being in control. Therefore, framing research on stressor controllability in a resilience context could bring a much-needed change in perspective and foster understanding of how we can utilize control to optimize stress responding and, in turn, promote mental health.

2. Methods

This section outlines two methods relevant to this dissertation: functional magnetic resonance imaging (fMRI) and translational research. While the former was used in the second study, the latter provides a framework in which both studies can be discussed.

2.1 Functional Magnetic Resonance Imaging

Building on conventional magnetic resonance imaging (MRI), fMRI was developed about 30 years ago as a neuroimaging technique to measure brain activation (Bandettini, 2012; Kwong et al., 1992; Ogawa et al., 1992). The method capitalizes on the finding that neuronal activation is coupled to cerebral blood flow (Ogawa et al., 1990a). When neurons are firing, their energy demand increases, triggering a surge in blood flow to the activated brain area in order to provide the required glucose and oxygen to support neuronal functioning (Huettel et al., 2014). Thus, variation in blood oxygenation in the brain may serve as an (indirect) indicator of changes in activation (Ekstrom, 2010). Specifically, fMRI targets the difference in magnetic susceptibility of oxygenated and deoxygenated blood. While the former is non-magnetic or diamagnetic, the latter evidently has paramagnetic properties that can alter magnetic resonance images (Ogawa et al., 1990a,b). In a proof-of-concept study, Ogawa et al. (1990b) successfully demonstrated in vivo assessment of the blood oxygenation level-dependent (BOLD) signal.

The typical signal shape in response to an intense but brief period of neural stimulation has been formalized in the canonical haemodynamic response function (HRF; Buckner, 1998; Soares et al., 2016). It is characterized by an initial dip in BOLD signal reflecting the sudden draining of oxygen as neurons begin to fire, followed by a steep rise in signal due to the influx of oxygenated blood to the activated region. Once neuronal firing ceases, the signal drops and temporarily even reaches values below the baseline (negative undershoot). Because there is a time lag between the onset of neuronal firing and the increase in cerebral blood flow, fMRI has lower temporal resolution compared to other neuroimaging methods such as electroencephalography (EEG; Bunge & Kahn, 2009). Nonetheless, it offers a non-invasive technique for obtaining images with high spatial resolution (Bandettini, 2009; Huettel et al., 2014) and has therefore become well-established in the neuroscientific community.

In order to study task-dependent brain activation, the start of the experiment is synchronized with the fMRI sequence (Poldrack et al., 2011). Thus, by matching the time course of measurement and presentation of stimuli, the BOLD signal for different experimental

conditions can later be extracted and contrasted. In short, fMRI permits the detection and localization of task-based brain activation (Logothetis, 2008; Soares et al., 2016).

2.2 Translational Research

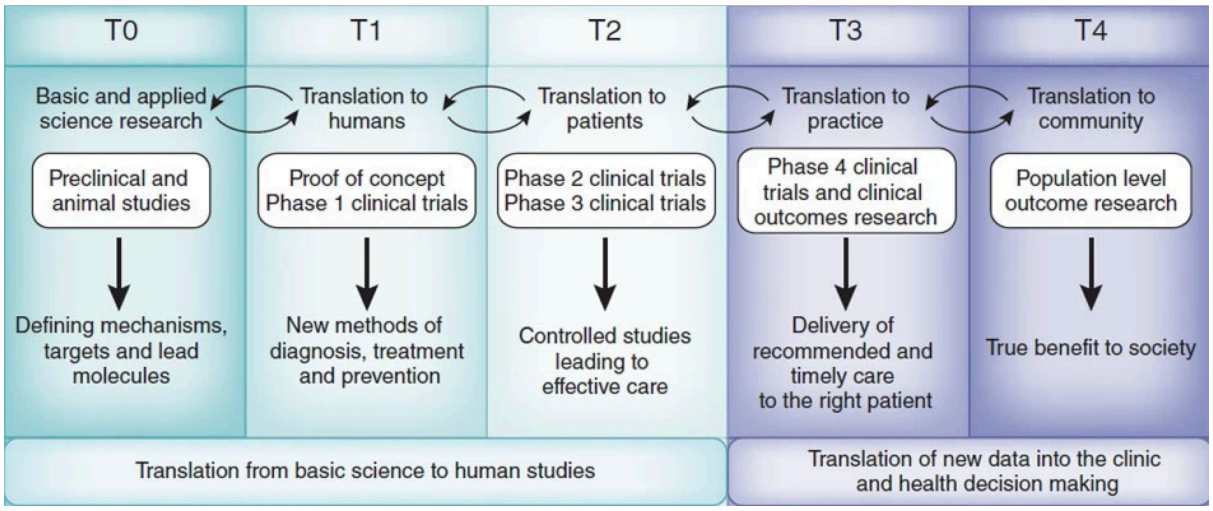
Translation describes the "carrying across" of findings from basic science to the clinical or community context (Austin, 2018; Fang & Casadevall, 2010). The phrase "from bench to bedside" is commonly associated with translational research (Woolf, 2008), but fails to capture the many phases of the essentially iterative process. According to Christopher Austin, the director of the US National Academy for Advancing Translational Sciences (NCATS):

> NCATS' definition of translation is broad and inclusive: translation is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioural changes. This definition is intentionally holistic with regard to directionality, stage of intervention development and modality. (2018; p. 455)

Based on a systematic literature review, Fort et al. (2017) describe the five phases of translational research (T0-T4; Figure 4) on which there is increasing consensus. T0 encompasses mainly basic research, e.g., animal studies, the discoveries and ideas of which are subsequently tested in humans in phase T1. The bridge from basic science to clinical applications spans to phase T2, which involves assessment in patients. Phases T3 and T4 cover the implementation and dissemination of research advances in routine practice as well as the evaluation of outcomes and effectiveness at the population level. This final stage may inform research in phase T0 by highlighting potential novel targets and mechanisms which merit further investigation (Venniro et al., 2020).

Figure 4

The Five Phases of Translational Research



Note. Adapted from "Unraveling the autoimmune translational research process layer by layer" by Blumberg et al., 2012, *Nature Medicine, 18*(1), p. 37 (https://doi.org/10.1038/nm.2632). Copyright 2012 by Nature America, Inc.

In response to an overall enthusiastic embracing of translational research, some have voiced concerns that basic science may take a back seat (Fang & Casadevall, 2010). However, most researchers acknowledge that a successful translational pipeline requires a concerted interdisciplinary effort (Mace & Critchfield, 2010; Marantz et al., 2020; Petscher et al., 2020).

3. Scientific Objective of this Dissertation

A body of research has shown that controllability is a highly relevant factor in processing and responding to stressors (Maier & Seligman, 2016), which can have a long-term impact on mental health (Pryce et al., 2011; Wadsworth, 2015). In particular, the experience of a lack of control over an adverse event can engender a generalized belief of low agency, which in turn can prevent the person from actively dealing with future difficulties (Moscarello & Hartley, 2017). Instead, they may show resignation and, in the worst case, develop clinical depression (Liu et al., 2015; Ly et al., 2019). By contrast, learning that one's actions are consequential in obtaining a goal, e.g., to terminate a stressor, appears very protective (Amat et al., 2010; Wang & Delgado, 2021).

These divergent effects of stressor controllability are described in the literature on LH and SI, respectively. Since much of the human research draws on earlier animal experiments, the work is essentially translational. In view of this, it should be noted that despite the many years of research, certain gaps remain. Although human research largely corroborates results from animal models, it is rather heterogeneous in its methodology, highlighting a need for more thorough translations. Furthermore, studies have mainly been concerned with the negative effects of uncontrollable stress. The increasing focus on protecting and maintaining mental health presents a welcome opportunity to expressly target the positive effects of control on stress processing in the context of resilience. Moreover, only a few studies have so far looked at the neurobiological mechanisms of stressor controllability in humans. This dissertation therefore has the following objectives:

(1) Considering that many of the human studies investigating LH are not explicitly translational in design, a more deliberate transfer of established animal paradigms to humans seems useful. The first aim therefore is to develop a translational design to further examine the effects of uncontrollable stress in humans. More specifically, the experimental setup should be firmly based on the established triadic animal design, allowing more direct comparisons. At the same time, the wealth of both animal and human research to date should be reviewed in detail so that obvious species-related differences and questions of feasibility can be addressed with due clarity and care. In the end, the resulting paradigm should provide a flexible tool for future translational research.

(2) The second aim is to expand our understanding of the neurobiological processes involved in SI in humans. Based on the newly developed translational paradigm, an MR compatible adaptation should be employed which allows the investigation of the neural correlates of stressor controllability in humans. In particular, the focus is on controllability-dependent differences in the processing of acute stress.

The empirical studies included in the next sections predominantly reflect the T1 phase of translational research, in which findings from animal research are translated to humans. Although the studies are therefore more concerned with the methodological and neurobiological aspects of stressor controllability, they were conducted in light of recent endeavours to identify resilience mechanisms (Kalisch et al., 2015, 2017). The relevance of controllability for stress resilience and more specifically the contribution of these two studies to more applied research is therefore addressed in the discussion. Closely related and currently ongoing projects are likewise drawn upon to emphasize the many future research directions and potential applications around controllability.

4. Empirical Studies

4.1 Study 1: A Translational Paradigm to Study the Effects of Uncontrollable Stress in Humans[2,3]

[2] Publication reference: Meine, L. E.*, Schüler, K.*, Richter-Levin, G., Scholz, V., & Wessa, M. (2020). A Translational Paradigm to Study the Effects of Uncontrollable Stress in Humans. *International journal of molecular sciences*, *21*(17), 6010. https://doi.org/10.3390/ijms21176010. *Both authors contributed equally to this work.

[3] Please note that the order of sections and certain formatting has been changed to enhance readability and ensure consistency in this dissertation, respectively.

4.1.1 Summary of Study 1

Theories on the aetiology of depression in humans are intimately linked to animal research on stressor controllability effects. However, explicit translations of established animal designs are lacking. In two consecutive studies, we developed a translational paradigm to study stressor controllability effects in humans. In the first study, we compared three groups of participants, one exposed to escapable stress, one yoked inescapable stress group, and a control group not exposed to stress. Although group differences indicated successful stress induction, the manipulation failed to differentiate groups according to controllability. In the second study, we employed an improved paradigm and contrasted only an escapable stress group to a yoked inescapable stress group. The final design successfully induced differential effects on self-reported perceived control, exhaustion, helplessness, and behavioural indices of adaptation to stress. The latter were examined in a new escape behaviour test which was modelled after the classic shuttle box animal paradigm. Contrary to the LH literature, exposure to uncontrollable stress led to more activity and exploration; however, these behaviours were ultimately not adaptive. We discuss the results and possible applications in light of the findings on learning and agency beliefs, inter-individual differences, and interventions aimed at improving resilience to stress-induced mental dysfunction.

4.1.2 Introduction

"Don't stress over what you can't control."—a common piece of advice that seems easier said than done. In fact, empirical evidence shows that lack of control over a situation makes it all the more stressful (Steptoe & Poole, 2016). Human stress theories, as well as extensive animal research, have suggested and compellingly demonstrated how controllability over an aversive event significantly modulates the corresponding reaction and appraisal (Maier & Seligman, 2016).

In human research, stressor controllability has thus far mostly been discussed in the context of depression pathogenesis, referring to the theory of LH (Maier & Seligman, 2016; Pryce et al., 2011; Seligman & Maier, 1967). The experience of uncontrollable stress induces a failure to escape aversive stimulation, alongside increased passivity and anxiety, overall termed LH. In the 1960s, Seligman and Maier (1967) developed the triadic design which compares three groups of subjects, one exposed to escapable electric shocks, another exposed to inescapable shocks, and a third group not receiving any aversive stimulation. Importantly, animals in the inescapable stress group are yoked to animals in the escapable condition, in order to ensure that both groups receive precisely the same number, duration, and overall pattern of shocks. Thus, the effects of controllability can be separated from mere stress effects. Subjects are subsequently tested in a novel environment, which exposes them to easily escapable shocks (shuttle box paradigm; Chourbaji et al., 2005; Overmier & Seligman, 1967; Seligman & Maier, 1967). Results consistently showed that, in contrast to the other groups, animals which had previously experienced inescapable stress, now failed to escape. Fifty years of research more thoroughly investigating this finding revealed that animals showed symptoms of greater passivity, reduced social interaction, neophobia, and decreased food intake in response to inescapable stress (Maier & Seligman, 2016)—behaviours mirrored in the symptoms of anxiety and depression in humans (Pryce et al., 2011). Indeed, studies in humans linked the lack of control over a stressor with increased subjective stress (Bollini et al., 2004), anxiety (Havranek et al., 2016), pain intensity perception (Bräscher et al., 2016), deficits in selective attention (Henderson et al., 2012), and impaired fear extinction learning (Hartley et al., 2014).

It has been pointed out previously that "LH is a proven translational concept" (Pryce et al., 2011, p. 244). In fact, as early as the 1970s, researchers applied the triadic design to humans, subjecting groups of university students to either controllable noise, uncontrollable noise, or no noise (Hiroto, 1974; Hiroto & Seligman, 1975). Thornton and Jacobs (1971) employed electric shocks to induce differential effects of stressor controllability. Importantly, these early

translations stayed close to the animal triadic design, focusing on proper yoking and even incorporating a test akin to the shuttle box. In particular, researchers assessed participants' success in terminating noise bursts by moving a lever from side to side (Alloy et al., 1984; Hiroto, 1974; Hiroto & Seligman, 1975). Exploiting the possibility for more complex cognitive testing, modifications of the triadic design were introduced which required participants to solve more demanding cognitive tasks in order to terminate aversive stimulation (Bongard, 1995; Hiroto & Seligman, 1975). With the advent of more powerful neuroimaging tools, studies also investigated the neural correlates of stressor controllability in humans, focusing more on group differences during stress exposure rather than on subsequent affective, cognitive, or behavioural assessments. Promising findings suggest modulations in event-related potentials (Diener et al., 2009; Reznik et al., 2017), in activation in e.g., the vmPFC (Kerr et al., 2012) and the amygdala (Salomons et al., 2015), as well as in connectivity measures (Bräscher et al., 2016). Human researchers have veered in different directions to study particular aspects potentially implicated in or altered by stressor controllability. However, there still remains a gap in translational experimental study designs that incorporate the triadic stress induction design as well as measures assessing stressor controllability effects on affect, cognition, and behaviour. Whereas animal research can boast established, well-standardized paradigms (Chourbaji et al., 2005), human studies are largely heterogeneous concerning their experimental setup and the outcome variables they investigate. To illustrate this, stressors ranged from physical stimuli, i.e., electric shocks (Hartley et al., 2014; Havranek et al., 2016), thermal stimulation (Bräscher et al., 2016; Salomons et al., 2015), and loud sounds (Bollini et al., 2004; Henderson et al., 2012) to video clips of snakes (Kerr et al., 2012) and unsolvable reasoning tasks (Bauer et al., 2003). Probably for reasons of feasibility, many studies opted for a within-subject design, rather than comparing three groups according to the triadic design. Salomons et al. (2015) omitted a control group which did not receive any aversive stimulation, contrasting instead only two groups. Diener et al. (2009) employed a forewarned design, i.e., participants in the controllable stress group were able to completely avoid stressful stimulation which led to imperfect yoking between conditions.

This lack of standardized procedures hampers ongoing efforts to fully characterize the mechanistic underpinnings of how stressor controllability modulates our response to stress and its consequences on behaviour, affect, and cognition. Because individuals' affect and cognitive functioning can be more readily assessed in humans than in animals, human research has mainly focused on self-report and cognitive tasks to assess effects of stressor controllability. In contrast, animal studies mostly rely on behavioural read-outs. Therefore, broader analyses

of stressor controllability effects in humans appear useful in strengthening translational approaches.

To this end, we sought to fill the gap in translational studies using a paradigm which more closely translates the established triadic animal design, and which provides a feasible means to investigate stressor controllability effects in humans on an affective, cognitive, and behavioural level. In two consecutive studies, we developed, validated, and adapted an experimental paradigm to study stressor controllability effects in humans. In the first study, we compared three experimental groups: (1) an escapable stress group exposed to controllable stress (EC), (2) a yoked group exposed to uncontrollable stress (YC), and (3) a control group without stress exposure (CC). Our main hypotheses were related to effects of stressor controllability (and not stress, per se), however, we included a control group to validate our stress-induction procedure with respect to both the mere stress effects as well as effects of stressor controllability (manipulation check). In order to characterize these effects on multiple response levels, we assessed RT and subjective ratings on helplessness, exhaustion, and frustration during stress exposure, as well as post stressor changes in affect, escape behaviour, and working memory. With respect to the manipulation check, we verified that EC and YC rated the stressor as aversive and that perceived control ratings differentiated the three groups, with CC reporting highest perceived control, followed by EC, and YC rating lowest perceived control.

Many studies have reported detrimental effects of acute stress on e.g., affect (Eckenrode, 1984; Jacobs et al., 2007) and cognition (Otto et al., 2013; Shields et al., 2016) in humans. Therefore, we expected both stress-exposed groups (EC and YC) to differ from CC in indices assessed during the stress exposure phase (subjective ratings, RT) as well as in subsequently measured affect, escape behaviour, and working memory. Our hypotheses were as follows: First, with respect to assessments during stress exposure, we expected YC to report highest exhaustion, frustration, and helplessness and show longest RT, followed by EC, then CC. Second, related to subsequent (post stress) measurements, we expected YC to show a greater increase in depressive symptoms, anxiety, and negative mood as well as a greater decrease in positive mood compared to EC. As CC was not exposed to stress, we expected no change in affective state in this group. For the escape behaviour test (comprising a stress-free exploration phase and subsequent exposure to a familiar stressor with the possibility to escape), we expected YC to show less exploration behaviour, fewer successful escapes from stress, and less efficiency in escaping stress compared to EC. Based on the animal literature, we expected CC to fall in between YC and EC with respect to successful escapes and escaping efficiency.

Furthermore, we hypothesized that YC would perform worst in the working memory test, followed by EC, with CC scoring highest.

Although group differences indicated successful stress induction in the first study, the manipulation failed to differentiate groups according to controllability-related effects on subsequent measurements of affect, cognition, and escape behaviour. In the second study, we therefore employed an improved paradigm, comparing EC and YC only, and testing the same hypotheses described above. In particular, we examined subjective ratings of helplessness and exhaustion (omitting frustration due to time constraints), RT, changes in affect, and escape behaviour. Due to time constraints, working memory was not assessed in this study.

4.1.3 Methods

Study 1: Initial Paradigm

Participants. A total of $N = 87$ healthy participants aged 18–40 took part. Recruitment included a semi-structured telephone interview similar to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV axis I disorders (SCID-I) to ensure that participants had no current or lifetime DSM-IV axis I disorders. Because the study involved a reading task, we excluded individuals with dyslexia. The complex laboratory setup during parallel testing of multiple participants in the second testing session (see "Procedure" in the next section) led us to constrain recruitment to right-handed individuals only. Further exclusion criteria comprised poor German language skills, current pregnancy, cardiac problems, tinnitus, and any other circumstances putting participants at risk during the stress induction procedure. Two participants broke off testing and three were excluded from analysis because of faulty experiment setup, poor German skills, and figuring out the experimental manipulation, respectively. Another two were excluded because health risks came up and they did not complete testing. All remaining participants were randomly assigned to three experimental groups: (1) EC ($n = 27$, age: $M = 23.48$, $SD = 3.74$, 56% female), (2) YC ($n = 26$, age: $M = 25$, $SD = 4.26$, 58% female), and (3) CC ($n = 27$, age: $M = 25.85$, $SD = 4.3$, 56% female). The study was approved by the ethics committee of the Institute of Psychology, Johannes Gutenberg University Mainz (2017-JGU-psychEK-003, 26/5/2017) and was conducted in accordance with the declaration of Helsinki. All participants provided written informed consent and were remunerated with 40 EUR.

Procedure. Participants attended two testing sessions. In the first session, they were provided with information on the study and planned procedures were explained briefly. We then assessed demographic variables and other questionnaires (not reported here) via the online platform Social Science Survey (Leiner et al., 2019). In addition, working memory was measured using the German version of the Wechsler Adult Intelligence Scale (Petermann, 2012). Finally, participants completed a test of alertness which is part of the Tests of Attentional Performance battery (Zimmermann & Fimm, 2002). The first session lasted 2 h. The second session was conducted in small groups of up to three participants—all assigned to the same experimental condition (EC/YC/CC). Participants were seated at their own desks, with walls restricting their field of view to their respective computer screens. We reminded participants that our research aimed at better understanding how individuals deal with stress. Therefore, they would be exposed to stressful stimulation in some of the tasks (CC was exposed to stress during the escape behaviour test; see page 32). Concerning stress induction (see the following section), EC and YC were told they could terminate the stressor, whereas CC participants were informed that they could effectively shorten trials to finish the task quicker. All participants were informed that their participation was voluntary and that they could stop the experiment at any time. First, participants reported their current mood, levels of anxiety, and depression (pre-stress assessment). Next, we calibrated shock intensity and participants underwent the stress induction procedure. This was followed by a post stress assessment of affect, a test of escape behaviour, and a reading span task. Finally, YC participants were debriefed and informed that—contrary to instruction—their responses had had no effect on stress durations. They subsequently re-consented. The second session also lasted 2 h.

Stress Induction. EC and YC were subjected to escapable or yoked inescapable aversive stimulation, respectively. The stressor consisted of electric shocks combined with intermittent 100ms white noise bursts at 85dB. Shocks were administered via a Digitimer DS7A current stimulator through an electrode attached to the back of the participant's left hand. Acoustic noise was conveyed via Sennheiser HD 380 Pro headphones. At the beginning of data collection, we employed a decibel meter to verify our decibel threshold and to ensure participants' safety. While the acoustic stressor was the same across participants, electric shocks were individually calibrated. After determining the threshold of perception, shock intensity was increased in 0.5 mA increments. Participants were able to administer shocks themselves by pressing a button. They rated each shock on a continuous paper-pencil scale with four anchors: "barely perceptible", "unpleasant", "very unpleasant", and "really painful".

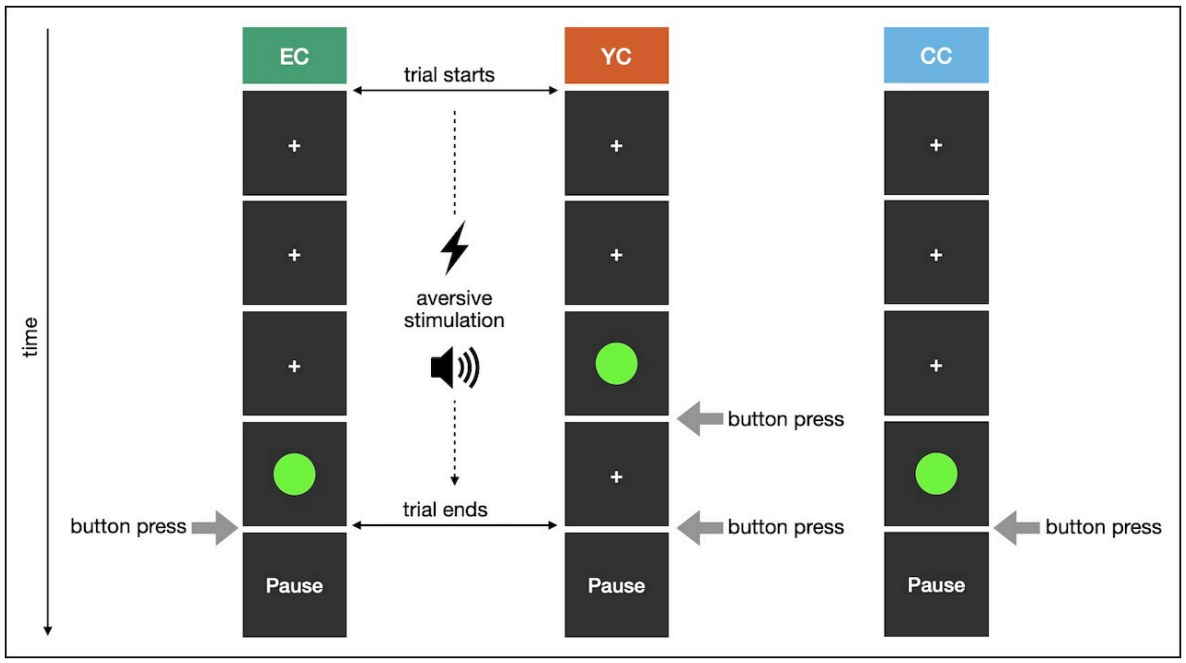
We encouraged participants to give honest responses by emphasizing natural diversity in stimulus perception. Upon reaching a shock intensity that the participant rated as very unpleasant, but not painful (approx. 7–7.5 out of 10), the calibration process was stopped. Shock intensity was maintained at this established threshold throughout the session. One-to-one yoking of EC and YC participants ensured equal number of shocks and duration of white noise across both groups.

Participants underwent 40 trials of stress exposure and were instructed to terminate aversive stimulation by pressing the space bar. In each trial, they received four shocks during six seconds of intermittent noise before a cue prompted them to react. For EC, stressful stimulation was immediately stopped if a response was given within one second after cue onset. In case of missing or late responses, aversive stimulation continued up to a maximum of 15 s. Trials otherwise ended upon stressor termination and were followed by an inter-trial interval lasting one second ±250 ms jitter. For each YC participant, the stress duration was predetermined based on the responses of the yoked EC participant. Moreover, cue onset was shifted forward in time such that YC participants experienced continued aversive stimulation regardless of their reaction. We uniformly distributed cue onsets within four seconds to one second before the yoked EC participant's reaction, which determined the end of stress exposure. This resulted in aversive stimulation stopping immediately or soon after button press in some trials but continuing for a few seconds in others. Thus, YC participants perceived the termination of the stressor as arbitrary and outside of their control. Notwithstanding this group-specific manipulation, our yoking ensured equal stress duration across EC and YC. CC received no aversive stimulation, but shock intensity was nevertheless calibrated. For better comparability, CC participants performed the task with the electrode attached and wearing headphones.

This experiment was implemented in Python 2.7 (Van Rossum & Drake, 2010), using mainly functionalities of the PsychoPy package (Peirce et al., 2019). Figure 1 illustrates the stress induction procedure.

Figure 1

Stress induction in study 1



Note. One trial; EC participant successfully terminated aversive stimulation.

Measurements.

Ratings and RTs during Stress Exposure. During the stress induction, we tracked participants' RTs, and, after every 10th trial, they supplied ratings to the following questions: (1) How aversive do you find the stressor? (2) How much control do you have over the task? (3) How exhausted do you feel? (4) How frustrated do you feel? (5) How helpless do you feel? We used a Likert scale ranging from 1 (not at all) to 7 (very). Note that we asked participants to rate perceived control over the task, not the stressor. This enabled us to compare ratings between all groups, including CC.

Pre-Post Affect Questionnaires. Approximately 10 min before and immediately after stress induction, participants completed two different questionnaires assessing state anxiety and depression, positive affect, and negative affect. The State-Trait Anxiety-Depression Inventory (STADI; Laux et al., 2013) consists of two sub scales for which excellent internal consistencies have been reported: anxiety (Cronbach's α = 0.90) and depression (Cronbach's α = 0.87; Geue et al., 2016). We used the STADI total score as an indicator of global state anxiety and depression. In addition, we examined total scores of the two subscales of the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996) as indicators of positive

(PANASpos; Cronbach's α = 0.85) and negative affect (PANASneg; Cronbach's α = 0.86), respectively.

Escape Behaviour Test. Highlighting our translational approach, we designed a new task inspired by the animal shuttle box paradigm (Chourbaji et al., 2005; Seligman & Maier, 1967; Seligman, 1972). This task assesses passivity and anxiety—behaviours commonly observed following uncontrollable stress in animal studies. After previous exposure to electric foot shocks, animals are placed in a two-compartment environment in which they, again, receive shocks. They can escape by shuttling from one compartment to the other, jumping a small barrier (Chourbaji et al., 2005). Specifically, the task requires some complexity (e.g., a two-way shuttle) in order to observe LH effects. Our escape behaviour test (Figure 4a) focused on translating important features of the shuttle box paradigm: free exploration of an open space without stress exposure, exposure to a familiar stressor, termination of this stressor through the participant's action, and sufficient complexity of the escape task to observe LH effects. A 15 × 15 grid was displayed on-screen, which participants were instructed to navigate, using the arrow keys. Their location was marked by a lighter shading of the respective grid cell. Four "safe spaces" were hidden at random locations on the grid and lit up green if encountered. As subjects had to learn these four random safe locations, we were able to include the element of task complexity, necessary to observe LH effects. Participants were informed that exposure to a stressor was possible, but no further instructions were given. They completed a total of five trials, starting in the middle of the grid each time. Trials started with a ten-second stress-free phase in which participants could freely explore the grid. In a subsequent stress phase, EC and YC encountered the familiar aversive stimulation, whereas CC experienced this stressor for the first time. Stress exposure lasted either until the trial ended after a maximum of 20 s or until the participant moved onto a safe space. Safe space locations remained the same throughout the task. Based on animal research, we chose three measures as indicators of proactive escape behaviour: (a) exploration—number of unique spaces visited within the stress-free phase; (b) escape rate—number of escapes, i.e., successful termination of the stressor by finding a safe space; and (c) efficiency—number of escapes in relation to the amount of activity (sum of moves within time spent on the task). Higher scores indicate less efficient behaviour.

Working Memory. To assess working memory performance, we used a reading span task (von der Malsburg, 2015). Reading span tasks are established measures of working memory capacity (Conway et al., 2005; Daneman & Carpenter, 1980). In short, participants were instructed to memorize and later recall single words which appeared in between unrelated sentences. For each sentence, participants indicated via button press whether or not it made

sense. We employed partial-credit load scoring, which is frequently used in working memory research. The partial-credit load score represents the sum of correctly recalled elements, allowing for little spelling mistakes (for a detailed description, see Conway et al., 2005).
Both the escape behaviour task and the reading span task were implemented in Python 2.7 (van Rossum & Drake, 2010).

Statistical Analysis. We performed a priori comparisons to verify that groups did not differ in sex, age, alertness, or working memory IQ. To assess differences in sex distribution, we computed a chi-square test. For all other comparisons, we employed one-way ANOVAs with group as the between-subject factor, or a Kruskal–Wallis test, if more appropriate. We then examined reported stressor aversiveness and perceived control as manipulation checks for our stress induction and manipulation of stressor controllability, respectively. To account for changes in ratings over trials, we conducted separate two-way repeated measures ANOVA (rmANOVA) with group (stressor aversiveness: EC, YC; perceived control: CC, EC, YC) as the between-subject factor and time (10th, 20th, 30th, 40th trial) as the within-subject factor. Using one-way ANOVA or a Kruskal–Wallis test, we separately investigated group differences in measurements assessed under acute stress (helplessness, exhaustion, frustration, and RT). To account for family-wise error due to the many dependent variables, we applied Bonferroni correction. Next, we investigated stress- and controllability-related effects on subsequently (post stress) measured dependent variables (changes in affective state, escape behaviour, and working memory). We analysed changes in affective state (global STADI score, PANASpos, PANASneg) from pre to post stress induction, using rmANOVAs with group as the between-subject factor and time (pre, post) as the within-subject factor. To investigate escape behaviour indices, we computed scores for exploration, escapes, and efficiency. Since we focused on group differences in exploration during the stress-free phase and in escapes and efficiency during the stress phase, we employed one-way ANOVA or a Kruskal–Wallis test for these analyses. In a final step, we investigated partial-credit load scores as indicators of working memory, using one-way ANOVA. We also applied Bonferroni correction to account for multiple dependent variables in our investigation of stress- and controllability-related effects on subsequently (post stress) measured dependent variables. Only corrected significance levels are reported.

In general, we used box plots to check for outliers. We excluded only extreme outliers (values above third quartile plus three times the interquartile range (IQR) or below the first quartile minus three times IQR). Furthermore, we set our level of significance at $p = 0.05$. For

rmANOVAs, we applied Greenhouse–Geisser correction in case of non-sphericity. Post hoc comparisons were assessed using paired *t*-tests, with Holm–Bonferroni correction (Holm, 1979) applied for multiple testing. Effect sizes are reported as partial η^2 (Cohen, 1973) for ANOVAs and η^2_H for Kruskal–Wallis tests (Tomczak & Tomczak, 2014). Further analyses including time and sex effects are reported in the supplemental material. Data were analysed in R (version 3.6.2; R Core Team, 2019) using the "rstatix" (Kassambara, 2020), "afex" (Singmann et al., 2020), and "lsmeans" package (Lenth, 2016) mainly.

Study 2: Improved Paradigm

Participants. A total of 122 healthy participants aged 18–41, were recruited using the software ORSEE (Greiner, 2015) and they took part in testing sessions in the Mainz Behavioral and Experimental Laboratory (MABELLA) at Johannes Gutenberg University Mainz. Due to time constraints, we decided to use this facility, which offers automated recruitment and allows simultaneous testing of up to 25 participants. Exclusion criteria comprised current or lifetime mental disorder, poor German language skills, and hearing problems. In total, 106 participants provided complete data; six participants, however, were excluded because they reported current or lifetime mental disorders. The remaining sample consisted of $N = 100$ participants, who were randomly assigned to two experimental groups, an EC ($n = 62$, $M = 22.77$ years, $SD = 3.99$, 53% female) and a YC ($n = 38$, $M = 24.26$ years, $SD = 4.2$, 58% female). To allow the analysis of inter-individual differences within EC, more participants were assigned to this group. However, we were unable to collect a sufficiently large sample ($N > 80$) within the duration of this project and such analyses also lie beyond the scope of this article. The unequal group sizes were considered in the statistical analysis (see "Statistical Analysis" on page 36). Because the stressfulness of the aversive stimulation had been successfully established in study 1, we did not include a control group this time. Study 2 specifically aimed at improving the experimental manipulation of stressor controllability and was expected to result in distinct read-outs for EC and YC. EC was tested first, and we used their average stress durations during the stress induction for pseudo-yoking (see "Stress Induction" on page 35 for details). The study was approved by the ethics committee of the Institute of Psychology, Johannes Gutenberg University Mainz (2017-JGU-psychEK-003, 26/5/2017) and it adhered to the declaration of Helsinki. All participants provided written informed consent and were remunerated with 9 EUR/hour.

Procedure. Participants attended a 1.5 h group testing session, including up to 25 people. First, they filled in online questionnaires pertaining to demographic variables and current wellbeing. Following this, participants completed a pre-stress assessment of affect. The procedure was shorter but overall equivalent to study 1, i.e., participants then (1) underwent a stress induction, during which they rated perceived stressor aversiveness, controllability, exhaustion, and feelings of helplessness; (2) they reported their post stress affect; and (3) performed the escape behaviour test. Upon completion of the session, YC participants were debriefed and they re-consented.

Stress Induction. The stress induction procedure differed from the setup described in study 1 (see page 29) in a number of features. We were interested in seeing whether acoustic noise alone might serve to induce significant stress. In contrast to electric shocks, noise requires a less involved experimental setup and can be presented more readily. The acoustic noise used in study 1—verified by decibel meter—was delivered over AKG K81 DJ headphones.
Three different cues (circle, triangle, square) were included in the button-press task, each displayed equally often across 60 trials. Participants were instructed to match one of three buttons to each cue. They were told to figure out the correct button–cue combination which would stop aversive stimulation. Using a trial-and-error approach, they were bound to initially give some wrong responses and experience continued stress exposure. This served to enhance EC's perception of action–outcome contingencies and enhance participants' feeling of control. In EC, correct responses immediately terminated the stressor, whereas incorrect or slow responses led to continued aversive stimulation up to a maximum of ten seconds. However, in order to further increase perceived control and the experience of shortened stress durations in EC, we decreased the maximum stress duration by 500 ms after every 15th trial. In YC, participants' responses had no effect on the stressor because stress durations were predetermined through pseudo-yoking. Specifically, the stress duration for each trial was set to the average obtained from EC. Additionally, we randomly shuffled mean durations to enhance the perception of arbitrary stress durations in YC. Pseudo-yoking is well-established in animal designs (Hadad-Ophir et al., 2017; Lucas et al., 2014) and more practical in group testing sessions. All other parameters (response limit in EC, shift of cue onsets in YC) were the same as in study 1.

Measurements. During stress induction, participants' RTs were measured. After every 15th trial, participants rated stressor aversiveness, perceived controllability, exhaustion, and

feelings of helplessness (four ratings each). Immediately before and after stress induction, participants completed the PANAS and STADI questionnaires. After stress exposure, participants performed the escape behaviour test (see page 32). However, the task was improved by several modifications. Participants completed two blocks with five trials each. To condense the task, we shortened the free exploration phase to five seconds and the stress phase lasted up to five seconds or until a safe space was found. In addition, the participant's position was reset to the middle space at the beginning of each new phase. Thus, we could directly compare behaviour during free exploration and stress exposure. Following the last trial of the first block, safe spaces were set to new random locations on the grid for the duration of the second block. Hence, participants were required to search anew for the safe places. This modification served to introduce a lack of control element. We sought to examine whether previous stressor controllability experience would lead to divergent reactions. We did not assess participants' working memory in this study.

Statistical Analysis. We performed a priori comparisons to verify that groups did not differ in sex, age, or level of education using a chi-square test, a *t*-test for independent samples, and the Wilcoxon rank sum test, respectively. As in study 1, we then examined stressor aversiveness and controllability ratings to ascertain successful stress induction and manipulation of stressor controllability. For analysis of group differences during acute stress exposure (helplessness, exhaustion, and RT), we used *t*-tests for independent samples to compare means. As in study 1, we applied Bonferroni correction to account for family-wise error. Next, we conducted separate rmANOVAs with group as the between-subject factor and time (pre, post) as the within-subject factor to analyse changes in affective state (global STADI score, PANASpos, PANASneg) from pre to post stress induction by group. Finally, as in study 1, we calculated exploration, escapes, and efficiency scores in the escape behaviour test. Exploration during the stress-free phase was analysed using rmANOVA with group as the between-subject factor and block (1, 2) as the within-subject factor. We computed escapes and efficiency across trials and examined only data pertaining to the stress phase, thus, employing rmANOVAs with group as the between-subject factor and block as the within-subject factor. Again, we corrected for family-wise error in our analysis of transfer stress effects during subsequent assessments, using Bonferroni correction.

As in study 1, we excluded extreme outliers and set our level of significance at $p = 0.05$. For rmANOVAs, we applied Greenhouse–Geisser correction. If residuals markedly deviated from normality, we employed a robust rmANOVA using the WRS2 package (Mair & Wilcox,

2020) and reported the effect size measure suggested by Algina et al. (2005). In general, we accounted for unequal group sizes by confirming the results using robust rmANOVA. Post hoc comparisons were assessed using paired *t*-tests, with Holm–Bonferroni correction (Holm, 1979) applied for multiple testing. Effect sizes are reported as partial η^2 (Cohen, 1973) for ANOVAs, η^2_H for Kruskal–Wallis test (Tomczak & Tomczak, 2014), and Cohen's *d* (Cohen, 1988) for *t*-tests. Further analyses including time and sex effects are reported in the supplemental material. As in study 1, analyses were conducted in R (version 3.6.2; R Core Team, 2019).

4.1.4 Results

Study 1: Results of the Initial Paradigm

A Priori Group Comparisons and Manipulation Check. We observed no a priori group differences with respect to sex, working memory IQ, and alertness. However, groups differed significantly in age ($X^2 = 6.52$, $df = 2$, $p < 0.05$, $\eta^2_H = 0.06$) (Table 1). We identified two outliers which we excluded from subsequent analyses. Because of missing data, we compared stressor aversiveness ratings between 26 EC participants and 23 YC participants only. Both groups equally rated the stressor as very aversive (global $M = 5.74$; $F(1, 47) = 0.48$, $p = 0.49$, partial $\eta^2 = 0.01$), suggesting successful stress induction (Figure 2a). We observed no significant habituation or sensitization effects, rather aversiveness ratings remained near-constant over trials ($F(3, 141) = 0.97$, $p = 0.38$, partial $\eta^2 = 0.02$ (Greenhouse–Geisser corrected, $\varepsilon = 0.64$)). Perceived control varied significantly between all three groups ($F(2, 74) = 29.67$, $p < 0.001$, partial $\eta^2 = 0.45$; all post hoc comparisons: $p < 0.001$) with CC reporting highest control, followed by EC, and YC reporting lowest control (Figure 2b). There was an effect of time ($F(3, 222) = 3.47$, $p < 0.05$, partial $\eta^2 = 0.04$ (Greenhouse–Geisser corrected, $\varepsilon = 0.63$)), reflecting a slight decrease in perceived control across trials. See the supplemental material for analysis of sex differences (Supplement 6).

Table 1

A priori group comparisons in study 1

Variable	Group			Statistical Test	*p*	Effect Size
	EC	YC	CC			
n^1	27	26	27			
Sex (% Female)	56	58	56	Chi-Squared	0.984	$X^2 = 0.03$
Mean Age (*SD*)	23.48 (3.74)	25 (4.26)	25.85 (4.3)	Kruskal–Wallis	<0.05	$\eta^2_H = 0.06$
Mean Working Memory IQ (*SD*)	100.89 (9.55)	104.58 (11.53)	104.3 (13.99)	One-Way ANOVA	0.45	Partial η^2 = 0.02
Mean Alertness (*SD*)	45.3 (6.31)	43.96 (6.99)	42.11 (6.31)	One-Way ANOVA	0.24	Partial η^2 = 0.04

[1]*Note. N = 80.*

Ratings and RTs during Acute Stress Exposure. Analysis of helplessness ratings indicated a significant effect of group ($X^2 = 26.18$, $df = 2$, $p < 0.001$, $\eta^2_H = 0.33$), but post hoc comparisons showed significant differences only between stress and control, with both EC and YC reporting greater helplessness compared to CC (EC vs. CC and YC vs. CC: $p < 0.001$). A comparison of EC and YC did not reach significance ($p = 0.12$), but we noted differences in the expected direction (Figure 2c). Similarly, analysis of mean exhaustion ratings supplied during stress exposure revealed a significant effect of group ($F(2, 75) = 10.24$, $p < 0.001$, partial $\eta^2 = 0.21$). However, post hoc comparisons showed significant differences only between stress and control with higher ratings in both EC and YC compared to CC (EC vs. CC: $p < 0.001$ and YC vs. CC: $p < 0.01$). EC and YC did not differ ($p = 0.37$) (Figure 2d). Regarding frustration, we also noted significant group differences ($X^2 = 16.75$, $df = 2$, $p < 0.001$, $\eta^2_H = 0.20$), but post hoc comparisons showed that only YC and CC differed significantly ($p < 0.001$), whereas EC vs. CC and EC vs. YC comparisons revealed only a trend effect (both

p = 0.07). As anticipated, YC reported greatest frustration, followed by EC, and then, CC (s. Supplemental Figure S1).

One CC participant who did not react to any cue and one EC outlier were excluded from RT analysis. We observed an effect of group (F(2, 73) = 4.98, p < 0.01, partial η^2 = 0.12). As expected, CC was fastest, followed by EC, with YC being slowest (Figure 2e). However, post hoc comparisons were not significant for EC vs. CC (p = 0.10) and EC vs. YC (p = 0.26). The difference between YC and CC was significant at p < 0.01. See the supplemental material for analysis of changes across trials and sex differences (Supplement 7).

Affective State, Escape Behaviour, and Cognitive Performance during Subsequent (Post Stress) Assessment.

Changes in Affective State. Two participants per group were missing data on depressive state and anxiety and had to be excluded from this analysis. Additionally, we removed one outlier who reported extremely high depressive state and anxiety before stress exposure. There was no significant effect of group (F(2, 68) = 0.49, p = 0.62, partial η^2 = 0.01) on state of depression and anxiety, but we observed a significant effect of time (F(1, 68) = 9.38, p < 0.01, partial η^2 = 0.12). This reflected an increase in depressive symptoms and anxiety from pre to post stress induction. Following correction for family-wise error, there was no significant interaction of group x time (F(2, 68) = 3.02, p = 0.39, partial η^2 = 0.08) on depressive symptoms and anxiety (Figure 3a). With respect to negative mood, ratings from four participants were missing and were thus, excluded from analysis. We observed a significant interaction of group x time on negative mood (F(2, 68) = 6.27, p < 0.05, partial η^2 = 0.16), reflecting an increase in negative mood across stress groups (EC and YC), albeit only significant in EC. CC, rather, showed a decrease in negative mood, though this was not significant (Figure 3b). With regard to positive mood, there was no significant effect of group (F(2, 75) = 0.29, p = 0.75, partial η^2 = 0.008), but a significant effect of time (F(1, 75) = 42.39, p < 0.001, partial η^2 = 0.36). Positive mood decreased from pre to post stress induction across groups (Figure 3c). No interaction of group x time emerged (F(2, 75) = 0.39, p = 0.68, partial η^2 = 0.01). For analysis of sex differences see Supplement 8.

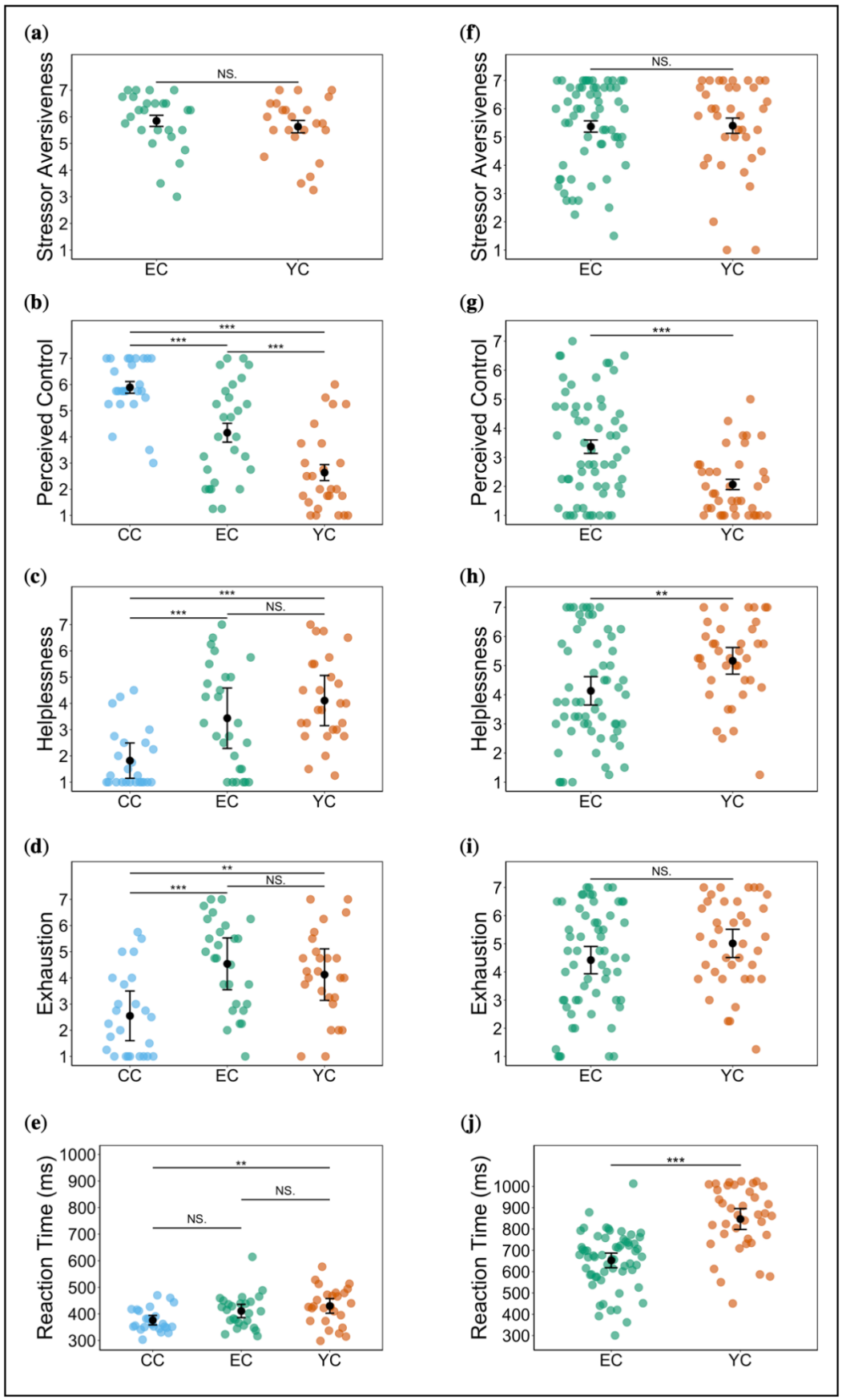
Escape Behaviour. We investigated exploration during the stress-free phase, i.e., the number of unique spaces visited per minute. Results revealed no group differences (X^2 = 2.60, df = 2, p = 0.27, η^2_H = 0.002) (s. Supplemental Figure S2). Next, we compared the total sum of successful escapes during the stress phase between groups and found no significant differences (X^2 = 0.95, df = 2, p = 0.62, η^2_H = −0.01) (s. Supplemental Figure S3). Finally, we examined

behavioural efficiency as the quotient of moves per minute and sum of escapes across trials. Again, no significant group differences emerged (X^2 = 1.54, df = 2, p = 0.46, η^2_H = −0.006) (Supplemental Figure S4). The striking lack of group differences in escape behaviour was contrary to our hypotheses. For analysis of sex differences see Supplement 8.

Working Memory. We analysed working memory in terms of partial-credit load in the reading span task. Four participants had missing data and had to be excluded from analysis. We observed significant group differences in partial-credit load scores (F(2, 71) = 6.67, p < 0.05, partial η^2 = 0.16). Contrary to our hypothesis, EC performed significantly worse than CC (p < 0.01). The differences between EC and YC (p = 0.11) as well as CC and YC (p = 0.11) were not significant (s. Supplemental Figure S5). For analysis of sex differences see Supplement 8.

Figure 2

Ratings and reaction times during stress induction in study 1 and 2



Note. (a) Stressor aversiveness in study 1; (b) perceived control in study 1; (c) helplessness in study 1; (d) exhaustion in study 1; (e) reaction times in study 1; (f) stressor aversiveness in study 2; (g) perceived control in study 2; (h) helplessness in study 2; (i) exhaustion in study 2; (j) reaction times in study 2. Error bars denote standard error (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

Study 2: Results of the Improved Paradigm

A Priori Group Comparisons and Manipulation Check. We observed no a priori group differences in sex, age, or level of education (Table 2). One participant had missing stressor aversiveness data and was excluded from this analysis. EC and YC both rated the stressor as very aversive (global M = 5.38; $F(1, 95) = 0.007$, $p = 0.93$, partial $\eta^2 = 0.0004$; Figure 2f). There was a trend effect of time, reflecting a slight increase in reported aversiveness over trials ($F(3, 285) = 2.59$, $p = 0.07$, partial $\eta^2 = 0.03$ (Greenhouse–Geisser corrected, $\varepsilon = 0.74$)). Groups differed significantly with respect to perceived control ($F(1, 96) = 16.23$, $p < 0.001$, partial $\eta^2 = 0.14$), with YC showing lower ratings, as hypothesized (Figure 2g). There was a significant effect of time on controllability ratings, indicating a decrease over trials ($F(3, 288) = 6.70$, $p < 0.001$, partial $\eta^2 = 0.07$ (Greenhouse–Geisser corrected, $\varepsilon = 0.84$)). Contrary to study 1, EC participants were required to figure out for themselves how to exert control and terminate the aversive stimulation. We examined rates of correct performance to assess whether this was in line with our intended manipulation. Aside from eight participants with rates below 30%, EC participants performed tolerably well (M = 0.60, SD = 0.49). We ascertained that participants with low performance did not substantially affect subsequent analyses before we decided to include them. For analysis of sex differences see Supplement 9.

Table 2

A priori group comparisons in study 2

Variable	Group		Statistical Test	*p*	Effect Size
	EC	YC			
n[1]	62	38			
Sex (% Female)	53	58	Chi-Squared	0.80	$X^2 = 0.06$
Mean Age (*SD*)	22.77 (3.99)	24.26 (4.2)	*t*-test	0.08	$d = -0.36$
Mean Level of Education (*SD*)	7.84 (1.43)	8.03 (1.55)	Wilcoxon Rank Sum	0.51	$r = 0.07$

[1]*Note*. N = 100.

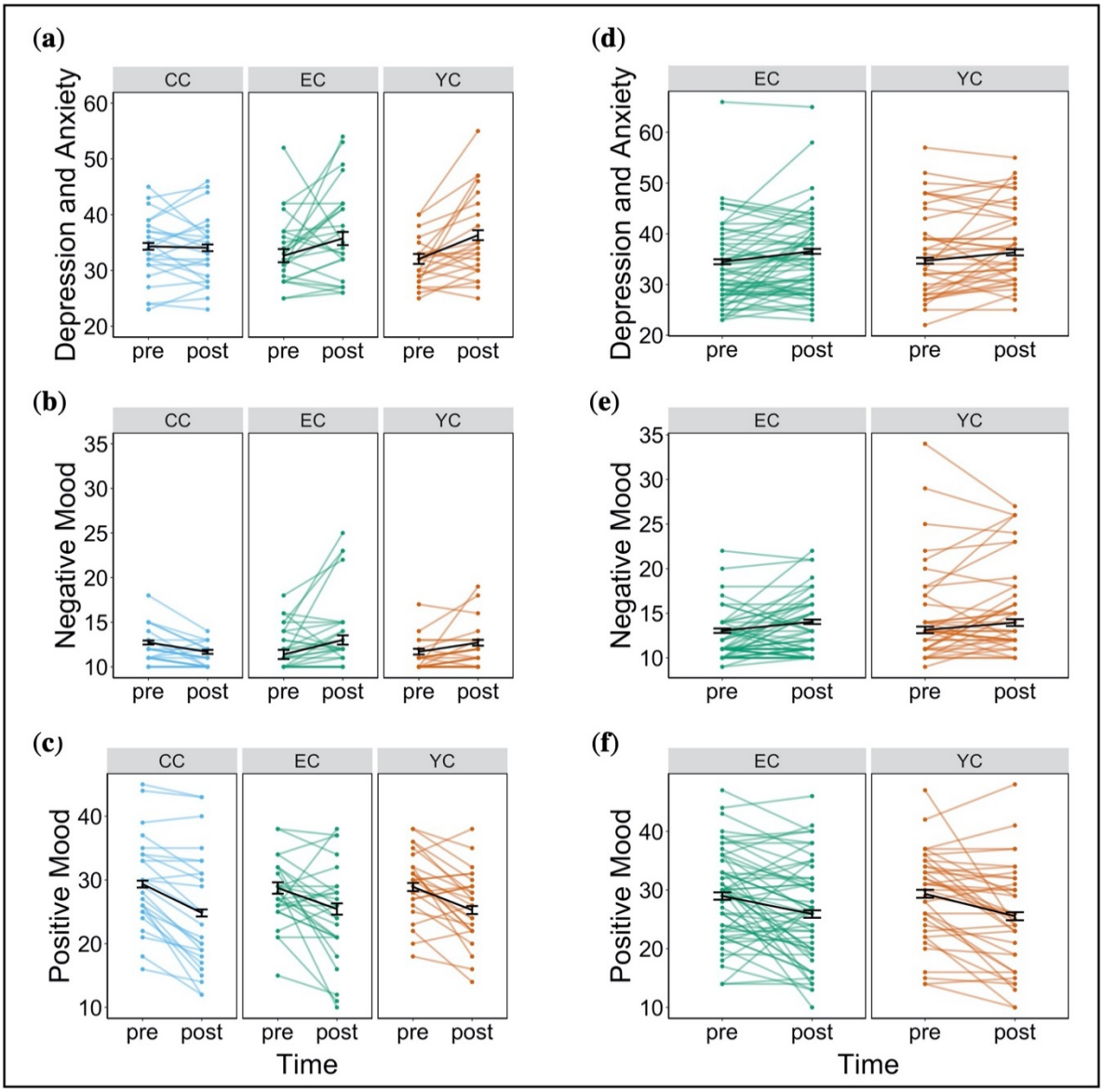
Ratings and RTs during Acute Stress Exposure. YC reported significantly greater feelings of helplessness compared to EC ($t(96) = -2.90$, $p < 0.01$, $-d = 0.60$; Figure 2h). Analysis of exhaustion ratings revealed no significant group difference ($t(96) = -1.62$, $p = 0.11$, $d = -0.34$; Figure 2i). EC reacted significantly faster than YC and a large effect was indicated ($t(96) = -6.67$, $p < 0.001$, $d = -1.38$; Figure 2j). See the supplemental material for analysis of changes across trials and sex differences (Supplement 10).

Affective State and Escape Behaviour during Subsequent (Post Stress) Assessment.

Changes in Affective State. We observed a trend for significant group differences ($F(1, 96) = 3.09$, $p = 0.08$, partial $\eta^2 = 0.03$) with respect to combined depressive state and anxiety. YC displayed overall higher scores compared to EC. There was an increase in scores from pre to post stress exposure across groups ($F(1, 96) = 11.13$, $p < 0.01$, partial $\eta^2 = 0.10$) but no interaction of group x time ($F(1, 96) = 0.14$, $p = 0.71$, partial $\eta^2 = 0.001$; Figure 3d). With regard to negative mood, we observed a significant difference between groups ($F(1, 96) = 7.10$, $p < 0.01$, partial $\eta^2 = 0.07$). YC showed higher negative mood scores both at pre- and post-stress exposure. Both groups reported an increase in negative mood from pre to post stress exposure ($F(1, 96) = 8.83$, $p < 0.01$, partial $\eta^2 = 0.08$). We found no interaction of group x time on negative mood ($F(1, 96) = 0.08$, $p = 0.78$, partial $\eta^2 = 0.0008$; Figure 3e). EC and YC did not differ in relation to positive mood ($F(1, 96) = 0.08$, $p = 0.77$, partial $\eta^2 = 0.003$) but there was a significant effect of time ($F(1, 96) = 25.72$, $p < 0.001$, partial $\eta^2 = 0.21$), indicating a decrease in positive mood from pre to post stress exposure in both groups. Again, there was no interaction between group x time ($F(1, 96) = 0.30$, $p = 0.58$, partial $\eta^2 = 0.003$; Figure 3f). Thus, we observed no evidence of differential change in affective state related to controllability. For analysis of sex differences see Supplement 11.

Figure 3

Changes in affective state from pre to post stress induction in study 1 and 2



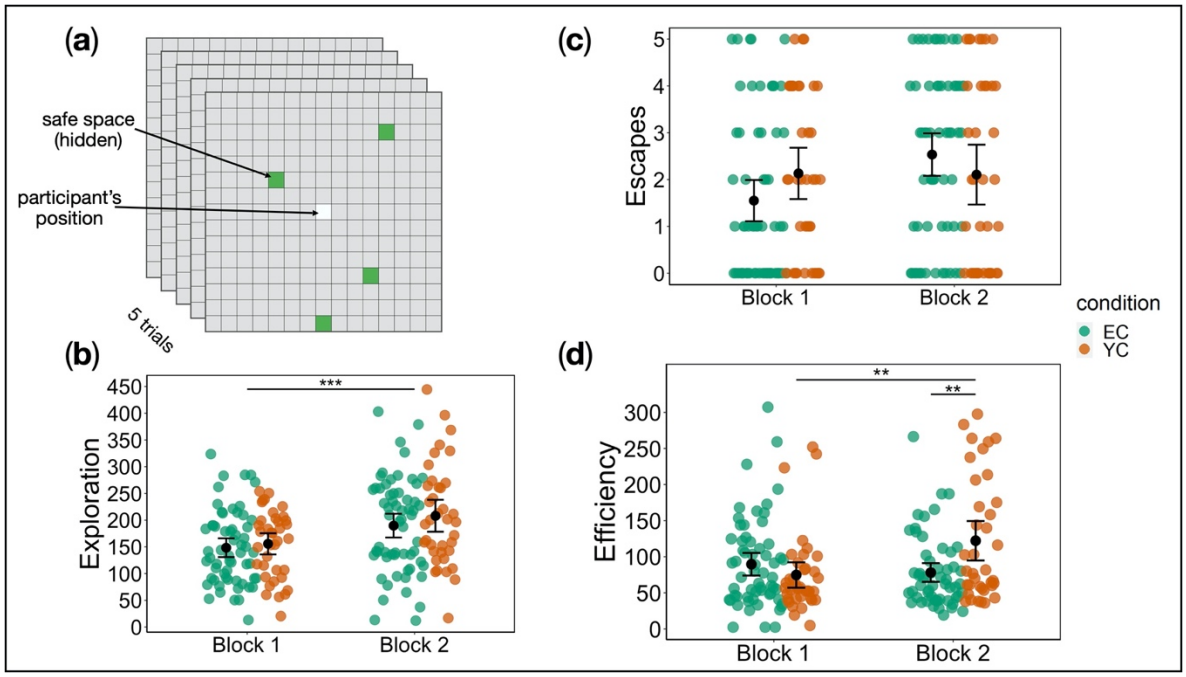
Note. (a) Depressive symptoms and anxiety in study 1. (b) Negative mood in study 1. (c) Positive mood in study 1. (d) Depressive symptoms and anxiety in study 2. (e) Negative mood in study 2. (f) Positive mood in study 2. Error bars denote standard error (*p < 0.05, **p < 0.01, ***p < 0.001).

Escape Behaviour. We analysed stress-free exploration behaviour and observed no significant effect of group ($F(1, 96) = 0.74$, $p = 0.39$, partial $\eta^2 = 0.008$). A significant effect of block indicated an increase in exploration from block 1 to block 2 across groups ($F(1, 96) = 48.58$, $p < 0.001$, partial $\eta^2 = 0.34$). There was no interaction of group x block ($F(1, 96) = 0.70$, $p = 0.40$, partial $\eta^2 = 0.007$; Figure 4b). Analysis of escape rates revealed an interaction of group x block, but this effect did not survive correction for family-wise error

($F(1, 96) = 5.11$, $p = 0.16$, partial $\eta^2 = 0.05$) (Figure 4c). Finally, investigation of escaping efficiency, i.e., the trade-off between level of activity and escape rate, showed a significant interaction of group x block ($F(1, 91) = 12.38$, $p < 0.001$, partial $\eta^2 = 0.12$). Whereas EC and YC did not differ in efficiency in block 1 ($p = 0.51$), YC showed significantly less efficient behaviour in block 2 compared to EC ($p < 0.01$). While the behaviour of YC participants represented a considerable performance decrement (block 1 vs. block 2: $p < 0.01$), participants in EC even improved slightly from block 1 to block 2, albeit not statistically significant ($p = 0.51$; Figure 4d). For analysis of sex differences see Supplement 11.

Figure 4

Escape Behaviour Test – setup and results



Note. (a) Escape behaviour test (one block). (b) Exploration during the stress-free phase in the escape behaviour test by group and block. Both groups explored more in block 2 compared to block 1; we observed no interaction effects. (c) Escapes from stress in the escape behaviour test by group and block. EC escaped the stressor more often in block 2 compared to block 1, whereas no such improvement was evident in YC. Despite that, the interaction of group x block did not survive family-wise error correction. (d) Interaction effect of group x block on efficiency in the escape behaviour test. Whereas EC and YC did not differ in efficiency in block 1, YC showed significantly less efficient behaviour (higher scores) in block 2 compared to EC. Error bars denote standard error. Only significant effects are indicated (*p < 0.05, **p < 0.01, ***p < 0.001).

4.1.5 Discussion

In two consecutive studies, we developed and validated a translational paradigm to induce controllable and uncontrollable stress in humans and examined the effects of this manipulation on affective state, escape behaviour, and working memory. We hypothesized that exposure to uncontrollable stress would lead to longer RT; higher ratings of helplessness, exhaustion, and frustration; greater increase in negative affect; less efficient escape behaviour; and poorer working memory performance compared to controllable stress. In study 1, we included a control group which was not exposed to any aversive stimulation and served to establish the stressfulness of our stressor.

In study 1, participants in both stress groups (EC and YC) perceived equally the stressor as very aversive and showed no habituation over trials. As expected, our results demonstrated a robust stress effect, evidenced by higher levels of exhaustion, frustration, greater increases in depressive symptoms, anxiety, and negative mood in both EC and YC compared to CC. However, stress effects were not evident with regard to working memory performance and escape behaviour. EC performed worst in the working memory task, but we had hypothesized YC would show the lowest scores. As working memory has previously been found to be impaired by acute stress (Shields et al., 2016) and lack of control (Wanke & Schwabe, 2019), this contradictory result may reflect problems with our manipulation of stressor controllability. Perhaps, EC experienced greater strain due to higher task demands compared to YC during the stress induction. Correspondingly, EC reported feeling slightly more exhausted than YC, albeit not statistically significant. Indeed, analysis of group differences only partly supported our hypotheses with respect to stressor controllability effects. Even though a manipulation check indicated differential effects on perceived control as hypothesized, stress effects were evidently not exacerbated by lack of control. Observed group differences across read-outs were largely limited to stress groups vs. control, while direct comparisons between EC and YC yielded few significant results. This suggests that the manipulation of stressor controllability was not successful. It is of note though that longer RTs and greater frustration and helplessness in YC compared to EC were in line with our hypotheses. The paradigm used in study 1, thus, provided a promising basis upon which to improve in study 2.

Two features of the stress induction procedure specifically seemed to be likely candidates for modification. First, our design required EC participants to endure a certain amount of aversive stimulation, until the cue signalled the option to terminate the stressor. Thus, they experienced similar lack of control to YC, at least in the beginning of trials. Other studies have circumvented this issue by employing a forewarned design which allows

participants to completely avoid aversive stimulation (Diener et al., 2009). However, as we were specifically interested in studying how control experience may moderate stress effects, reducing stress exposure in EC was not an option. Stress constitutes a pervasive fact of life (Chmitorz et al., 2020a; Kalisch et al., 2017) from which it is hard to escape. This rings true, especially in today's society, where we are increasingly expected to multitask, show proficiency in a variety of subjects, and to shoulder ever more responsibility. Therefore, the study of factors or mechanisms which may moderate stress effects presents a more ecologically valid avenue of research than promoting total stress avoidance. Moreover, this feature of the paradigm represents an important parallel to commonly used animal designs and serves the purpose of translational research (Chourbaji et al., 2005).

Second, given that EC participants could easily achieve perfect performance on the button-press task, they hardly ever experienced aversive stimulation up to the maximum duration of 15 s. Therefore, they lacked a negative reference to compare to successfully shortened stress durations in trials in which they responded fast enough. A large body of research on learning and decision-making emphasizes the importance of action–outcome contingencies (Huys & Dayan, 2009; Moscarello & Hartley, 2017). By reacting to novel stimuli and observing the consequences, individuals can infer the level of control they have over the respective outcome. An outcome that is contingent on an action results in a high-agency estimate, whereas a non-contingent outcome is suggestive of low controllability and thus fosters a belief in low agency (Moscarello & Hartley, 2017). It becomes clear, therefore, that the experience of both reward and punishment (or a lack of reward) is critical (Guitart-Masip et al., 2012). In study 2, we aimed at facilitating the observation of contingency of the outcome (stress stops vs. stress continues) on the action (button press vs. miss), thereby enhancing perceived control in EC. We expected that such a modification would suffice to render the manipulation of stressor controllability more successful, i.e., lead to significant differences in read-outs between EC and YC. Note that stressfulness of the aversive stimulation was established in study 1; hence, study 2 did not include a control group and the investigation of stressor aversiveness ratings was, thus, perfunctory only.

Results of study 2 on stressor aversiveness ratings were in line with study 1. As hypothesized, YC participants reported feeling less in control than EC participants. Not surprisingly, this EC group reported slightly lower perceived control compared to EC in study 1. Contrary to study 1, EC participants in study 2 were required to figure out through trial and error which of three possible buttons to press to terminate the stressor. They were, thus, bound to initially give some wrong responses and experience continued stress exposure which

may have dampened perceived control. On the whole, however, the group difference in perceived control reflected a considerably larger effect compared to study 1. This suggests that enhancing action–outcome contingencies crucially improved our manipulation of stressor controllability. Robust group differences in the expected direction were now evident, with YC showing longer RTs and higher ratings of exhaustion and helplessness. These findings point to crucial improvements in the manipulation of stressor controllability. In line with study 1, however, stressor controllability did not differentially affect changes in affective state. Results on pre to post stress induction depressive state, anxiety, and positive and negative mood highlight the overall negative effect that stress exerts on an individual's affective state. While the two groups were not perfectly comparable in their negative mood scores before stress induction, it seems that stress here generally overrode any putative differences with respect to perceived control. Taken together, the findings from study 1 and 2 suggest that self-reported affective state—while certainly a valid measure with respect to stress reactivity—may not be the most sensitive indicator of differential control experience. It would have been interesting to have also investigated effects on working memory, but no such measurement was included in study 2. Substantial group differences in the escape behaviour test further corroborate the notion that objective, performance-based indices are better discriminated. YC showed behavioural patterns markedly different from EC, as both, again, tried to escape aversive stimulation in the grid-navigation task. However, EC and YC showed differences specifically in efficiency rather than in the more conventional measurements of exploration and escape rate. Although we did observe a tendency for differential escaping, the analysis of efficiency as the trade-off between level of activity and escape rate proved to be more sensitive. Differences between groups are clearly linked to the introduction of an element of lack of control represented by the unannounced relocation of safe spaces following the first five trials (block 1). Whereas EC seemed to recover quite quickly and even improved their escape rate from block 1 to block 2, YC showed considerable performance decrements. Based on a large body of LH research (Maier & Seligman, 2016), we had anticipated that YC participants would show rather passive, resigned behaviour in response to renewed stress exposure. Despite their efforts, YC participants were not very successful in escaping the stressor. They ineffectively squandered resources for strategic thought on frantic searches of the grid. In fact, studies investigating learning and decision-making have demonstrated how stress renders individuals less able to critically evaluate potential actions and consequences in order to best achieve a present goal (Brown et al., 2020; Otto et al., 2013; Radenbach et al., 2015; Voon et al., 2017).

Similarly, studies have linked impulsive behaviour to stress history and psychopathology (Fineberg et al., 2014; Ousdal et al., 2018).

Individual differences have long been the focus of research on stress and control. Schönfeld et al. (2017) recently discussed dimensional effects of self-efficacy on stress response, noting that high subjective control beliefs are not always beneficial. Bollini et al. (2004) showed that locus of control moderated the association between perceived control over a stressor and related cortisol output. Generally, we did not have a sufficient sample size to investigate variation in the individual stress response or to explore moderating factors, nor was this our focus. We would be interested in examining individual differences in future studies. In study 2, we have included a larger number of EC participants to address the finding that not all EC participants were successful in escaping the stressor, even though it was objectively possible. However, the assessment of a sufficient number of participants ($N > 80$) was not possible within the duration of the project. Psychopathology research increasingly focuses on individual differences (Bzdok & Meyer-Lindenberg, 2018). For instance, most individuals do not develop post-traumatic stress disorder following a single exposure to trauma. In fact, a traumatic event alone is seldom sufficient to induce clinical symptoms; more often, it is a combination of a traumatic event and additional risk factors (Richter-Levin et al., 2019). To address individual differences in response to traumatic stress, recent research in rodents suggests incorporating individual predispositions and behavioural profiling (Richter-Levin et al., 2019).

Future studies could use our paradigm to investigate clinical populations, seeing as LH is widely considered a key concept in the aetiology of depression. Nonetheless, research on the mechanisms underlying LH is largely limited to the animal domain. Uncontrollable stress affects individuals across a variety of species (Pryce et al., 2011) and has detrimental effects on a broad spectrum of functions (Steptoe & Poole, 2016). Yet, differences in the experimental design of animal and human studies remain a challenge for translational research (Hooijmans & Ritskes-Hoitinga, 2013). In this study, we successfully developed a translational paradigm to investigate effects of uncontrollable stress in humans. In keeping with early translational studies (Alloy et al., 1984; Hiroto & Seligman, 1975; Thornton & Jacobs, 1971), the design unifies several essential features of the animal triadic design, i.e., use of a physical stressor, yoking of stress exposure, the operationalization of control in terms of stressor termination, not prevention, a relatively simple task by which to exert control, and the assessment of escape behaviour (Chourbaji et al., 2005). However, our paradigm critically expands read-outs to encompass affective state, cognitive performance, and behaviour. Although we did not observe

robust group differences in changes in affective state and did not assess cognitive performance in study 2, our paradigm allows flexible testing of a range of read-outs. Naturally, stress effects in animal research are commonly assessed through behavioural indices after stress induction. Consequently, early translational studies focused on examining behavioural read-outs (Alloy et al., 1984; Hiroto & Seligman, 1975; Thornton & Jacobs, 1971), emulating the rather simple tasks employed in animal research (Chourbaji et al., 2005; Overmier & Seligman, 1967; Seligman & Maier, 1967). Making use of modern methods, recent research has largely concentrated on cognitive read-outs (Hartley et al., 2014; Henderson et al., 2012; Otto et al., 2013). Our escape behaviour test translates indices traditionally used in animal studies (e.g., exploration and escape rate) to humans. However, considering that a certain level of complexity strengthens compliance and induces interesting variance in the data, our task markedly differs from early setups. Translational research often involves finding the sweet spot between rigorously imitating the original animal paradigm and allowing for obvious differences between species. With this in mind, the design of our escape behaviour test permits back-translation into animals. It, thus, contributes to bridging the gap in translational research between animal models and clinical practice (Gururajan et al., 2019; Mak et al., 2014).

This gap is particularly evident in research on stressor controllability. Animal researchers have, for a long while, shifted focus from investigation of LH to studying the experience of control. In a series of experiments (Amat et al., 2010; Baratta et al., 2008; Maier & Seligman, 2016; Maier & Watkins, 2005), they could show compellingly that experience of control over a stressor protects against the negative consequences of later uncontrollable stress. Neurobiologically, this SI is thought to reflect persistent changes in pathways connecting the vmPFC with the dorsal raphe nucleus (Maier & Seligman, 2016). With increasing mechanistic insight, researchers have already started to develop pharmacological interventions to enhance perceived control (Amat et al., 2008, 2016). However, it remains unclear how these findings translate to humans, as only a few studies have examined the neural underpinnings. Wanke and Schwabe (2019) examined the effects of stressor controllability on working memory performance using an fMRI design to elucidate differential effects on a neural level. They report that perceived control, in contrast to objective control, altered prefrontal activation during the memory task. Unpublished work from our own group (see empirical study 2) showed increased vmPFC activation under controllable stress compared to uncontrollable stress—a finding that ties in with animal research.

In general, studies now increasingly focus on investigating putative protective factors and mechanisms which keep individuals mentally healthy, despite considerable stress exposure

(Kalisch et al., 2017). Our paradigm is well-suited to investigate both LH and SI. Observed group differences—especially in the escape behaviour test—lend support to control experience as a potent resilience mechanism.

There are, however, some limitations to consider. First, our results are based on a sample of healthy, rather well-educated, and relatively young adults. This was a necessary constraint to establish the paradigm. Future studies should investigate stressor controllability effects in more diverse samples and populations of increased vulnerability to LH, e.g., depressed patients. Second, while we verified that there was no difference in alertness as a baseline assessment of RT in study 1, no such a priori group comparison was conducted in study 2. Therefore, it is not clear whether participants in EC and YC showed inherently different baseline RT. Nevertheless, given the high degree of homogeneity of the sample, in terms of demographic variables, this should not pose a major limitation to interpreting the results. Third, we did not examine physiological or endocrine indicators of stress reactivity. Such measurements could offer additional mechanistic insight into stressor controllability effects. For instance, stress typically evokes an increase in cortisol and heart rate (Dickerson & Kemeny, 2004). Physiological assessment could easily be incorporated in the experimental setup and would constitute further improvement to the paradigm. Fourth, as human research allows the analysis of self-report data, we asked participants to supply various ratings. However, in the context of the triadic design, it is not a trivial task to phrase instructions in a way that allows comparison of all three groups. Especially, the question of perceived control proved difficult. CC was not exposed to aversive stimulation which made the omission or rephrasing of some instructions necessary. We ensured comparability of perceived control ratings through equal phrasing of the item across groups ("How much control do you have over the task?") at the cost of specifically asking EC and YC how much control they perceived over the termination of the stressor. Given that LH refers specifically to control over a stressor, our choice of phrasing may represent a serious drawback. However, true to the classic animal literature, we manipulated stressor controllability, not task controllability. Even if the assessment of perceived control was not ideal, we should still be able to infer that the observed group differences were due to our manipulation of stressor controllability. If comparing only EC and YC, future studies should explicitly assess perceived control over the stressor. Fifth, stressor controllability effects may vary, in respect to duration and intensity of stress induction as well as the length of time elapsed between exposure and subsequent assessment. In this regard, translating animal protocols proves near impossible. Stress research on humans is subject to thorough ethical scrutiny, as is research on animals. However, animal stress

induction paradigms are often in the order of days or weeks (Lucas et al., 2014), either because prolonged stress exposure is critical to the study subject (e.g., chronic antidepressant effects; Dulawa & Ren, 2005; Yin et al., 2016) or because it is more ecologically valid. For instance, chronic stress is commonly discussed as a precursor to disorders such as depression and anxiety (Lupien et al., 2018). Hence, animal models that are constrained to acute stress exposure may not fully capture the underlying mechanisms (Gururajan et al., 2018). Even if human research cannot easily employ a prospective design to study the long-term effects of experimentally induced controllable and uncontrollable stress, future studies could vary the time interval between stress exposure and outcome tests. It may be the case that control experience requires some processing before it exerts full effects on affective state, cognition, and behaviour. Note that our paradigm was not designed to induce a pathological state of LH which would clearly be unethical. Nonetheless, we were able to show that manipulation of stressor controllability, using a simple acoustic noise stressor, was effective in inducing significant effects in a very healthy sample. In a next step, it would be interesting to examine clinical populations and employ this paradigm to advance our knowledge of how control is implicated in mechanisms of both disease and resilience.

Conclusion

Translational research is essential to assess the extent to which animal findings replicate in humans. We developed and validated a new stress paradigm that translates the animal LH protocol to human research. Our final manipulation robustly induced differential effects in behaviour, but we did not observe effects on changes in affective state, and putative differences in cognitive performance remain to be tested. An independent study incorporating affective state measurements as well as cognitive and behavioural tasks would certainly be useful. Our paradigm shows promise as a feasible and flexible way to study the different effects of controllable and uncontrollable stress on various levels. Future studies could employ a further improved version of our design to promote clarification of the mechanisms by which control experience moderates our reaction to and appraisal of stressful events. Such research serves to improve our understanding of the aetiology of mental disorders and opens up new perspectives on resilience mechanisms. Applications might also inspire back-translation, thus, fostering fruitful and necessary synergies between human and animal research.

Availability of Data and Code

Data and analysis code are publicly available at https://osf.io/pw4m5/. The experiment code is available upon reasonable request from the corresponding author.

Declaration of Conflicting Interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Funding

This research as well as the APC was funded by the German Research Foundation (DFG), Collaborative Research Centre 1193, Project C07.

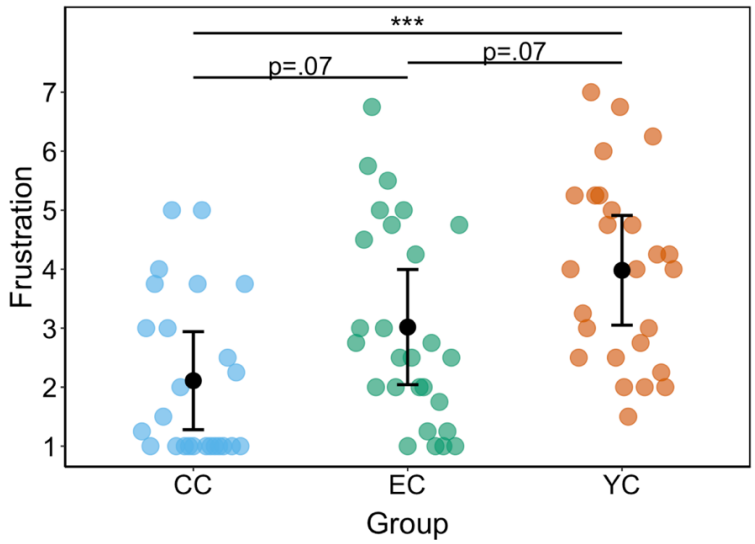
Acknowledgments

We thank all members of Project C07 for their vital contribution, and all participants for taking part in the study. Special thanks go to [redacted] and [redacted] for help with coding the experimental paradigm, [redacted] for help with creating figures, and [redacted] for proofreading. We thank the reviewers for their helpful comments.

4.1.6 Supplement

Figure S1

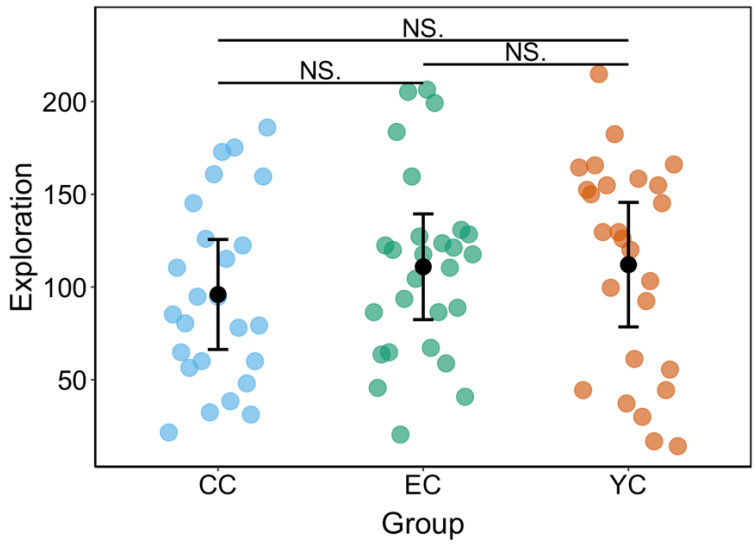
Frustration ratings under acute stress exposure in study 1



Note. Frustration ratings during acute stress exposure by group. Error bars denote standard error.

Figure S2

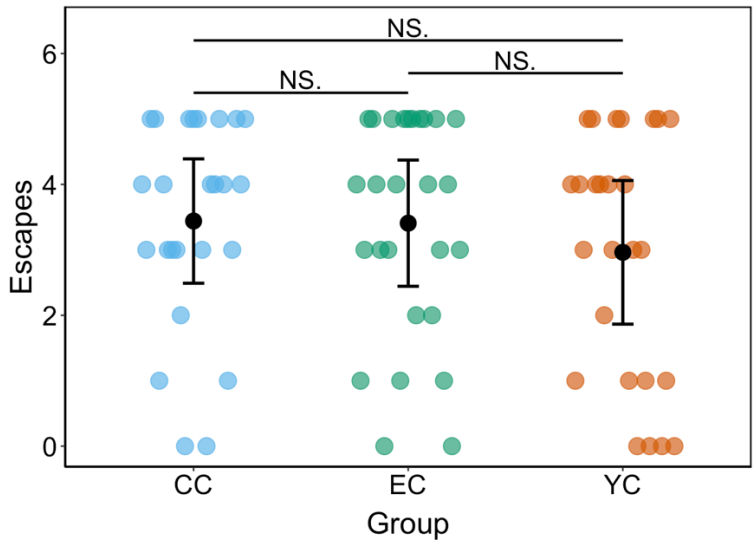
Exploration in the escape behaviour test by group in study 1



Note. Exploration during the stress-free phase in the escape behaviour test by group. Error bars denote standard error.

Figure S3

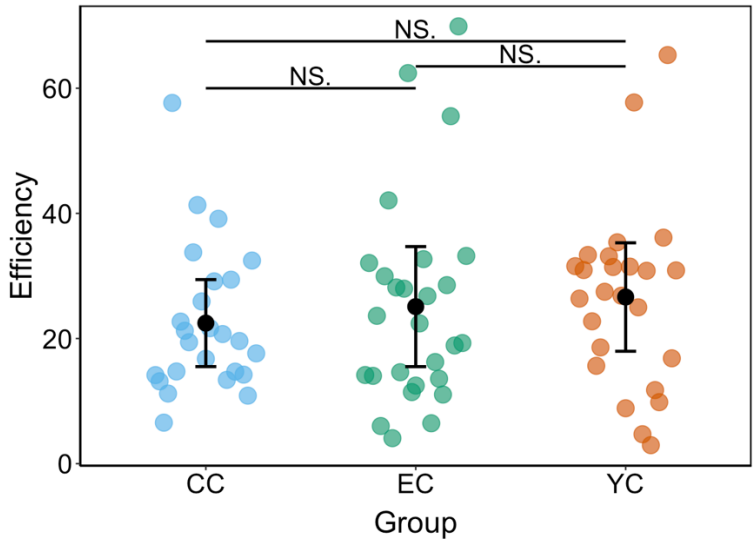
Escapes from stress in the escape behaviour test by group in study 1



Note. Escapes from stress in the escape behaviour test by group. Error bars denote standard error.

Figure S4

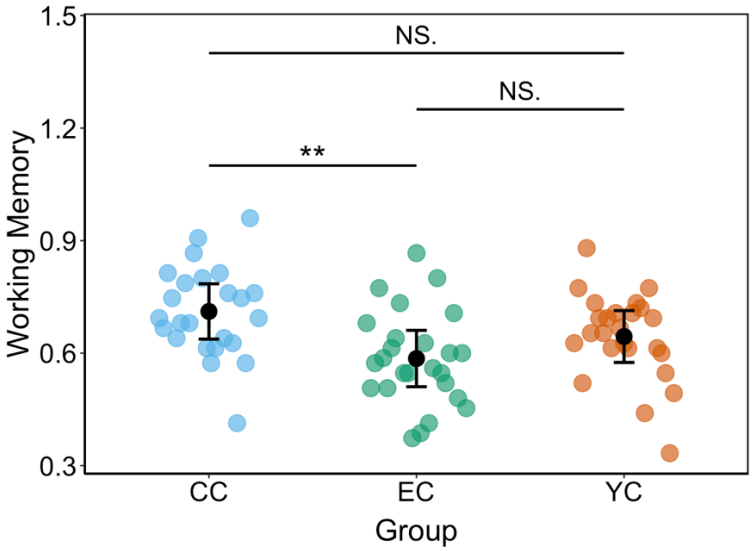
Efficiency under stress in the escape behaviour test by group in study 1



Note. Efficiency under stress in the escape behaviour test by group. Error bars denote standard error.

Figure S5

Working memory by group in study 1



Note. Working memory following the stress induction by group. Error bars denote standard error.

Considering that the paradigms described in study 1 and study 2 represent the development of a new design, we report exploratory analyses of time and sex effects on ratings and RT under acute stress. We conducted separate repeated measures ANOVA with group (study 1: EC, YC, CC; study 2: EC, YC) and sex (male, female) as between-subject factor and time (ratings: 10th, 20th, 30th, 40th trial; RT: 1-40 trials) as within-subject factor. Furthermore, we explored sex differences in subsequent assessments, i.e., in respect of changes in affective state, escape behaviour, and working memory. Results are reported in the following paragraphs. We hope that these additional analyses will be useful to future applications.

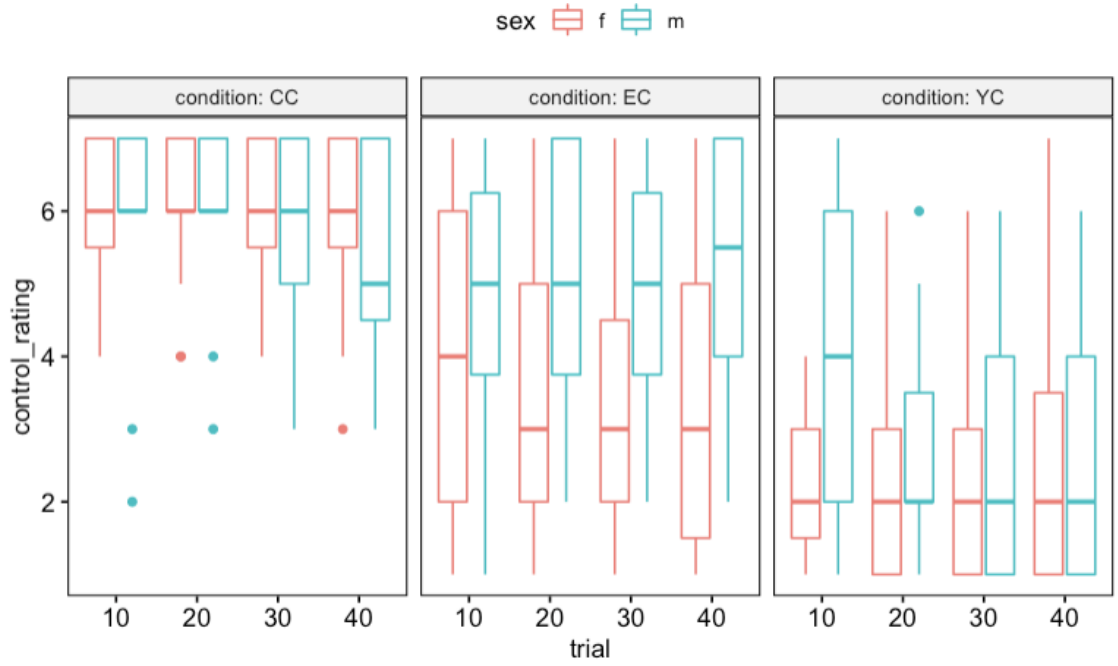
Supplement 6

Effects of sex on stressor aversiveness ratings and perceived control in study 1

Men reported lower stressor aversiveness compared to women ($F(1, 45) = 14.70$, $p < .001$, partial $\eta^2 = 0.25$). Concerning perceived control, no significant sex differences emerged ($F(1, 72) = 2.71$, $p = .10$, partial $\eta^2 = 0.04$). However, we observed a significant three-way-interaction between group x sex x time on perceived control ($F(6, 213) = 4.27$, $p < .01$, partial $\eta^2 = 0.11$ (Greenhouse-Geisser corrected, $\varepsilon = 0.65$), s. Figure S6 below).

Figure S6

Perceived control ratings by group and sex across trials



Note. Boxplots split by group (CC, EC, YC) and sex across trials showing perceived control ratings.

Supplement 7

Effects of time and sex under acute stress exposure in study 1

Helplessness ratings remained constant over time ($F(3, 216) = 0.45$, $p < .62$, partial $\eta^2 = 0.006$ (Greenhouse-Geisser corrected, $\varepsilon = 0.59$)). Exhaustion ratings slightly increased ($F(3, 216) = 4.29$, $p < .05$, partial $\eta^2 = 0.06$ (Greenhouse-Geisser corrected, $\varepsilon = 0.63$)). Concerning frustration, we observed a significant interaction of group x time ($F(6, 216) = 3.00$, $p < .05$, partial $\eta^2 = 0.08$ (Greenhouse-Geisser corrected, $\varepsilon = 0.80$)). This finding reflected increased frustration over time in YC, whereas ratings stayed relatively constant in CC and EC. In respect of RT, there was an effect of time ($F(39, 2652) = 3.49$, $p < .001$, partial $\eta^2 = 0.05$ (Greenhouse-Geisser corrected, $\varepsilon = 0.40$)), RTs decreased sharply in the first few trials.

Analysis of helplessness ratings revealed a group x sex interaction ($F(2, 72) = 5.82$, $p < .01$, partial $\eta^2 = 0.14$). Whereas men and women did not differ in reported helplessness in CC, men rated less helplessness in both EC and YC, with ratings markedly differing between sexes especially in EC. We also observed a significant interaction effect of group x sex on exhaustion ratings ($F(2, 72) = 5.77$, $p < .01$, partial $\eta^2 = 0.14$). Men in both EC and YC reported less exhaustion compared to women, whereas, in CC, women reported less exhaustion. Across

groups, men reported less frustration compared to women ($F(1, 72) = 9.35$, $p < .01$, partial $\eta^2 = 0.12$). No sex effects were found for RT ($F(1, 68) = 0.87$, $p = .35$, partial $\eta^2 = 0.01$).

Supplement 8

Effects of sex on subsequent assessment in study 1

Overall, men reported lower combined depressive state and anxiety compared to women ($F(1, 65) = 10.11$, $p < .01$, partial $\eta^2 = 0.14$). Concerning negative mood, men also displayed lower scores compared to women ($F(1, 65) = 14.32$, $p < .001$, partial $\eta^2 = 0.18$). With regard to positive mood, a trend for sex differences emerged ($F(1, 72) = 3.27$, $p = .07$, partial $\eta^2 = 0.04$). No sex differences were evident for indices of escape behaviour or working memory.

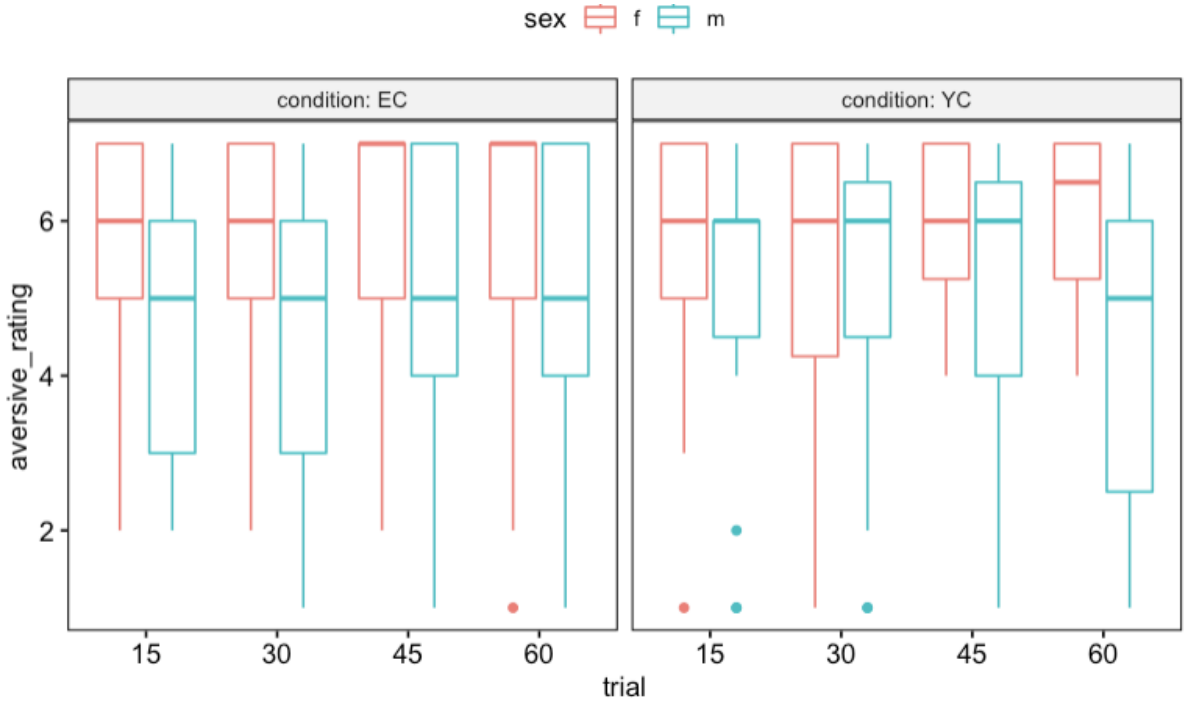
Supplement 9

Effects of sex on stressor aversiveness ratings and perceived control in study 2

We observed a three-way-interaction between group x sex x time on stressor aversiveness ratings ($F(3, 279) = 3.80$, $p < .05$, partial $\eta^2 = 0.04$ (Greenhouse-Geisser corrected, $\varepsilon = 0.77$); s. Figure S7 below). No sex differences emerged for perceived control ratings ($F(1, 94) = 1.55$, $p = .22$, partial $\eta^2 = 0.02$).

Figure S7

Stressor aversiveness ratings by group and sex across trials



Note. Boxplots split by group (EC, YC) and sex across trials showing stressor aversiveness ratings.

Supplement 10

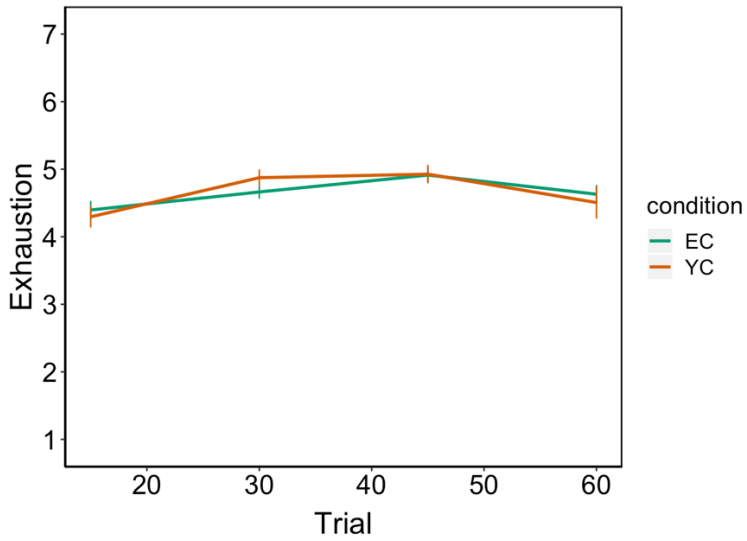
Effects of time and sex under acute stress exposure in study 2

Helplessness ratings decreased over time in both groups ($F(3, 282) = 9.20$, $p < .001$, partial $\eta^2 = 0.09$ (Greenhouse–Geisser corrected, $\varepsilon = 0.88$)). There was a significant effect of time on exhaustion ($F(3, 282) = 6.95$, $p < .001$, partial $\eta^2 = 0.07$ (Greenhouse–Geisser corrected, $\varepsilon = 0.77$)). Across groups, reported exhaustion increased, then decreased again (s. Figure S8 below). There was no significant effect of trial on RT ($F = 0.96$, $p = .57$, $\delta_R = 0.25$).

No effects of sex were observed on helplessness ratings ($F(1, 94) = 0.90$, $p = .35$, partial $\eta^2 = 0.01$) but men reported less exhaustion compared to women ($F(1, 94) = 9.43$, $p < .01$, partial $\eta^2 = 0.09$). RTs did not differ between men and women.

Figure S8

Exhaustion ratings over trials split by group (EC, YC)



Supplement 11

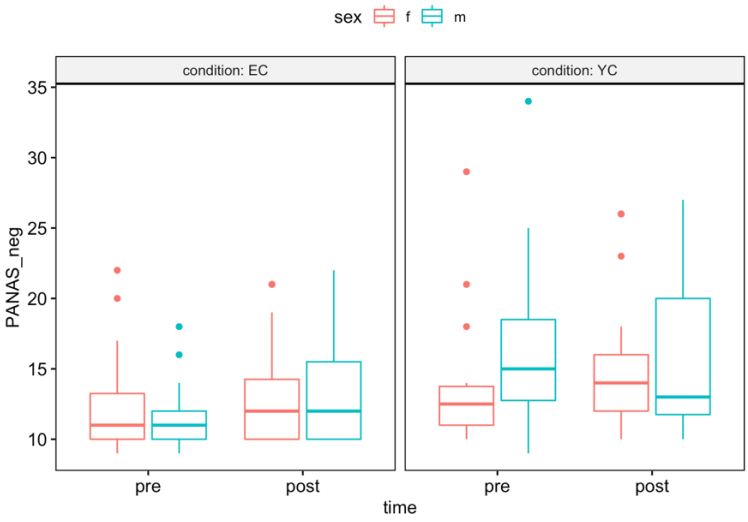
Effects of sex on subsequent assessment in study 2

Concerning depressive state and anxiety, no sex differences emerged ($F(1, 94) = 0.13$, $p = .71$, partial $\eta^2 = 0.001$). We observed a three-way-interaction between group x sex x time on negative mood ratings ($F(1, 93) = 8.74$, $p < .01$, partial $\eta^2 = 0.09$; s. Figure S9 below). There was a sex x time interaction on positive mood ($F(1, 94) = 5.28$, $p < .05$, partial $\eta^2 = 0.05$), reflecting less decrease in positive mood in men compared to women.

With regard to exploration in the escape behaviour test, we observed a significant sex x block interaction ($F(1, 94) = 4.99$, $p < .05$, partial $\eta^2 = 0.05$). Men showed a greater increase in exploration from block 1 to block 2 compared to women. Even so, men did not escape the stressor more often than women — there was no significant difference in escape rate ($F(1, 94) = 2.50$, $p = .12$, partial $\eta^2 = 0.03$). Analysis of efficiency revealed a significant sex x block interaction ($F(1, 89) = 5.73$, $p < .05$, partial $\eta^2 = 0.06$). Whereas, men became slightly more efficient over blocks, women behaved less efficiently in block 2 compared to block 1.

Figure S9

Changes in negative mood from pre to post stress exposure by group and sex



Note. Boxplots split by group (EC, YC) and sex across mood assessments (pre- and post-stress exposure) showing differential changes in negative mood.

4.2 Study 2: Don’t Stress, It’s Under Control: Neural Correlates of Stressor Controllability in Humans[4,5]

[4] Publication reference: Meine, L. E., Meier, J., Meyer, B., & Wessa, M. (2021). Don’t Stress, It’s Under Control: Neural Correlates of Stressor Controllability in Humans. *bioRxiv.* https://doi.org/10.1101/2021.03.30.437657

[5] Please note that certain formatting has been changed to ensure consistency in this dissertation.

4.2.1 Summary of Study 2

Animal research has repeatedly shown that experience of control over an aversive event can protect against the negative consequences of later uncontrollable stress. Neurobiologically, this effect is assumed to correspond to persistent changes in the pathway linking the vmPFC and the dorsal raphe nucleus. However, it remains unclear to what extent these findings translate to humans. During functional magnetic resonance imaging, we subjected participants to controllable and uncontrollable aversive but non-painful electric stimuli, as well as to a control condition without aversive stimulation. In each trial, a symbol signalled whether participants could terminate the stressor through correct performance in a button-matching task or whether the stressor would be randomly terminated, i.e., uncontrollable. Along with neural responses, we assessed participants' accuracy, reaction times, and heart rate. To relate neural activations and subjective experience, we asked participants to rate perceived control, helplessness, and stress. Results were largely in line with our hypotheses. The vmPFC was generally deactivated by stress, but this effect was attenuated when participants could terminate the stressor compared to when their responses had no effect. Furthermore, activation in stress-responsive regions, including the bilateral insula, was reduced during controllable trials. Under uncontrollable stress, greater vmPFC recruitment was linked to reduced feelings of helplessness. An investigation of condition-dependent differences in vmPFC connectivity yielded no significant results. Our findings further corroborate animal research and emphasize the role of the vmPFC in controllability-dependent regulation of stress responses. Based on the results, we discuss future directions in the context of resilience research and mental health promotion.

4.2.2 Introduction

The reaction to and appraisal of an aversive event is closely linked to actual or perceived control over the event (Steptoe & Poole, 2016). Specifically, animal studies have compellingly demonstrated that uncontrollable stress induces a failure to escape aversive stimulation and increases anxiety (Chourbaji et al, 2005; Maier & Seligman, 2016; Overmier & Seligman, 1967). This finding has been formalized in the prominent *theory of learned helplessness* which posits that a passive response to an inescapable stressor may generalize and thus render the individual helpless in the face of subsequent aversive stimulation, even if they could escape it (Maier & Seligman, 2016; Overmier & Seligman, 1967). In contrast, the experience of control over a stressor was shown to be protective. Animals that could terminate aversive stimulation were not susceptible to subsequent uncontrollable stress, as evidenced by e.g., lack of freezing (Amat et al., 2010; Maier & Seligman, 2016). To harness the potential of this latter effect, its underlying neurobiological mechanisms have already been delineated in animals (Amat et al., 2005, 2006, 2008; Baratta et al., 2008; Maier & Seligman, 2016; Maier & Watkins, 2010). The results suggest that sensitization of a pathway connecting the DRN with the amygdala might explain the symptoms of LH. Building on these findings, the researchers targeted the vmPFC as a cortical input structure to the DRN. They describe how the potential for control registers in the vmPFC which then inhibits the DRN via glutamatergic projections to GABAergic interneurons. In turn, serotonergic signalling from the DRN to the amygdala (and other stress-related regions) is reduced. Because changes in the vmPFC-DRN pathway persist, the individual appears *immunized* against later uncontrollable stress.

Since the first findings on differential effects of stressor controllability in animals emerged, researchers have investigated translations to humans, placing particular focus on LH (Abramson et al., 1978; Taylor et al., 2014; Thornton & Jacobs, 1971; see also empirical study 1). Consequently, the effect of uncontrollable stress has long been discussed in terms of depression pathogenesis (Pryce et al., 2011). More recently, Henderson et al. (2012) could show a beneficial effect of control over a noise stressor on executive control functions. Similarly, Hartley et al. (2014) noted improvements in fear extinction following the experience of control over a stressor. Despite this, only few studies have addressed stressor controllability effects on a neural level in humans. A direct test of the model put forward by Maier and Seligman (2016), using neuroimaging techniques, proves difficult due to the small size of the DRN (Kranz et al., 2012). Existing studies therefore tend to focus on the vmPFC and stress-related brain regions. In the context of pain processing, Salomons et al. (2015) described increased vmPFC-amygdala connectivity under controllable pain and Bräscher et al. (2016)

reported a pain-inhibiting function of the dorsolateral prefrontal cortex for controllable heat stimuli. Kerr et al. (2012) examined participants' response to aversive videos which could either be avoided or not. They showed that vmPFC activity increases under anticipation of control and exerts an inhibitory effect on the amygdala. In line with this, Cremers et al. (2020) reported greater vmPFC efficiency in participants who could avoid mild shocks compared to another group who could not. A very recent study showed that vmPFC activation was predictive of recovered active avoidance behaviour following passivity under uncontrollable stress (Wang & Delgado, 2021). Others observed diminished stress effects on the vmPFC only if threats were both controllable and predictable (Wood et al., 2015). Using a fear conditioning paradigm, Wanke & Schwabe (2020) directly contrasted instrumental control with passive extinction and found more pronounced fear reduction in the former condition. However, they noted increased activation of the vmPFC under uncontrollable stress, but not under instrumental control. Another recent study showed the expected decrease in activation of threat-responsive brain regions when participants could terminate mild electric shocks, however, they observed no involvement of the vmPFC (Limbachia et al., 2021). Inconsistencies in results may at least in part be explained by differences in experimental designs (e.g., between- vs. within-subject) and the type of stressor used (e.g., electric shocks, thermal stimulation, noise, or social-evaluative stress). Many have studied aversive stimuli which are signalled by a cue and can be avoided (Cremers et al., 2020; Diener et al., 2009; Kerr et al., 2012; Wanke & Schwabe, 2020). However, we feel that researchers should also investigate controllability-dependent responses in human behaviour and brain function under acute stress. Since stress describes an omnipresent fact of life, and its avoidance may not be possible under all circumstances, the study of factors or mechanisms that can alleviate stress effects certainly presents an ecologically valid research endeavour.

In the present study, we therefore aimed at further elucidating the neural correlates of control over acute stress in humans. We chose a within-subject design to maximize comparability of conditions and focus on immediate effects of controllability, as opposed to effects on post-stress read-outs. To this end, we conducted an event-related fMRI experiment in which participants were subjected to controllable stress, uncontrollable stress, and a baseline condition without aversive stimulation. Along with neural activation, performance and RTs were assessed and heart rate was recorded. To allow associations between neurophysiological results and participants' subjective experience, they also supplied ratings on perceived control, helplessness, and stress. We expected to observe effects of both stress and controllability on outcomes of interest. Specifically, we hypothesized that, compared to baseline, participants

would react more slowly, make more errors, report higher stress ratings, show enhanced activation of stress-related brain regions (e.g., amygdala, insula), and elevated heart rate under stress (controllable and uncontrollable). Concerning stressor controllability, we expected faster and more accurate responses, higher ratings of perceived control, but lower stress and helplessness ratings, greater vmPFC activation along with reduced activation in stress-activated regions, and lower heart rate in controllable compared to uncontrollable experimental trials. As DRN imaging in humans remains a challenge (Kranz et al., 2012), we only anticipated to observe controllability-dependent differences in vmPFC-amygdala functional connectivity.

4.2.3 Methods

Participants

52 participants aged 19-30 took part in this study. Prior to data collection, all were screened for acute or chronic physical diseases as well as current or past DSM-IV axis I disorders using a semi-structured telephone interview similar to the SCID-I. We included only healthy participants who were fluent in German, MR compatible, right-handed, reported a body mass index (kg/m2) between 18.5 and 26, had no history of mental disorders, and took no psychopharmaceuticals. To prevent adverse health effects of our stress induction procedure, we confirmed that participants were neither pregnant, nor suffering from critical cardiac problems, or diagnosed with migraine. Seven participants were excluded from analysis: one broke off testing, two figured out the experimental manipulation (see manipulation check in the results section for details), one reported stimulus electrode malfunctioning, and three rated stressor aversiveness very low (< 25/100 in more than half the runs), also suggesting electrode malfunction/loosening. The remaining sample consisted of 45 participants (47% female, age: M = 24.64, SD = 3.05). For fMRI analyses, another participant was disregarded due to excessive motion (> 2mm translation, > 2° rotation between volumes) and a further two were excluded because of data storage problems (missing data).

This study was approved by the ethics committee of the Institute of Psychology, Johannes Gutenberg-University, Mainz, Germany (2017-JGU-psychEK-003, 26/5/2017), and was conducted according to the Declaration of Helsinki.

Procedure

Participants attended a 2 h MRI session. Upon arrival, they received information on the study along with a brief overview of procedures and provided written informed consent.

Participants then completed a questionnaire on stress experiences and current well-being and entered the scanner. Inside the scanner, electric stimuli were calibrated, and participants underwent the stress induction procedure. During the stress induction, their heart rate (i.e., beats per minute; BPM) was tracked at a sampling rate of 50 Hz using a MR-compatible pulse-oximeter with an infrared emitter fixed to the participant's left index finger. Participants were remunerated with 10€/hour or – if preferred – received course credit.

Stress induction

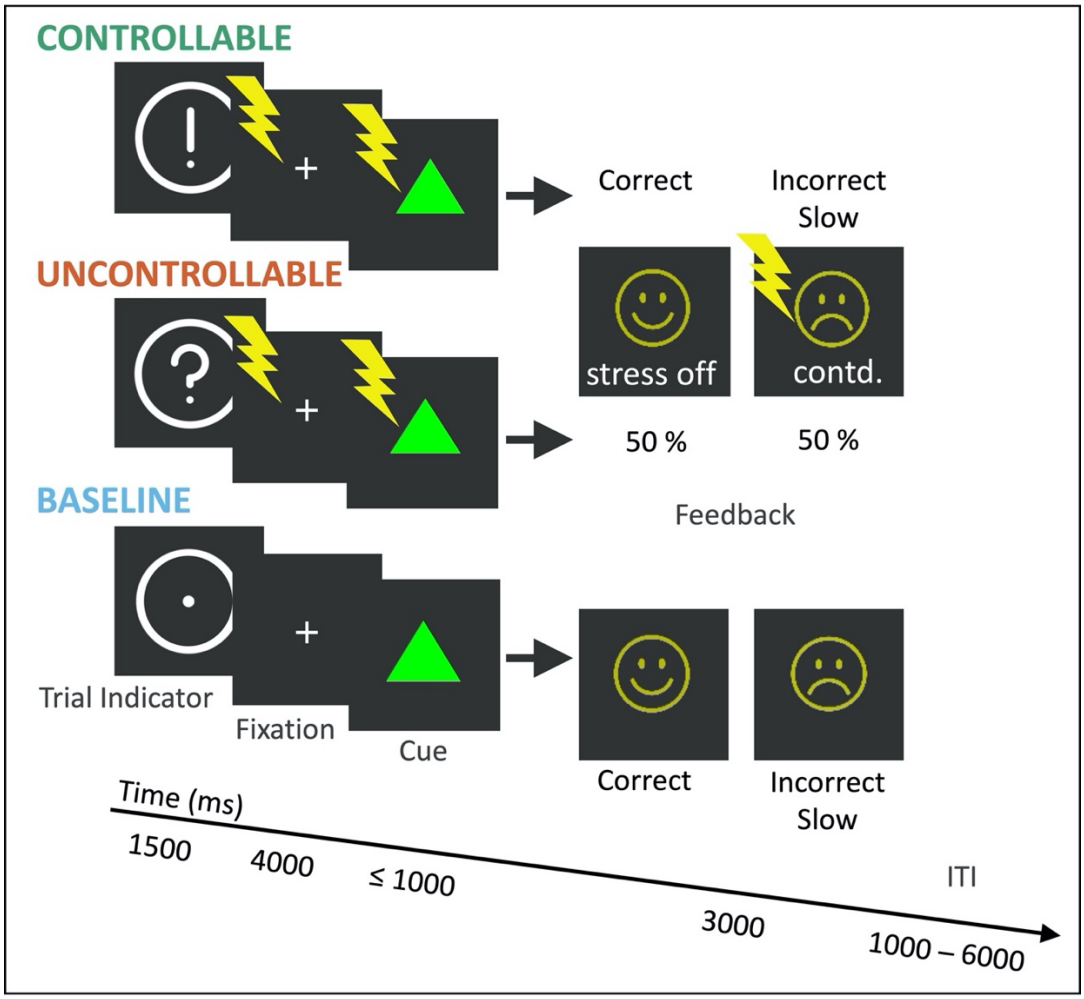
Stress was induced through individually calibrated intermittent double electric stimuli (two stimuli 20 ms apart every 1000 ± 250 ms for the duration of the stress phase). These were administered via Digitimer DS7A current stimulator through an electrode attached to the participant's right ankle. After determining the perception threshold, stimulus intensity was increased in 0.5 mA increments. Participants rated each stimulus on a scale with four anchors: "barely perceptible", "unpleasant", "very unpleasant", and "really painful". We emphasized natural diversity in stimulus perception and encouraged honest responses. Calibration concluded with the participant reaching a very unpleasant, yet not painful intensity (5-6 out of 10; $M = 5.33$, $SD = 0.58$). This level was maintained for the duration of the experiment. To avoid startle responses and movement, participants were familiarized with the intermittent pattern of the electric stimuli. In contrast to distinct single stimuli, the relatively high-frequency stimulation represented a more continuous stress phase.

In an event-related fMRI design, adapted from a behavioural experiment (empirical study 1), participants underwent four runs, each comprising 12 controllable stress (CON) trials, 12 uncontrollable stress (UNCON) trials, and 6 baseline trials without aversive stimulation (Figure 1). For each run, we created a pseudorandomized trial sequence using optseq2 (Dale, 1999; http://surfer.nmr.mgh.harvard.edu/optseq/) to consider slow changes in haemodynamic responses. Optseq2 effectively decorrelates regressors by shifting the inter-trial interval (ITI). In each trial, participants first saw a symbol indicating the trial type (! for CON, ? for UNCON, and a dot for baseline trials; 1500 ms) before a fixation cross appeared and aversive stimulation set in. Participants received intermittent electric stimuli for 4000 ms before a cue (circle, square, or triangle; distributed equally within condition and run) prompted them to press a corresponding button (index, middle, or ring finger of the right hand) to terminate the stimulation. Button presses were registered on a Current Designs response pad with four buttons of which participants were instructed to use only three. A feedback phase (3000 ms) followed, then a variable ITI (1000-6000 ms; $M = 2000$ ms, $SD = 1280$). In CON

trials, correct responses given within 1000 ms immediately terminated electric stimuli with a happy smiley appearing on-screen. Responses that were incorrect or too slow led to continued stimulation throughout the feedback phase in which a sad smiley was displayed. In UNCON trials, positive feedback (i.e., termination of electric stimuli) was randomly given in 50% of trials, irrespective of the participant's response. Baseline trials corresponded to CON trials excluding the aversive stimuli. Before the first run, participants completed a 12-trial stress-free training phase in which they learned the correct cue-button assignment (counterbalanced across participants), showing at least 80% correct performance. They were told that, in CON trials, stressor termination directly depended upon their response, whereas, in UNCON trials, it was up to chance. Nonetheless, we explicitly instructed participants to respond as quickly and correctly as possible in all trials.

Figure 1

Stress induction paradigm



Note. In controllable stress trials, participants' response to a cue was instrumental for stressor termination. In uncontrollable stress trials, aversive stimulation was terminated randomly in 50% of trials, irrespective of participants' response. Trials without stress served as baseline.

At the end of each run, participants indicated how stressed they had felt in each condition and – only for CON and UNCON – how much control over the stressor they had perceived and how helpless they had felt. Additionally, following the eighth CON and UNCON trial of each run, they rated stressor aversiveness. A scale from 0 (not at all) to 100 (very) in increments of 5 was used.

Given our manipulation, participants should have received on average more electric stimuli in UNCON (50% negative feedback) compared to CON trials (potentially 0% negative feedback). However, to ensure equal exposure, we extended the stress-phase prior to the cue in CON trials using a trial-by-trial approach. Specifically, correct responses in CON trials were tracked and the corresponding time required to match negative feedback in UNCON trials

(6 x 3000 s in each run) was divided up and added to subsequent CON trials in a systematic fashion so as to make it barely noticeable. Other studies have followed a similar approach (Diener et al., 2009). Immediately after they had left the scanner, we asked participants if they had noticed any differences in the total number of electric stimuli between conditions.

This experiment was programmed in Python 2.7 (Van Rossum & Drake, 2010), using mainly the PsychoPy package (Peirce et al., 2019).

FMRI data acquisition and preprocessing

Structural and fMRI data were acquired using a 3T Siemens Trio Scanner with a 32-channel head coil. First, T2*-weighted echo-planar images were obtained with a multiband sequence (axials co-planar with anterior-posterior commissure, 4 runs with 480 volumes and 60 slices per volume each, slice thickness = 2.5 mm, distance factor = 0%, FOV = 210 mm, voxel size = 2.5 mm isotropic, TR = 1000 ms, TE = 29 ms, flip angle = 56°, multiband acceleration factor = 4). Structural scans were acquired using a high-resolution T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (sagittal orientation, slice thickness = 0.8 mm, distance factor = 50%, FOV = 260 mm, voxel size = 0.8 mm isotropic, TR = 1900 ms, TE = 2.54 ms, flip angle = 9°). We applied generalized autocalibrating partially parallel acquisitions (GRAPPA) with an acceleration factor of 2 for parallel imaging. T1 origin was subsequently reoriented to the anterior commissure to improve normalization during preprocessing. Data were preprocessed and analysed using Statistical Parametric Mapping (SPM12; The Wellcome Centre for Human Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm/software/spm12) running on MATLAB R2017b (The MathWorks Inc., Natick MA, USA; https://www.mathworks.com/products/matlab.html). To allow for signal equilibration, the first four volumes of each functional scan were discarded as dummy volumes. Images were realigned to the mean functional image using a 6-parameter rigid body transformation, then coregistered to the individual structural scan, normalized to Montreal Neurological Institute (MNI) space with resampling to 3 mm isotropic voxel size, and finally spatially smoothed with a Gaussian kernel of 6 mm full-width at half-maximum. Successful coregistration and normalization were verified through visual inspection.

Analysis approach

Behavioural data were processed and analysed in R (version 3.6.2; R Core Team, 2019). First, we checked for outliers and excluded runs with extreme values (above the third quartile plus three times the IQR or below the first quartile minus three times the IQR; Kassambara et al., 2020). The few instances where we excluded data are described in the respective results sections. Next, we constructed linear mixed-effects models (LMEMs; Brauer & Curtin, 2018) based on the tutorial referenced in Singmann & Kellen (2019), using the afex package (Singmann et al., 2020). To confirm that stressor aversiveness and perceived control did not differ between conditions or over runs, we set up models with condition and run as fixed effects, including an interaction term. Given that condition and run were nested within participants, we incorporated by-participant random intercepts, random slopes for condition and run, and an interaction term to capture random variation. Models testing for condition-dependent differences in outcome measurements (stress and helplessness ratings, RTs, correct responses, BPM) comprised the same random effects. However, only condition was included as a fixed effect because we were not focused on time-dependent changes. For RTs and correct responses trial-by-trial data could be used. Hence, the latter was analysed using a generalized LMEM, appropriate for binary dependent variables (i.e., correct/incorrect). We began by fitting each model with the maximal random effects structure in order to minimize Type I error (Barr et al., 2013). We applied the "bobyqa" optimizer and set the number of model iterations to 10,000. If a model failed to converge or represented a singular fit, we pruned the random effects structure until the model converged without warnings. More precisely, we first removed correlations between random intercepts and random slopes, then random slopes themselves. All final models included participant-level random intercepts (see the supplement for details on final models). We verified that effects held across the maximal and reduced model. For post-hoc comparisons, we used the emmeans package (Lenth, 2020) and employed Holm-Bonferroni correction. Additionally, we applied Bonferroni correction to account for multiple dependent variables in our investigation of controllability-related effects. Only corrected significance levels are reported. We describe model details as suggested by Meteyard and Davies (2020) and state denominator degrees of freedom with decimals as recommended by Brauer & Curtin (2018).

With regard to the fMRI data, we followed SPM's two-level general linear modelling approach to investigate effects of stress and controllability, focusing on the indicator (anticipation-phase) and subsequent fixation phase. We decided to disregard the feedback phase because the procedure employed to match stress durations across CON and UNCON

trials resulted in slightly different trial structures making the feedback phase potentially less comparable. The first-level model comprised six regressors: indicator (CON, UNCON, baseline) and fixation (CON, UNCON, baseline), each modelled using the onset and length of the event (1500 ms and 4000 ms, respectively) convolved with the haemodynamic response function. Additionally, six parameters were included as nuisance regressors to account for any variance associated with motion (the Supplemental Figure S1 visualizes the model design matrix). The high pass filter cut-off period was set to 128 s Two contrasts were computed at the participant level, each for indicator and fixation: stress (CON + UNCON) versus baseline and CON versus UNCON. We also examined the inverse contrasts. The resulting beta images were then subjected to a second-level flexible factorial model comprising condition and the individual participant factor. Main effects of stress were assessed at the whole-brain level. Family-wise error (FWE) correction was performed for voxel-level inference at a threshold of alpha = 0.01 and a cluster-extent threshold of 10 voxels. Controllability effects were investigated in the same manner, however, for the fixation phase, we restricted analyses to our a priori defined regions of interest (ROIs) – the vmPFC and the bilateral amygdala (SVC = small volume correction). The vmPFC mask was taken from Bhanji et al. (Supplement 1 from Delgado et al., 2016) and the left and right amygdala mask was created based on the Harvard-Oxford brain atlas (Desikan et al., 2006), including only voxels with at least a 25% tissue probability. For the ROI analysis, FWE-correction was performed for voxel-level inference using a threshold alpha = 0.05. Peak voxel locations were labelled using the automated anatomical labelling toolbox (AAL3; Rolls et al., 2020).

In light of the animal research findings on controllability-dependent connections between the vmPFC, DRN and its output-regions (e.g., amygdala), we also examined differences in vmPFC connectivity under CON versus UNCON (see Supplement 13 for details).

Finally, we extracted parameter estimates from the vmPFC region more activated under CON compared to UNCON. Specifically, we output beta weights for CON and UNCON regressors for each participant and each run. Firstly, this served to more thoroughly address what might be driving the observed effect, i.e., differences in activation or deactivation or possibly a mixture of both. Secondly, it enabled us to examine links between vmPFC activation and ratings (stress and helplessness) for each condition separately. To this end, mean centered beta weights and an interaction term of beta weight and condition were added as fixed effects to the previously constructed LMEMs investigating stress and helplessness ratings.

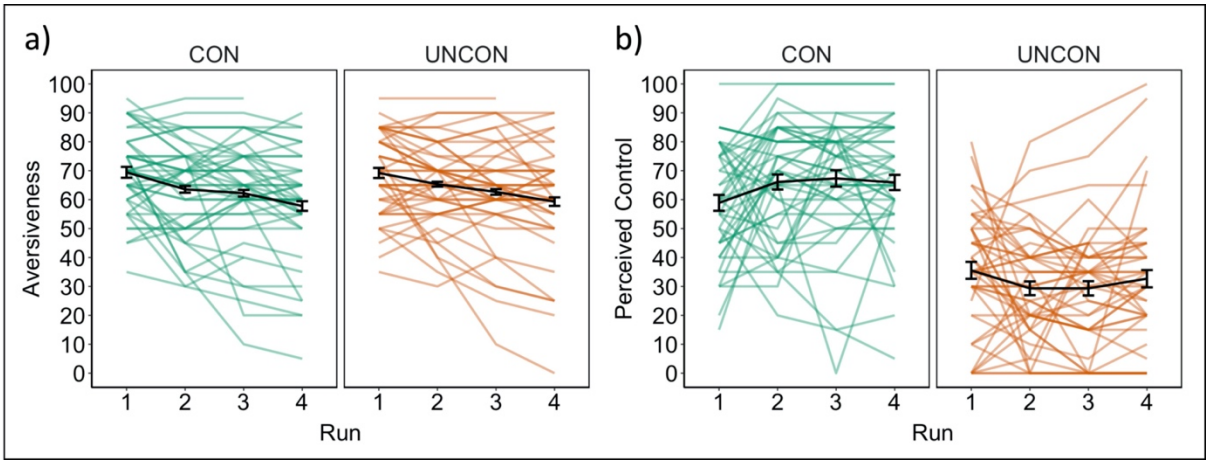
4.2.4 Results

Manipulation check

First, we compared average stress durations between CON and UNCON conditions. A *t*-test indicated imperfect yoking: participants had experienced on average slightly longer stress phases in CON compared to UNCON trials ($t(44) = 6.33$, $p < .0001$, $d = 1$, CON-UNCON stress duration difference: $M = 1.73$ s, $SD = 1.83$). Two participants reported receiving more electric stimuli in CON compared to UNCON trials, effectively noticing this imbalance. They were thus excluded from analysis. To account for the mismatch and its varying magnitude between participants, we included random slopes for the CON-UNCON stress duration difference in subsequent LMEMs. All results remained unchanged. We assessed stressor aversiveness ratings (Figure 2a) and observed no differences between conditions, participants generally rated the electric stimuli as aversive (global $M = 63.75$; $F(1, 264.15) = 2.16$, $p = .143$). There was a small decrease in ratings over runs, indicating slight habituation to the stressor ($F(1, 44.12) = 11.66$, $p = .001$). No interaction of condition x run was indicated ($F(1, 264.15) = 0.53$, $p = .469$). In line with our manipulation, participants perceived significantly more control in CON compared to UNCON trials ($F(1, 44.24) = 104.04$, $p < .0001$). These differences became more pronounced over runs with ratings increasing for CON, but decreasing for UNCON ($F(1, 217.75) = 6.08$, $p = .014$; Figure 2b). Detailed model results can be found in the supplemental material (Supplemental Tables S1 and S2).

Figure 2

Manipulation checks



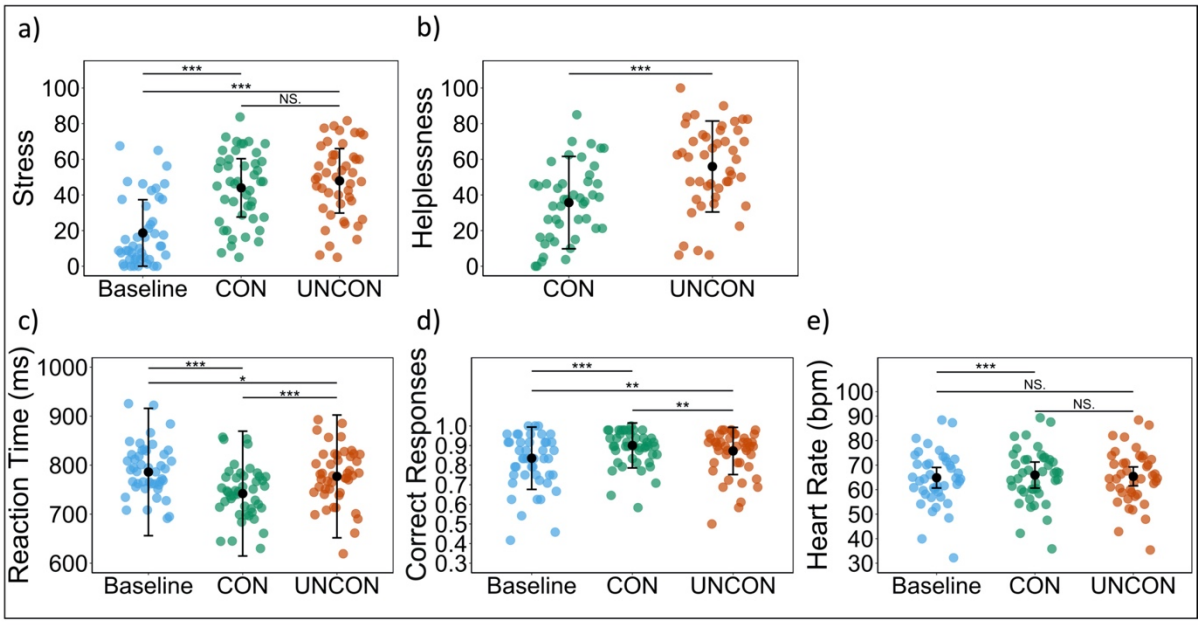
Note. (a) across conditions, participants rated the stressor as very aversive with only slight habituation over runs. (b) They reported perceiving significantly more control for controllable stress (CON) trials compared to uncontrollable stress (UNCON) trials. This effect became slightly more pronounced over runs. Error bars denote within-subject standard errors.

Ratings, RT, accuracy, and heart rate

Participants' stress ratings were significantly higher for stress compared to baseline trials ($F(2,44.12) = 36.41$, $p < .0001$; CON vs. baseline and UNCON vs. baseline: $p < .0001$), however, there was no difference between CON and UNCON ($p = .423$; Figure 3a). As expected, helplessness ratings were lower for CON compared to UNCON ($F(1, 40.65) = 34.03$, $p = .001$; Figure 3b). For the analysis of RTs, one run from one participant was excluded as an outlier due to extremely short RTs. Participants responded faster in CON compared to both UNCON and baseline trials ($F(2, 4743.88) = 84.02$, $p < .0001$; CON vs. UNCON: $p = .001$ and CON vs. baseline: $p < .0001$). RTs were slightly shorter under UNCON compared to baseline ($p = .014$; Figure 3c). Concerning correct responses, data from one participant and one run each from four other participants were excluded from analysis because they demonstrated extremely low performance. In general, participants showed high accuracy ($M = 0.87$, $SD = 0.14$), but differences across conditions emerged ($X^2 = 27.96$, $df = 2$, $p < .0001$; Figure 3d). Performance was significantly better under stress compared to baseline (CON vs. baseline: $p < .0001$; UNCON vs. baseline: $p = .007$). Accuracy was slightly higher in CON compared to UNCON trials ($p = .035$). In terms of heart rate, data from one participant and one run each from two other participants were excluded from analysis because their BPM represented extreme deviations from the sample mean, probably reflecting recording equipment issues. Participant's heart rate differed across conditions ($F(2, 375.83) = 7.01$, $p = .001$; Figure 3e). It was significantly higher under CON compared to baseline ($p = .001$), though differences in absolute values were small. No differences in BPM were observed between CON and UNCON or UNCON and baseline (both contrasts: $p = .580$). The supplemental material contains detailed model results (Supplemental Tables S3-S7).

Figure 3

Ratings, RT, accuracy, and heart rate



Note. (a) subjectively rated stress levels were higher for stress trials compared to baseline. (b) Participants reported feeling less helpless under controllable stress (CON) compared to uncontrollable stress (UNCON). (c) Reaction times were fastest in controllable trials, followed by uncontrollable trials, then baseline. (d) accuracy was generally highest in controllable trials, followed by uncontrollable trials, then baseline. (e) Heart rates were higher under controllable stress compared to baseline, but no differences emerged between controllable and uncontrollable trials. Error bars denote within-subject standard errors.

Neuroimaging results

To examine effects of stress during anticipation and fixation, we contrasted stress (CON+UNCON) and baseline trials. During fixation we observed increased activation in e.g., the anterior and posterior insula (peak voxel: -32 24 8, Z > 8, $p_{FWE\_ROI} < .001$, 2313 voxels and -34 -20 16, Z > 8, $p_{FWE\_ROI} < .001$, 362 voxels, respectively; Figure 4a), the left postcentral gyrus, and the supplementary motor area (SMA; Figure 4b; see Table 1 for all clusters). Areas less activated under stress compared to baseline included the right paracentral lobule (Figure 4c), the right postcentral gyrus, the right inferior occipital gyrus, the left fusiform gyrus (Figure 4d), and the hippocampus among others (Table 1). During anticipation, similar clusters of significant BOLD response changes emerged (Supplemental Table S9).

Table 1

Brain activations associated with stress during fixation

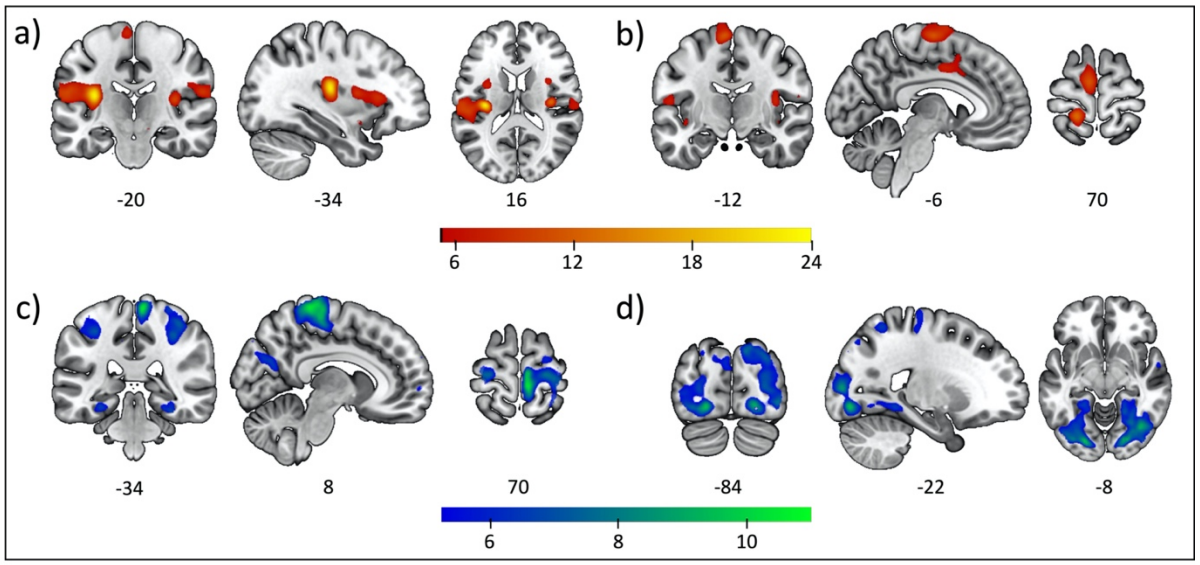
Region		MNI coordinates			*Z*	p_{FWE}	# voxels
Stress > Baseline							
Insula	L	-34	-20	16	> 8	< .001	2313
		-32	24	8	> 8	< .001	362
	R	36	-16	14	> 8	< .001	169
Postcentral gyrus	L	-18	-42	70	> 8	< .001	231
Supramarginal gyrus	R	48	-28	26	> 8	< .001	570
Rolandic Operandum	R	54	2	6	> 8	< .001	1258
Supplementary motor area	L	-6	-12	70	> 8	< .001	457
Lobule IV, V of Vermis		0	-54	-2	> 8	< .001	114
Middle cingulate gyrus	L	-8	-4	40	7.29	< .001	415
Cerebellum	R	20	-32	-24	6.94	< .001	21
Precentral gyrus	L	-46	-2	56	5.93	< .001	25
Baseline > Stress							
Paracentral lobule	R	8	-34	70	> 8	< .001	3766
Inferior occipital gyrus	R	38	-66	-10	> 8	< .001	4912
Fusiform gyrus	L	-22	-84	-8	> 8	< .001	1907
	L	-40	-50	-18	5.96	< .001	49

Postcentral gyrus	L	-50	-20	56	> 8	< .001	1858
Superior parietal gyrus	L	-20	-58	62	6.48	< .001	86
	L	-22	-80	48	5.92	< .001	39
temporal pole: superior temporal gyrus	R	40	18	-28	6.35	< .001	85
Superior temporal gyrus	R	64	-22	6	5.69	< .001	10
Superior frontal gyrus, medial	R	6	62	0	5.98	< .001	50
	R	12	60	28	5.68	< .001	23
Superior temporal gyrus	R	58	-2	-6	5.94	< .001	52
Hippocampus	R	30	-12	-18	5.89	< .001	41
	L	-30	-8	-20	5.88	< .001	20
Angular gyrus	L	-46	-70	28	5.84	< .001	71
Lingual gyrus	L	-14	-64	-4	5.78	< .001	23
Middle occipital gyrus	L	-26	-84	38	5.50	< .001	15
Precuneus	L	-8	-60	62	5.40	< .001	10

Only maxima of clusters significant at $p_{FWE} < .01$, whole-brain corrected with a cluster-defining threshold of $p = .001$ and at least 10 voxels are reported; smoothness of FWHM = 9.0 x 8.9 x 8.8 mm, volume of 1885.4 resels. L = left; R = right; MNI = Montreal Neurological Institute.

Figure 4

Stress effects



Note. The differential contrast Stress > Baseline revealed activation in e.g., (a) the bilateral insula, (b) the supplementary motor area and premotor cortex. The inverse contrast (Baseline > Stress) yielded significant clusters in e.g., (c) the paracentral lobule, (d) fusiform and parahippocampal gyrus. Thresholded T-maps overlaid with the MNI 152 template.

To investigate effects of controllability during fixation, we contrasted CON trials with UNCON trials and restricted our analyses to our ROIs, the vmPFC and the amygdala. The CON > UNCON contrast yielded a significant cluster in the left vmPFC with two local maxima (peak voxel: -6 36 -8, $Z = 4.78$, $p_{FWE\_ROI} = .004$ and -12 44 -6, $Z = 4.68$, $p_{FWE\_ROI} = .007$, respectively, 169 voxels; Figure 5a; Figure 6a). No significant clusters emerged in the bilateral amygdala. An additional exploratory whole-brain analysis revealed no sizeable suprathreshold clusters. The inverse contrast indicated less activation of stress-activated areas, i.e., the insula (Figure 5b), as well as the cingulate gyrus, hippocampus, fusiform gyrus, motor and visual cortices under CON compared to UNCON (Table 2). A ROI analysis restricted to the bilateral amygdala also revealed a significant cluster with two local maxima in the right amygdala (peak voxel: 26 -2 -18, $Z = 3.69$, $p_{FWE\_ROI} = .014$ and 28 2 -20, $Z = 3.56$, $p_{FWE\_ROI} = .021$, respectively, 15 voxels) and a smaller cluster in the left amygdala (peak voxel: -24 -4 -14, $Z = 3.25$, $p_{FWE\_ROI} = .048$, 1 voxel). These results remained unchanged after we included the stress duration as a covariate at the second level.

Table 2

Brain activations related to stressor controllability during fixation

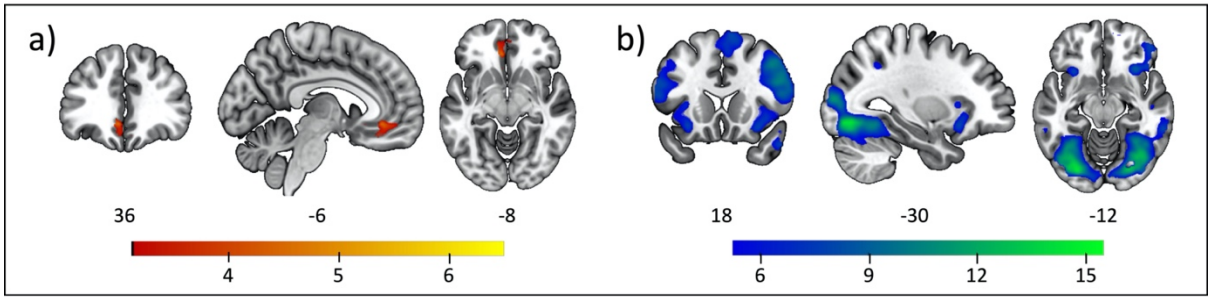
Region		MNI coordinates			*Z*	p_{FWE}	# voxels
CON > UNCON							
no suprathreshold clusters ≥ 10 voxels							
UNCON > CON							
Cuneus	R	18	-98	10	>8	<0.001	10202
Inferior frontal gyrus							
pars triangularis	R	52	28	26	>8	<0.001	4741
	L	-56	20	26	>8	<0.001	1154
pars orbitalis	L	-48	46	-8	7.24	<0.001	155
Superior frontal gyrus							
medial	L	4	40	42	>8	<0.001	1821
medial orbital	R	14	60	-8	7.03	<0.001	65
Inferior parietal gyrus	R	42	-52	46	>8	<0.001	2090
	L	-42	-50	46	7.84	<0.001	797
Precuneus	R	10	-64	40	7.50	<0.001	695
Middle cingulate gyrus	R	2	-22	34	7.13	<0.001	176
Insula	L	-30	18	-12	7.79	<0.001	278
	L	-40	-4	10	5.45	<0.001	15
Thalamus lateral geniculate	R	22	-28	-2	6.94	<0.001	52

	L	-20	-28	-2	6.59	<0.001	28
Middle temporal gyrus	L	-50	-28	-6	6.90	<0.001	64
Postcentral gyrus	L	-58	-20	22	6.64	<0.001	103
Supramarginal gyrus	L	-62	-48	26	6.57	<0.001	188
Lingual gyrus	L	-8	-68	6	6.34	<0.001	265
Middle temporal gyrus	L	-56	-58	12	6.33	<0.001	61
		-60	-42	-12	5.96	<0.001	12
Crus 1 of cerebellar hemisphere	R	12	-78	-30	5.91	<0.001	35

Only maxima of clusters significant at $p_{FWE} < .01$, whole-brain corrected with a cluster-defining threshold of $p = .001$ and at least 10 voxels are reported; smoothness of FWHM = 9.0 x 8.9 x 8.8 mm, volume of 1885.4 resels. CON = controllable stress; UNCON = uncontrollable stress; L = left; R = right; MNI = Montreal Neurological Institute.

Figure 5

Stressor controllability effects



Note. Region of interest analysis contrasting controllable stress (CON) and uncontrollable stress (UNCON) trials revealed activation in (a) the vmPFC. The inverse contrast (UNCON > CON) demonstrated decreased activation in stress-responsive areas, e.g., (b) insula. Thresholded T-maps overlaid with the MNI 152 template

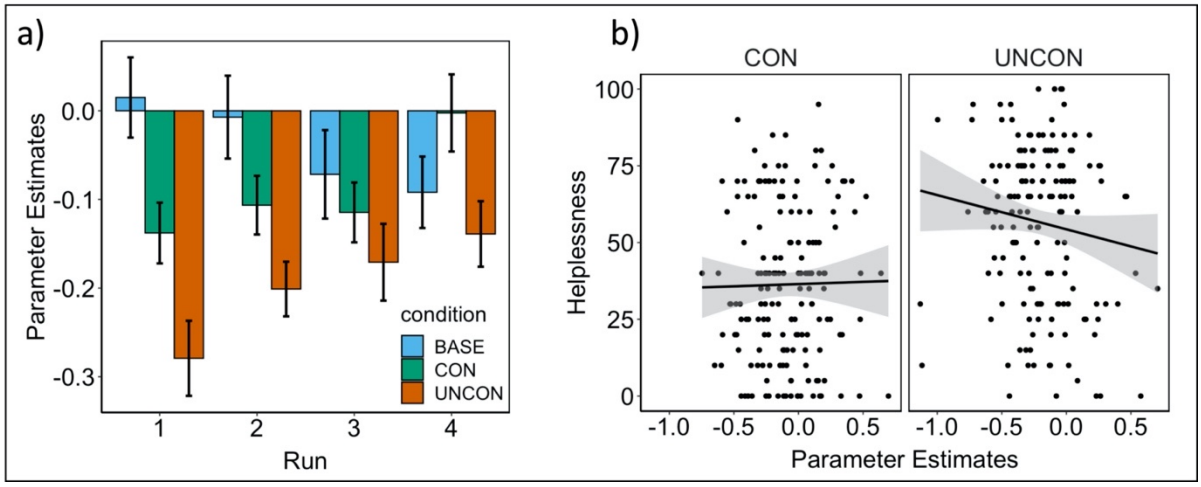
During anticipation, for CON > UNCON, significant clusters emerged in the inferior frontal, middle temporal, and middle frontal gyrus (Supplemental Table S10). Regions that were less activated under anticipation of control compared to lack of control included the inferior occipital and lingual gyrus as well as a vmPFC area overlapping with the cluster that

had emerged from the CON > UNCON contrast during fixation. The analysis of vmPFC connectivity yielded no suprathreshold clusters, neither at the whole-brain level nor when restricting the analysis to the cluster in the right or left amygdala that had emerged in the GLM analysis for the UNCON>CON contrast.

Parameter estimates extracted from the vmPFC cluster reflected a general deactivation of this region under acute stress, which was further supported by an additional ROI analysis comparing neural activation at baseline vs stress during fixation (Supplemental Table S11). Interestingly, the vmPFC parameter estimates were differentially associated with helplessness ratings for UNCON and CON, as evidenced by a significant condition x beta weight interaction ($F(1, 296.20) = 7.89$, $p = .005$; CON vs. UNCON slopes: $p = .005$; Figure 6b; model details in Supplemental Table S8). Specifically, higher beta weights were associated with lower helplessness ratings for UNCON, whereas no such modulation was observed under CON. No interaction effect emerged for stress ratings ($F(2, 387.48) = 1.97$, $p = .14$).

Figure 6

Analysis of parameter estimates



Note. (a) Parameter estimates for baseline (BASE), controllable stress (CON) and uncontrollable stress (UNCON) extracted from the vmPFC cluster. Error bars denote within-subject standard errors. (b) VmPFC activation modulates helplessness ratings for UNCON, but not CON. One data point per participant and run in each condition (as used for mixed-effects modelling).

4.2.5 Discussion

The present study used a translational experimental design drawing upon animal research on LH in order to investigate the differential effects of stressor controllability (controllable vs. uncontrollable stress) on neural activation patterns, subjective ratings of stress and feelings of helplessness, RT and task performance as well as heart rate. In line with our hypotheses, we observed more vmPFC recruitment and lower helplessness ratings under controllable compared to uncontrollable stress. Both conditions were rated similarly stressful compared to baseline, however, contrary to our hypothesis, no differences between controllable and uncontrollable stress emerged. We also noted differences in RTs and performance that were not anticipated. Specifically, participants responded faster and more accurately under stress compared to baseline. The finding that RTs were shortest and accuracy highest under controllable compared to uncontrollable stress was, however, in line with our hypotheses. In terms of heart rate, we had expected more BPM under stress compared to baseline, and an even more elevated heart rate under uncontrollable than controllable stress. Contrary to our hypothesis, we recorded more BPM under controllable stress compared to baseline and observed no other significant contrasts. In the following, we will first discuss the behavioural and heart rate results and then the neuroimaging results in more detail.

Behavioural and heart rate results

As anticipated, ratings indicated greater perceived control for controllable compared to uncontrollable stress, which confirms that our experimental manipulation aligned with participants' subjective experience. This might seem trivial as the objective controllability was explicitly signalled at the beginning of each trial. However, we still observed inter-individual variation in subjectively rated controllability, suggesting that – as in previous between-group designs (empirical study 1; Wanke & Schwabe, 2019) – objective and subjectively experienced controllability does not match in each individual for every trial. Furthermore, ratings of perceived control for controllable trials were generally not at ceiling, likely reflecting the fact that participants had to endure a certain amount of stress even in these trials. This was a necessary constraint to allow the investigation of direct effects of stressor controllability under acute stress. Feelings of helplessness were correspondingly higher for uncontrollable compared to controllable stress, replicating effects from our earlier studies (see empirical study 1). Since LH is commonly discussed as a model for depression (Pryce et al., 2011; Maier & Seligmann, 2016), the evident modulation of helplessness by controllability bears significant potential for clinical intervention.

Participants reported feeling more stressed in trials with aversive stimulation, but they showed concurrently faster RTs and greater task accuracy compared to baseline. Whereas the ratings are partly in line with our hypotheses and reflect successful stress induction, we had expected stress-related RT and performance decrements. However, given the stressfulness of the aversive stimulation, the results can easily be explained by the motivation to terminate the stressor. Baseline trials offered no such pressing need for correct responses. Previous research has shown some beneficial effects of stress on concentration (Degroote et al., 2020) and performance (Beste et al., 2013; Travis et al., 2020), particularly under low task demands (Kim et al., 2017). Indeed, our task was quite simple, as confirmed by the generally high rate of correct responses. Control over the stressor evidently served as further encouragement to perform well. As expected, participants responded more quickly and accurately when their response was instrumental in terminating the stressor than when aversive stimulation was uncontrollable. Surprisingly, performance was better under uncontrollable stress than in the baseline condition. This was unexpected because participants knew that their responses had no consequence in uncontrollable trials. However, since accurate and fast responses were equally inconsequential in baseline trials (where no stressor was applied), two explanations might be considered for these findings. First, participants may just have complied with the instruction to respond as quickly and accurately as possible in all conditions and, second, they may have harboured hope that their responses might show some effect after all, especially when subjected to uncontrollable stress.

Contrary to our hypothesis and in spite of the apparent effectiveness of our manipulation, no robust differences in heart rate emerged. Recordings showed only slightly higher heart rate under controllable stress compared to baseline. Yet, a large body of research has described elevated heart rates under acute stress (Hellhammer & Schubert, 2012; Orem et al., 2019; Sandner et al., 2020). Since we employed an event-related design with relatively short trials, this setup may have prevented a full return to baseline heart rate levels between conditions. Hence, contrasts may have been confounded by carry-over effects and should be interpreted with caution. Possibly, the analysis of heart rate variability – an increasingly popular stress marker (Thayer et al., 2012) – could offer more fine-grained results, but this generally requires electrocardiogram recordings (Schäfer & Vagedes, 2013). Furthermore, guidelines advocate durations of at least five minutes for short-term assessments (Malik et al., 1996). Unfortunately, this suggests that our data do not yield a reliable assessment of differences in heart rate, however, this was not our main focus. Instead, our main objective was to unravel neurobiological differences underlying stressor controllability.

Neuroimaging results

In line with our hypotheses, results demonstrate stressor-induced activation in brain regions commonly implicated in the stress response, e.g., the insula (Sandner et al., 2020; van Oort et al., 2017). Research indicates functionally diverse roles of the anterior and posterior insula, ascribing roles in affective- and pain processing, respectively (Singer et al., 2004). For instance, paradigms employing negative feedback to induce stress have reported corresponding activations in the anterior insula in particular (Sandner et al., 2020). Following the principles of translational research, we employed a physical stressor akin to animal paradigms. However, we found both posterior and anterior parts of the insular cortex to be activated in response to this stressor. In general, human stress research spans many different types of stressors, e.g., electric stimuli (Hartley et al., 2014), thermal stimulation (Bräscher et al., 2016), loud sounds (Henderson et al., 2012), video clips of snakes (Kerr et al., 2012), and unsolvable reasoning tasks (Bauer et al., 2003). Furthermore, research has shown stress-related deactivations of frontal areas (Arnsten, 2015) and the limbic system (Pruessner et al., 2008). Our finding that the hippocampus was less activated under stress compared to baseline is consistent with this literature.

Critically, we observed the expected controllability-dependent differences in vmPFC activation. More precisely, vmPFC recruitment under stress was greater when participants knew they could end the aversive stimulation compared to when there was no contingency between their response and stressor termination. As stress was shown to suppress cortical regions involved in higher-order cognition, i.e., the vmPFC (Arnsten, 2015), the analysis of parameter estimates extracted from the vmPFC helped clarify what was driving the significant contrast. The vmPFC was in fact deactivated both during controllable and uncontrollable stress, but considerably more so in the latter condition. Hence, we observed a controllability-dependent difference in the magnitude of deactivation rather than activation. This finding lends further support to the notion that uncontrollable stress in particular presents a powerful switch which effectively shuts down the PFC (Datta & Arnsten, 2019). Instrumental control, on the other hand, is deemed a protective factor that attenuates stress effects (Henderson et al., 2012; Hartley et al., 2014; Maier & Seligman, 2016). In line with this, control was associated with decreased activation of the amygdala as well as deactivation of the insula, postcentral and middle cingulate gyrus – regions responsive to stress as identified in our analysis. Many of these areas have previously been found to be modulated by stressor controllability. Indeed, Wang and Delgado (2021) observed lower amygdala activation under exposure to controllable aversive tones compared to uncontrollable tones and reported cluster coordinates comparable

to ours. Similarly, another very recent study noted decreased activation in the insula and other threat-related areas under controllable aversive electric shocks (Limbachia et al., 2021).

Contrary to our hypothesis, we observed no differences in vmPFC connectivity between controllable and uncontrollable stress. The overall down-regulatory effect that stress exerts on the vmPFC may well have prevented putative differences from reaching suprathreshold levels. In fact, studies that have found the expected condition-dependent connectivity patterns in humans have largely focused on anticipatory responses rather than investigating BOLD signalling under acute stress (Kerr et al., 2012; Wanke & Schwabe, 2020). Because the fixation phase in our design captures participants' neural responses just before they were prompted to terminate the stressor, it effectively also constitutes an anticipatory phase, albeit under acute stress. Interestingly, during the presentation of the indicator (i.e., anticipation without stress), participants showed more activation in the vmPFC when an uncontrollable trial was signalled, but under stress they subsequently displayed enhanced vmPFC recruitment when they knew they could terminate the stressor. Although the former finding replicates results by Wanke & Schwabe (2020), the apparent reversal in vmPFC recruitment induced by aversive stimulation encourages further research into timing-dependent effects.

Taken together, our results are consistent with animal research in which the vmPFC was shown to downregulate the stress response upon detecting control (Maier & Seligman, 2016). If the neural mechanisms by which controllability modulates our reaction to and appraisal of stressful events are parallel to those found in animals, translational research may offer great promise for the treatment of stress-related mental dysfunction. Animal research has already begun to test pharmacological interventions aimed at enhancing vmPFC activation to ameliorate stress effects. Although these studies can boast considerable successes (Amat et al., 2016), it seems important to consider and pursue further non-pharmacological treatment routes. Alongside behavioural interventions, advances in neuroimaging are starting to open up opportunities for non-pharmacological clinical interventions, such as neurofeedback. In a recent study, Keynan et al. (2019) employed simultaneous EEG-fMRI to individually identify signals from the amygdala in military personnel. Using only EEG, they subsequently targeted this so-called amygdala electrical fingerprint in neurofeedback sessions and trained participants to deliberately downregulate activation. Although further validation may be required, a similar approach can be envisaged in clinical contexts. A recent finding showing that vmPFC activation varies with subjective stress ratings (Orem et al., 2019) supports this idea. In this study, we did not observe a relationship between vmPFC recruitment and stress ratings. However, we could show that increased vmPFC recruitment was associated with reduced

feelings of helplessness under lack of control. Since helplessness has been heavily implicated in the aetiology of depression (Pryce et al. 2011), this finding represents a critical contribution to the literature. Perhaps, modulations of vmPFC activation might be particularly beneficial in uncontrollable contexts. VmPFC recruitment was already shown to be predictive of recovered active avoidance behaviour following passivity induced by uncontrollable stress (Wang & Delgado, 2021). Future research should further investigate the link between vmPFC activation and coping behaviours.

In general, interventions must be directed not only at modulating stress responses on the neurophysiological level, but also in terms of subjective experience. After all, the self-report necessarily describes the symptoms most relevant to the patient and can readily be assessed by clinicians. Moreover, research has highlighted the importance of subjectively perceived controllability over objectively given control. Wanke and Schwabe (2019) found impaired working memory processes to be associated specifically with perceived lack of control over an aversive stimulus rather than objective control or even stress per se. Similarly, Hancock & Bryant (2018a, 2018b) reported links between controllability expectations and stress-avoidance, especially in patients with posttraumatic stress disorder (PTSD).

Limitations and future directions

The present study has some limitations that must be considered when interpreting the results.

First, the within-subject nature of the design led us to explicitly indicate the different trial types and instruct participants as to the correct responses. This helped participants capitalize on the opportunity to terminate the stressor in controllable trials, in line with our intended manipulation. Hence, we were able to clearly differentiate controllable and uncontrollable stress trials from the start of the experiment, but at a cost to our translational efforts. In the original animal experiments, the subjects are required to figure out by themselves how to terminate aversive stimulation. Furthermore, as discussed in the introduction, the experience of control over a stressor may affect responses to subsequent uncontrollable events – and vice versa (Maier & Seligman, 2016). Moreover, any within-subject design is potentially vulnerable to carry-over effects. To prevent such problems, we set up a trial sequence optimized for detecting condition-dependent differences in BOLD signal. The explicitly indicated constant change in trial type also precluded the establishment of an enduring sense of control or feeling of helplessness. In fact, the ratings of perceived control for controllable and uncontrollable trials became more differentiated over time (Figure 2b) and parameter

estimates extracted from the vmPFC likewise showed no evidence of overlapping controllability effects (Figure 6a). After all, we were not interested in controllability-dependent effects on measurements following stress exposure, but rather examined the immediate effects of stressor controllability. For this reason, we also refrained from measuring cortisol – an indicator of the stress response characterized by a rather slow activation profile. Ratings, RTs, and task performance should not have been significantly influenced by the event-related experiment structure, but differences in heart rate may have been clearer in a block design. However, our main focus was on detecting differences in neural activation depending on stressor controllability. Expecting stronger contrasts, we deliberately chose the within-subject design because the same participant could experience all conditions. Furthermore, we anticipated that the variation across trials would increase motivation and compliance. In addition, the smaller sample size required allowed more rapid testing and restricted the number of participants that had to undergo this rather uncomfortable experience.

Second, our experimental manipulation of control resulted in imperfect yoking of stress durations. Specifically, participants suffered slightly longer aversive stimulation in the controllable compared to the uncontrollable condition. Nevertheless, most participants noticed no difference or even reported receiving more electric stimuli in the uncontrollable condition. To account for the mismatch, we included the CON-UNCON stress duration difference in our LMEMs and re-ran relevant fMRI analyses, adding it as a covariate at the second level. If our manipulation is to be used in future studies, this slight imbalance demands improvements to our yoking algorithm. Still, it does not diminish the validity of our results. Rather, the fact that the vmPFC was less deactivated in controllable trials, even though stress phases were, on average, slightly longer than in uncontrollable trials, highlights the robustness of the reported condition-dependent neural activation patterns.

Third, the lack of a jittered time interval between indicator and fixation in our design precludes a clean differentiation of these two phases in terms of BOLD signal. However, results point to marked differences between phases. In response to the indicator announcing uncontrollable rather than controllable stress, the vmPFC was more activated. In contrast, under acute stress, vmPFC recruitment was greater for controllable compared to uncontrollable trials.

Fourth, this study investigated a rather homogeneous sample of healthy, well-educated young participants and results may not be generalized to the whole population. Follow-up investigations focusing on inter-individual differences could further validate controllability-dependent neural processing as a critical mechanism in human stress processing. For instance,

the assessment of participants stratified for resilient outcome (Chmitorz et al., 2020b) could provide important insights to fostering mental health.

Conclusion

This study provides further evidence that controllability in anticipation of as well as under acute stress is associated with distinct neural processes. Results largely corroborate animal findings in a human sample: we showed that the vmPFC was particularly involved in instrumental control and that its activation under stress was associated with a more favourable response. Specifically, our results indicate that vmPFC recruitment under uncontrollable stress attenuated feelings of helplessness. These findings encourage further research into targeted interventions that can promote mental health and resilience in the face of stress.

Availability of Data and Code

Behavioral data and analysis code will be made available on the Open Science Framework: https://osf.io/8qpme/ and will be live upon publication. Due to data protection issues, the MRI data cannot be made available to the public, but we have uploaded our code. The experiment code is available upon reasonable request from the corresponding author.

Declaration of Conflicting Interests

The authors declare no conflict of interest.

Acknowledgements

This research was funded by the German Research Foundation (DFG), Collaborative Research Centre 1193, Project C07. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. We thank all members of Project C07 for their vital contribution, and all participants for taking part in the study. Special thanks go to [redacted] for help with coding the experimental paradigm and [redacted] for help with data acquisition.

4.2.6 Supplement

Table S1

Stressor aversiveness ratings – model details

Fixed Effects						
Predictor		*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept		63.84	2.19	59.55 – 68.12	29.19	**< .001**
Condition		-0.44	0.30	-1.02 – 0.15	-1.470	.143
Run		-3.71	1.09	-5.84 – -1.58	-3.414	**.001**
Condition x Run		-0.22	0.30	-0.80 – -0.37	-0.725	.469
Random Effects						
		Variance		*SD*	*Correlation*	
Participant	(Intercept)	211.18		14.53		
	Run (Slope)	49.01		7.00	0.42	
Model Fit						
Marginal R^2/Conditional R^2: 0.046/0.898						

Note. Model equation: aversiveness ~ condition * run + (1 + run | participant)

Table S2

Perceived control ratings – model details

Fixed Effects

Predictor	*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept	48.21	1.84	44.61 – 51.81	26.23	**< .001**
Condition	16.44	1.61	13.28 – 19.60	10.20	**< .001**
Run	0.87	1.12	-1.32 – 3.06	0.78	.442
Condition x Run	1.79	0.73	0.37 – 3.22	2.47	**.014**

Random Effects

		Variance	*SD*	*Correlation*
Participant	(Intercept)	128.08	11.32	
	Condition (Slope)	93.24	9.66	-0.06
	Run (Slope)	31.99	5.66	0.27 -0.04

Model Fit

Marginal R^2/Conditional R^2: 0.385/0.738

Note. Model equation: perceived control ~ condition * run + (1 + condition + run | participant)

Table S3

Stress ratings – model details

Fixed Effects						
Predictor		*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept		37.89	2.45	33.08 – 42.70	15.45	**< .001**
Condition-CON		-17.39	2.07	-21.44 – -13.34	-8.41	**< .001**
Condition-UNCON		7.10	1.33	4.49 – 9.70	5.34	**< .001**
Random Effects						
		Variance		*SD*	*Correlation*	
Participant	(Intercept)	267.23		16.35		
	Condition-CON (Slope)	180.09		13.42	-0.24	
	Condition-UNCON (Slope)	64.51		8.03	0.20	-0.79
	Run (Slope)	23.98		4.90	0.14	0.15 -0.01
Model Fit						
Marginal R^2/Conditional R^2: 0.249/0.855						

Note. Model equation: stress ~ condition + (1 + condition + run | participant)

Table S4

Helplessness ratings – model details

Fixed Effects						
Predictor		*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept		45.78	2.56	40.77 – 50.79	17.91	**< .001**
Condition		-10.50	1.80	-14.03 – -6.97	-5.83	**< .001**
Random Effects						
		Variance		*SD*	*Correlation*	
Participant	(Intercept)	240.03		15.50		
	Condition (Slope)	138.45		11.77	-0.09	
	Run (Slope)	36.61		6.05	-0.03	-0.13
	Stress Duration Difference (Slope)	88.44		9.40	0.13	0.51 -0.22
	Condition x Run (Slope)	8.12		2.85	-0.22	0.46 0.03
Model Fit						
Marginal R^2/Conditional R^2: 0.167/0.739						

Note. Model equation: helplessness ~ condition + (1 + condition * run + stress duration difference | participant)

Table S5

Reaction times – model details

Fixed Effects						
Predictor		*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept		769.38	6.17	757.28 – 781.47	124.65	**< .001**
Condition-CON		18.65	2.55	13.65 – 23.65	7.31	**< .001**
Condition-UNCON		-27.04	2.09	-31.13 – -22.94	-12.94	**< .001**
Random Effects						
		Variance		*SD*	*Correlation*	
Participant	(Intercept)	1038.02		32.22		
	Run (Slope)	84.66		9.20	0.37	
	Stress Duration Difference (Slope)	1502.21		38.76	-0.02 -0.36	
Model Fit						
Marginal R^2/Conditional R^2: 0.031/0.116						

Note. Model equation: reaction time ~ condition + (1 + run + stress duration difference | participant)

Table S6

Correct responses – model details

Fixed Effects					
Predictor	*Estimate*	*SE*	*95% CI*	*z*	*p*
Intercept	2.05	0.11	1.84 – 2.26	19.12	**< .001**
Condition-CON	-0.31	0.07	-0.44 – -0.18	-4.63	**< .001**
Condition-UNCON	0.30	0.06	0.18 – 0.42	4.86	**< .001**

Random Effects				
		Variance	*SD*	*Correlation*
Participant	(Intercept)	0.17	0.41	
	Stress Duration Difference (Slope)	0.36	0.60	

Model Fit

Marginal R^2/Conditional R^2: 0.015/0.062

Note. Model equation: correct ~ condition + (1 + stress duration difference | | participant)

Table S7

Heart rate – model details

Fixed Effects						
Predictor		*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept		64.44	1.67	61.17 – 67.71	38.57	**< .001**
Condition-CON		-0.53	0.17	-0.86 – -0.21	-3.22	**.00137**
Condition-UNCON		0.54	0.17	0.22 – 0.87	3.26	**.00122**
Random Effects						
		Variance		*SD*	*Correlation*	
Participant	(Intercept)	105.85		10.29		
	Run (Slope)	8.19		2.86		
	Stress Duration Difference (Slope)	13.72		3.70		
Model Fit						
Marginal R^2/Conditional R^2: 0.002/0.943						

Note. Model equation: heart rate ~ condition + (1 + run + stress duration difference | | participant)

Table S8

Helplessness ratings and vmPFC parameter estimates

Fixed Effects

Predictor	*Estimate*	*SE*	*95% CI*	*t*	*p*
Intercept	46.61	2.68	41.36 – 51.86	17.41	**< .001**
Condition	-10.00	1.10	-12.12 – -7.89	-9.28	**< .001**
Beta Weight	-0.45	1.29	-2.98 – 2.07	-0.35	.72535
Condition x Beta Weight	3.08	1.10	0.93 – 5.23	2.81	**.00531**

Random Effects

		Variance	*SD*	*Correlation*
Participant	(Intercept)	182.30	13.50	
	Stress Duration Difference (Slope)	103.10	10.15	-0.15

Model Fit

Marginal R^2/Conditional R^2: 0.168/0.442

Note. Model equation: helplessness ~ condition * beta weight + (1 + stress duration difference | participant)

Table S9

Brain activations associated with stress during anticipation

Region		**MNI coordinates**			***Z***	p_{FWE}	**# voxels**
Stress > Baseline							
Rolandic Operandum	L	-50	-6	10	> 8	< .001	1287
	R	44	-4	8	> 8	< .001	916
Hippocampus	R	30	-12	-12	> 8	< .001	132
	L	-30	-10	-12	> 8	< .001	54
Inferior occipital gyrus	R	40	-82	-6	> 8	< .001	386
	L	-22	-86	-6	6.55	< .001	44
Postcentral gyrus	R	22	-44	74	7.40	< .001	176
Paracentral lobule	L	-8	-18	68	7.28	< .001	580
Calcarine fissure	R	14	-92	-6	6.92	< .001	128
Middle occipital gyrus	L	-24	-90	6	6.88	< .001	65
	L	-44	-86	4	5.58	< .001	11
Middle cingulate gyrus	L	-6	-6	42	6.78	< .001	40
	R	6	-6	40	5.88	< .001	25
Insula	R	40	0	-6	5.91	< .001	27
ventral striatum		6	0	-10	5.86	< .001	12
temporal pole: superior temporal gyrus	R	58	4	-8	5.83	< .001	44

supplementary motor area	R	8	-12	80	5.75	< .001	12
Calcarine fissure	L	-12	-48	6	5.55	< .001	12
Mediodorsal medial magnocellular thalamus	L	-4	-20	4	5.35	< .001	10
Baseline > Stress							
no suprathreshold clusters ≥ 10 voxels							

Note. Only maxima of clusters significant at $p_{FWE} < .01$, whole-brain corrected with a cluster-defining threshold of $p = .001$ and at least 10 voxels are reported; smoothness of FWHM = 8.8 x 8.7 x 8.6 mm, volume of 2010.3 resels. L = left; R = right; MNI = Montreal Neurological Institute.

Table S10

Brain activations related to stressor controllability during anticipation

Region		MNI coordinates			*Z*	p_{FWE}	# voxels
CON > UNCON							
Inferior frontal gyrus pars triangularis	R	54	28	24	6.93	< .001	229
Middle temporal gyrus	R	58	-38	2	6.08	< .001	54
Middle frontal gyrus	R	42	18	44	6.06	< .001	72
Cerebellum	L	-8	-80	-30	5.90	< .001	22
Angular gyrus	R	44	-58	54	5.65	< .001	52
UNCON > CON							
Inferior occipital gyrus	L	-20	-94	-6	> 8	< .001	245
Lingual gyrus	R	20	-90	-6	> 8	< .001	207
Superior frontal gyrus, medial orbital	L	-6	38	-10	6.08	< .001	51

Note. Only maxima of clusters significant at $p_{FWE} < .01$, whole-brain corrected with a cluster-defining threshold of $p = .001$ and at least 10 voxels are reported; smoothness of FWHM = 8.8 x 8.7 x 8.6 mm, volume of 2010.3 resels. CON = controllable stress; UNCON = uncontrollable stress; L = left; R = right; MNI = Montreal Neurological Institute.

Table S11

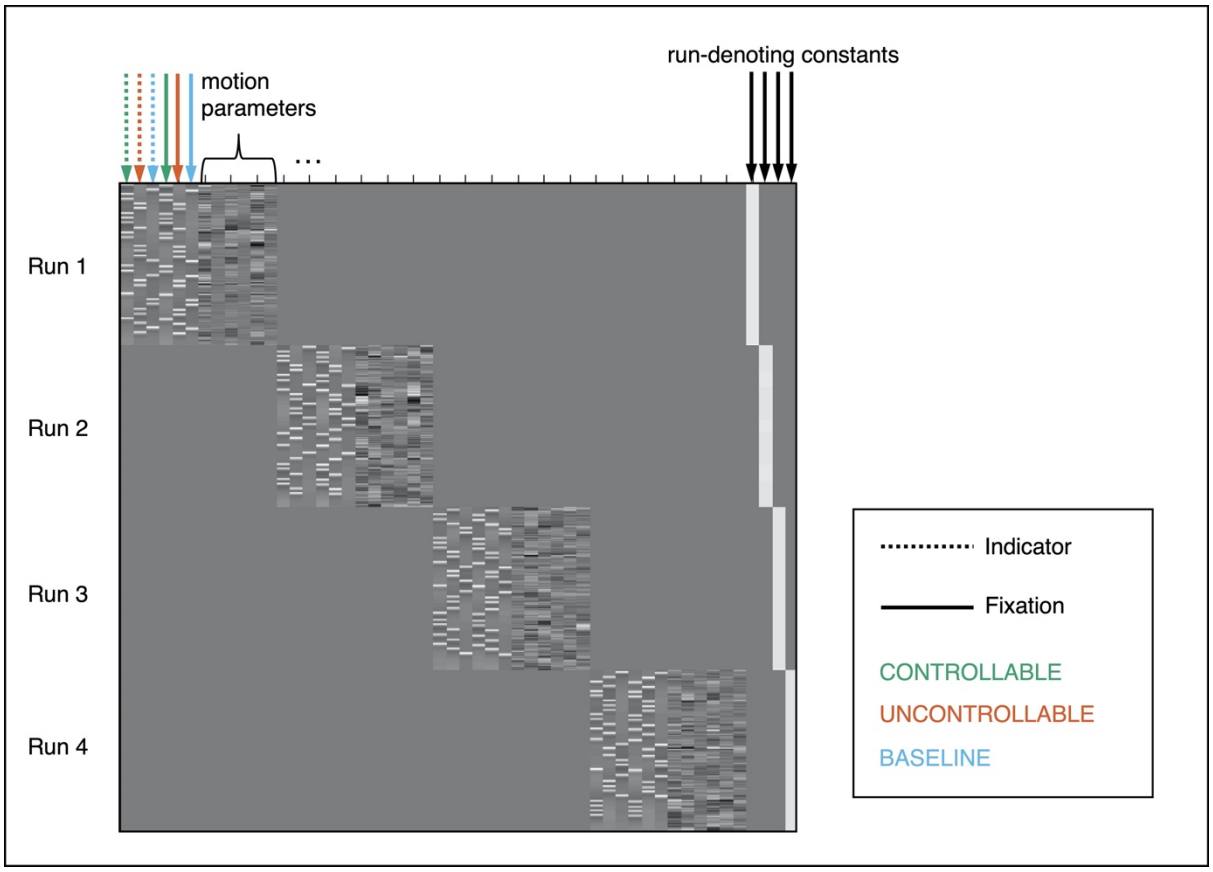
Local maxima of the cluster in the ventromedial prefrontal cortex (980 voxels) associated with the baseline condition during fixation

Region		MNI coordinates			*Z*	p_{FWE}
Baseline > Stress						
Ventromedial prefrontal cortex	R	4	62	-2	5.93	<0.001
		2	36	-20	5.05	<0.001
		0	40	-20	4.97	<0.01
		4	48	-10	4.37	<0.01
		0	46	-20	4.27	<0.05
		4	22	-18	4.23	<0.05
	L	-6	24	-18	5.35	<0.001
		-4	44	-8	4.24	<0.05
		-10	44	-10	4.00	<0.05

Note. Only maxima significant at $p_{FWE} < .05$, small-volume corrected with a cluster-defining threshold of $p = .001$ are reported; smoothness of FWHM = 9.0 x 8.9 x 8.8 mm, volume of 33.3 resels. L = left; R = right; MNI = Montreal Neurological Institute.

Figure S1

First-level model design matrix



Note. All runs comprised the same parameters as visualized for run 1.

Supplement 13

Connectivity analysis

We performed a generalized form of psychophysiological interaction analysis (gPPI; McLaren et al., 2012) using Statistical Parametric Mapping (SPM8; The Wellcome Centre for Human Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm/software/spm8/). We based the analysis on our general linear model which included six regressors representing the indicator (1500 ms) and fixation phase (4000 ms) of each condition (CON, UNCON, baseline), all convolved with the HRF. However, we focused only on the fixation phase. Physiological regressors were extracted as the 1st eigenvariate of a sphere (6 mm radius) around the first local maximum of the vmPFC cluster which resulted from the CON > UNCON contrast (Figure 5a in main text). Next, PPI regressors were generated by deconvolving the physiological regressors with the HRF, multiplying with each of the condition vectors (fixation only) and reconvolving with the HRF. Thus, six task regressors, three PPI regressors, one physiological

regressor, six motion regressors of no interest, and a run-denoting constant comprised the final model. For each participant and run, we then generated the PPI contrasts controllable > uncontrollable stress. The resulting contrast images were entered into a group level analysis and we conducted a one-sample t-test to assess condition-associated modulations of vmPFC-connectivity.

5. General Discussion

This dissertation introduced the concept of stress and outlined its diverse effects as well as how these may be modulated. In this regard, control was discussed as a powerful factor. Whereas the absence of control over a stressor can result in passivity and anxiety, even depression, the experience of control appears protective (Hartley et al., 2014; Henderson et al., 2012; Maier & Seligman, 2016; Wang & Delgado, 2021). Although this observation generally holds true across different studies and applies to both animals and humans (Maier & Seligman, 2016), the field can benefit from more explicit translations and requires further elucidation of the associated neurobiological mechanisms in humans. Thus, in two consecutive studies, (1) a new translational study design was developed and (2) the neural correlates of stressor controllability were examined in humans by means of fMRI. This work provides useful tools for future experiments involving the induction of controllable and uncontrollable stress and contributes to a better understanding of controllability-dependent stress processing in humans. Furthermore, this research was conducted in light of recent developments in resilience research and encourages further investigations of control experience as a putative resilience mechanism. The main findings and their implications, beyond what has already been considered, are discussed in detail in the following sections.

5.1 Summary and Evaluation of Major Findings

The first study includes a review of animal and human research on stressor controllability with a focus on the methodological aspects of translational research. It emphasizes the rather high degree of heterogeneity in human study designs, indicating a lack of explicit translations. Given that findings from animal research are used as a model for the development of psychopathology in humans (Pryce et al., 2011; Vollmayr & Gass, 2013), this gap is significant and should be addressed. The translational paradigm developed in the first study thus represents a useful contribution to the field. It is firmly based on the established triadic animal design and offers a means to contrast the effects of controllable and uncontrollable stress on changes in affect, cognitive function, and behaviour. Rather than limiting read-outs to cognitive markers, as most human researchers are accustomed to doing, additional behavioural indices were devised which more directly translate observations from animals to humans. The resulting escape behaviour test yielded an interesting finding: participants exposed to uncontrollable stress displayed less goal-directed behaviour and greater impulsiveness, compared to participants who had experienced control. Specifically, they

required comparatively more resources to escape another stressor, indicating a lack of planning and conscious strategy formation. This observation draws striking parallels to reports from the literature on reinforcement learning. Studies in this field have repeatedly shown that learning processes and corresponding behaviour are modulated by stress and controllability (Dorfman & Gershman, 2019; Hartley et al., 2014; Leder et al., 2013; Smeets et al., 2019; Wanke & Schwabe, 2019).

Researchers commonly distinguish between two strategies employed in decision-making: model-based and model-free learning (Daw et al., 2005, 2011; Gläscher et al., 2010). Model-based learning describes a process by which an internal model of potential actions and consequences is built and referred to in order to best achieve a present goal. This model is amenable to adaptation given changes in the environment; however, this requires cognitive resources. Model-free learning on the other hand is computationally less demanding since it only considers whether or not an action previously led to a positive or negative outcome and thereby estimates the value of reflexively repeating that action. Critically, the specific outcomes themselves are not represented (Potter et al., 2017). Model-free learning is also associated with greater Pavlovian bias, i.e., the impulse to approach reward-predictive cues and avoid cues indicative of punishment (Guitart-Masip et al., 2012; Raab & Hartley, 2020).

An increasing number of studies has linked stress - acute or chronic - and mental disorders to diminished use of model-based learning and therefore decreased flexibility (Otto et al., 2013; Radenbach et al., 2015; Smeets et al., 2019; Voon et al., 2017). In line with this, the degree of Pavlovian bias has been positively linked to stress history and psychopathology (Mkrtchian et al., 2017; Ousdal et al., 2018). Thus, the overall literature points to reduced flexibility and increased impulsiveness in learning processes under stress and in stress-related disorders.

With regard to controllability, Dorfman & Gershman (2019) could show that it effectively governs the choice of strategy. Under controllable situations a more flexible, i.e., model-based learning strategy is called for, but when the environment is objectively uncontrollable, less flexibility can become the more cost-effective tactic. Correspondingly, participants displayed greater Pavlovian bias when facing an uncontrollable compared to a controllable environment.

The less efficient escape behaviour of the group previously exposed to uncontrollable stress, observed in the first study, can be understood in terms of a shift from model-based to model-free learning, prompted by uncontrollable stress. Furthermore, the fact that the group exposed to controllable stress displayed greater efficiency could be interpreted in terms of a

protective effect of control. Given that research on the interplay of stress, controllability, and decision-making has thus far mostly been discussed against the backdrop of risk, vulnerability, and psychopathology, it seems high time for resilience research to pick up on these findings.

Despite the clear contrast in behaviour induced by the manipulation of stressor controllability, participants' responses were less differentiated at the affective and cognitive levels. In addition to study-specific limitations, the first study underlines the many difficulties faced by translational researchers, which may account, at least in part, for the mixed results. Translation is hampered by the fact that human researchers are seldom aware of the many subtleties surrounding subject recruitment, study design, and data preparation in animal research, and vice versa. Whereas animal researchers try to account for confounding variables such as genetic strain and the impact of handling (Gururajan et al., 2019), the importance of, e.g., the specific wording of task instructions in human research became clear in the first study. Mace and Critchfield (2010) lament the lack of coordination between basic and applied science, stating that "such coordination compromises neither while benefiting both" (p. 293). Regardless of the population studied, the devil is in the details. Hence, thorough documentation, transparency, and open communication appear paramount to successful interdisciplinary research.

In the second study, a modified version of the paradigm developed in the first study was used. Specifically, a within-subject design was employed and optimized for use within the MR environment to track the neural correlates of stressor controllability in humans. Overall, the results replicated findings from the first study, indicating the successful induction of controllable and uncontrollable stress. Importantly, participants showed condition-dependent differences in BOLD signal. Activation in the vmPFC was generally attenuated under stress, but this effect of down-regulation was significantly less pronounced when the stressor was controllable. These results align with previous research in both animals (Datta & Arnsten, 2019) and humans (Bräscher et al., 2016; Kerr et al., 2012; Salomons et al., 2015) and appear evolutionarily plausible. As described in the introduction, stress triggers hard-wired biological and behavioural sequelae that alert the organism and facilitate a rapid response. The ensuing reaction focuses on quickly shutting down or escaping the perceived threat and therefore relies on instinctive rather than planned behaviour (Chrousos, 2009; Godoy et al., 2018). This "one-track mind" kind of state is achieved by suppressing brain regions associated with higher-order cognition, i.e., the vmPFC (Arnsten, 2015). The finding that the vmPFC was less deactivated when participants knew they could soon terminate the stressor demonstrates the powerful

modulatory effect that control appears to exert on stress processing. Given the opportunity for instrumental action in the face of adversity, more complex cognitive functions are maintained and utilized to produce the most adaptive response.

Human beings seem to have a built-in system for choosing between flexible yet complex and costly strategies and more rigid but quick and reflexive behaviours, depending on the situation at hand. However, this system may be slightly biased. Studies have shown that humans prefer to be in control, even if this does not confer any benefits, but comes at a cost (Bobadilla-Suarez et al., 2017). A belief in low agency has been linked to maladaptive stress coping and psychopathology (Fassett-Carman et al., 2019; Ford et al., 2018; Liu et al., 2015). Consequently, research has emphasized the protective effects of control. Based on observations that earlier experiences of control seemed to act as a buffer, shielding animals from the negative effects of later uncontrollable stress, Maier and Seligman (2016) suggested that the control experience essentially constituted an "immunization". Furthermore, they reported that activation of the underlying neural mechanism is sufficient to produce this effect (Amat et al., 2008, 2016; Maier & Seligman, 2016). In support of this, the second study revealed that participants felt less helpless under uncontrollable stress when they showed greater recruitment of the vmPFC.

Although the results of the second study are well in line with the previous literature, the experimental design did not directly allow the investigation of the described SI effect. In order to study this phenomenon, it would be necessary to first expose participants to controllable stress before subjecting them to uncontrollable stress and finally testing the effects on various read-outs. While such a setup already puts significant strain on the participants, several control groups would be required to disentangle the effects of controllability and stress. An attempt at such a complex design has recently been made, albeit with limited success (Meine et al., 2019). Since the bulk of experimental research to date has been conducted on animals, there are many open questions around the timing and intensity of stress exposure suitable to induce an immunization effect in humans.

The experience of control over a stressor has proved highly relevant to clinical and resilience research and deserves further investigation. However, the uncomfortable nature of these experiments begs the question whether excessive trial and error is the best way forward. Future research may instead focus on longitudinal projects to track real-life experiences of control and their effects. While the first study argues for more deliberately planned translational research, it does not deny the utility of human stressor controllability paradigms based more

loosely on the animal design. Moving forward, a good balance should be struck between well-standardized and controlled laboratory experiments using explicitly translational study designs and more ecologically valid field research, targeting diverse populations. These approaches can improve our understanding of neurobiological and molecular mechanisms of stressor controllability on the one hand and increase our knowledge of the many inter-related variables involved on the other hand. The ultimate goal is to identify opportunities for both pharmaceutical and cognitive-behavioural interventions.

5.2 Control Experience as a Putative Resilience Mechanism

The empirical studies discussed in this dissertation have largely been motivated by the search for mechanisms that mediate the effects of identified resilience factors (Feder et al., 2019; Kalisch et al., 2015, 2017). This research agenda centers on the notion that factors such as social support (van Harmelen et al., 2017), good emotion regulation capacity (Zahniser & Conley, 2018), and recall of specific positive memories (Askelund et al., 2019) are predictive of resilient functioning. However, it takes an active mechanism to harness these qualities and ultimately bring about a resilient response in the face of adversity. In other words, it is not enough to have all the ingredients for the cake, you have to bake it, too. At the risk of exhausting the metaphor, the process of baking is affected by the experience and concentration of the baker, the room temperature, the model of the oven, etc. In much the same way, resilience mechanisms represent dynamic processes that "not only depend on a person's personality, genotype or brain architecture, but very much also on the nature of the stressor(s) and the complex and time-varying constellations of intra-, inter- and extra-individual circumstances present during and after stressor exposure." (Kalisch et al., 2017, p. 786).

Based on the literature, perceived control or a belief in high agency is considered a resilience-promoting factor (Masten et al., 2021). The process of recognizing and seizing an opportunity to effect change through one's own actions, and most importantly, internalizing this experience to inform future behaviour, may represent a resilience mechanism. A belief in high agency is crucially dependent on previously observed action-outcome contingencies and is therefore inherently dynamic. Moscarello and Hartley (2017) propose that individuals evaluate the degree of control they have exercised over a given situation and extrapolate from their cumulative experiences. Thus, an individual who has primarily experienced control over important outcomes adopts a more proactive behavioral repertoire. As they meet future challenges with this strategy, their perception of control is reinforced, further perpetuating their

high agency estimate. Consistent with this, high perceived self-efficacy and a more internal locus of control have been linked to more proactive behaviour, which is regarded as advantageous (Bandura, 1977; Dijkstra et al., 2011; Tielemans et al., 2015). For instance, active problem-solving is commonly considered an adaptive coping strategy, whereas distraction tends to be viewed as maladaptive (Compas et al., 2001). Similarly, planned, goal-directed behaviour is associated with more favourable outcomes than reflexive, habitual behaviour, which is discussed as a feature of mental disorders (Voon et al., 2017). On a related note, a large longitudinal study by Hovenkamp-Hermelink et al. (2019) has recently shown that more positive life experiences are predictive of a more internal locus of control, whereas negative life events predicted the development of a more external locus of control. The latter was also linked to greater anxiety and depression.

In laying out their framework for the study of resilience mechanisms, Kalisch et al. (2015, 2020) proposed that there may in fact exist one unifying resilience mechanism subsuming all other processes. They formalized this notion in the Positive Appraisal Style Theory of Resilience (PASTOR), which postulates that the common path to resilience lies in viewing potential threats as manageable challenges and assessing one's own required coping resources as abundant (Kalisch et al., 2017; Veer et al., 2021). While PASTOR has been criticized for being overly narrow (Hermans & Fernández, 2015; Juslin, 2015; Luyten et al., 2015) and failing to incorporate social (Bennett & Windle, 2015; Ungar, 2015a), contextual (Egloff, 2015; Troy, 2015), and developmental factors (Nederhof, 2015), the theory does manage to integrate different literatures on resilience mechanisms. For example, the concept of a positive appraisal style draws parallels to the construct of optimism (Carver et al., 2010) and has consequently been found to be positively associated with optimistic tendencies (Veer et al., 2021). A belief in high agency may likewise reflect a facet of PASTOR, namely the assessment of one's own high coping potential. In line with this, a more positive appraisal style has been linked to higher perceived self-efficacy (Veer et al., 2021). The process of forming control beliefs through repeated experience sampling and contingency learning ideally leads to the individual forming a belief in high agency and acting in accordance with it (i.e., proactively). It can, therefore, be understood to converge in a positive appraisal style, as outlined by PASTOR.

By virtue of conceptualizing control belief formation as a resilience mechanism, it follows that this process is flexible and can be supported to promote mental health.

5.3 Taking Control: Possibilities for Intervention

Different strategies present themselves for utilizing the effects of control experience, both in the context of preventing psychopathology as well as in terms of improving clinical symptoms towards the point of remission.

Investigations of the neural mechanisms, underlying the effects of stressor controllability, have identified the vmPFC and the amygdala as key brain regions mediating the response to controllable and uncontrollable aversive events. This suggests that a modulation of activation of these regions, by means of pharmaceutical intervention, could aid adaptive stress responding. In line with this notion, animal researchers administered ketamine and noted its prophylactic effect on processing future uncontrollable stressors (Amat et al., 2016; Brachman et al., 2016). It appeared to imitate the neural effects of instrumental control, as the typically observed behavioural effects triggered by uncontrollable stress were blunted or even absent altogether in injected animals. Recent studies in humans have demonstrated the usefulness of ketamine as an antidepressant drug with anti-suicidal effects for the treatment of patients for whom established methods have proved ineffective (Matveychuk et al., 2020).

The excitement around ketamine as a fast-acting antidepressant, however, is dulled by observations of side effects, e.g., headache, hypertension, dizziness, blurred vision, and dissociative states (Short et al., 2018; Swainson et al., 2020), as well as its potential for abuse (Trujillo & Iñiguez, 2020). There is still a scarcity of longitudinal studies which could provide much-needed information on the efficacy and safety of ketamine over time. To date, ketamine has not been officially approved as an antidepressant, but it is increasingly employed as a third-line treatment for depression (Wilkinson et al., 2017). A 2017 consensus statement urged health care providers to thoroughly consult the available literature and carefully weigh the risks and benefits associated with off-label ketamine treatment (Sanacora et al., 2017).

Less invasive, non-pharmaceutical means such as neurofeedback may similarly be employed to modulate the activity of relevant brain regions. In this regard, studies have targeted brain regions implicated in the stress response, aiming to down-regulate these and thereby diminish reactivity (e.g., Keynan et al., 2019). For example, a lot of research has focused on the regulation of amygdala activation in PTSD (Nicholson et al., 2017; Zweerings et al., 2020). However, deliberately training individuals to manipulate the circuits that have been found to underlie stressor controllability effects remains challenging. Selective targeting of the vmPFC has proved difficult because the region is heavily connected and hard to functionally separate from areas of the default mode network (Mayeli et al., 2019). Grizzell et al. (2020) have also expressed doubt as to whether artificially stimulating vmPFC-DRN cells, without the necessary

selectivity to reach specific vmPFC afferents, can really be compared to endogenous activity. Nevertheless, the measurement of vmPFC-amygdala connectivity may serve as an indicator of treatment efficacy. This marker has, for instance, been found to predict cognitive behavioural therapy outcome in patients with obsessive-compulsive disorder (Fullana et al., 2017).

Aside from approaches focused on the neural level, considerable research has been conducted on behavioural interventions. Brown et al. (2016) tested procedures to boost perceived self-efficacy in patients with PTSD. These tend to show increased avoidance behaviour in an effort to steer clear of any triggers that might arouse recollections of their trauma (Criterion C; American Psychiatric Association, 2013). The intervention increased self-efficacious future thinking, especially in patients, and appeared to boost social problem solving in general (i.e., also in controls). Liu et al. (2015) also highlighted the therapeutic potential of providing adaptive feedback to adjust overly negative inferential styles. In this regard, family and friends of depressed patients could be trained to provide adaptive feedback and, in turn, foster a more positive (less hopeless) inferential style (Panzarella et al., 2006).

In general, perceived control is thought to provide a good target for treatments (Ly et al., 2019; Wang & Delgado, 2021). In this context, Ly et al., (2019) cite behavioural activation therapy (Jacobson et al., 1996; Hopko et al., 2011) and growth mindset interventions (Grant & Dweck, 2003) as promising approaches to enhance perceived control. The former is focused on increasing patient activity, thereby creating more opportunities for positive reinforcement (Hopko et al., 2003). The latter also targets experience-dependent learning by emphasizing active learning goals. According to Grant and Dweck (2003), framing failure or improvement as independent of one's fixed abilities and rather grounded in experiential learning, can prevent loss of motivation in the face of setbacks. For example, students living in poverty or low-income families, who exhibited a growth-mindset, showed academic performance comparable to that of students from affluent backgrounds (Claro et al., 2016). The buffering effect of students' growth mindset on the relationship between poverty and achievement is thought to reflect a belief that intelligence is not fixed but can actively be promoted. Both methods lend themselves well to the psychotherapeutic setting.

Despite multiple avenues for treatment, more research is needed to strengthen and fine-tune procedures. The challenge is always to establish an intervention that is minimal, limited in time and space, and thus easy to implement in clinical practice, but at the same time powerful, generalizable, and long lasting.

Overall, the different approaches described are not clearly separable given that behavioural interventions can be expected to have an effect on related neurobiological processes and vice versa. However, all these strategies make the assumption that behaviours or beliefs induced by the experience of control are advantageous, whereas the previously described reactions to uncontrollable stressors are considered maladaptive in the long run. This view does not account for contextual factors which may play a significant role (Troy et al., 2013; Wirz et al., 2018).

5.4 Why Context Matters

The theory of LH posits that the experience of a lack of control over adverse events contributes significantly to the development of mental illnesses such as depression (Miller & Seligman, 1975; Pryce et al., 2011). Although the literature describes passivity and resignation in response to uncontrollable stress as maladaptive in the long term (Liu et al., 2015), many reports concede that these behaviours may also be adaptive, at least in the short term (Santiago & Wadsworth, 2009; Wirz et al., 2018). Conversely, an excessive increase in perceived control can also be described as "too much of a good thing" and can equally cause problematic behaviours (Ly et al., 2019).

This is where context comes into play. After all, if a situation is objectively beyond the individual's control, it makes little sense to devote resources to active coping strategies that are doomed from the outset to accomplish nothing. As stated earlier, researchers in the field of learning and decision-making have demonstrated that, depending on the controllability of the environment, different strategies become optimal for obtaining a reward or avoiding a punishment (Dorfman & Gershman, 2019). Similarly, the effectiveness of emotion regulation has been shown to depend on context (Troy et al., 2013). In uncontrollable situations, where instrumental actions are inconsequential, regulating one's emotions through reframing was linked to fewer depressive symptoms. However, in controllable situations where actions can bring about change, cognitive reappraisal was not optimal and was instead associated with greater levels of depression. According to PASTOR, positive reappraisal tendencies that underlie resilience range from realistic to slightly positively biased but exclude unrealistically positive or delusional assessments (Kalisch et al., 2015; Veer et al., 2021). Such balanced appraisals are thought to promote essential stress responses and prevent unnecessarily extended reactions. In short, optimal behaviour takes the circumstances such as the degree of controllability into account.

While a lack of control can be tied to specific situations, there are also environments where it can be pervasive. Poverty describes such an environment; it is commonly associated with deprivation in resources needed to meet basic needs and deficits in health and education (Pogge & Wisor, 2016; United Nations; 2021). However, beyond the more easily quantifiable aspects, poverty is characterized by low degrees of control, predictability, stability and structure (Evans et al., 2010; Lister, 2016). In particular, studies on child development have highlighted frequent moves, poorly defined daily routines, inconsistent parenting, and chaos in the home environment (Bartlett, 1997; Evans, 2004; Marsh et al., 2020). In fact, Oxfam defined poverty as "a state of powerlessness in which people are unable to exercise their basic human rights or control virtually any aspect of their lives" (Hocking, 2001, p. 236). Correspondingly, studies report that individuals who live in poverty tend to make less use of active coping strategies (Evans & Kim, 2013; Wolff et al., 2010). Furthermore, low socioeconomic status has been associated with greater benefits of self-regulation, because opportunities to actively change the situation are limited (Troy et al., 2017).

The behavioural and cognitive patterns identified in individuals from disadvantaged backgrounds reportedly transmit a higher risk of developing mental disorders (Ridley et al., 2020) and are therefore commonly interpreted as deficits (Frankenhuis & Nettle, 2020). However, there is no denying that they can be at least temporarily adaptive because they match the given environmental constraints. Rather than as a deficit, some attributes of people living in poverty may ultimately reveal themselves as hidden talents (Frankenhuis et al., 2020). For instance, lower social class was linked to more adaptive reasoning in the domain of interpersonal conflicts. No such benefit was found for intergroup conflicts, indicating that poverty-related enhancements pertain only to domains which are relevant to survival (Brienza & Grossmann, 2017). In a similar vein, youths who had greater exposure to violence were found to display poorer memory for age relations, but better memory for dominance relations (Frankenhuis et al., 2019). Based on such findings, recent accounts advocate for a strengths-focused perspective to be integrated with the prevailing deficit model (Frankenhuis et al., 2020; Frankenhuis & Nettle, 2020). This view acknowledges that adversity provides opportunities for growth and prompts the development of resilience mechanisms. After all, resilience is defined only in relation to stress (Kalisch et al., 2017; Malhi et al., 2019). Taking it further, Wadsworth et al. (2015) reasoned that coping strategies commonly labelled "maladaptive" could be reconceptualized as functionally adaptive, given the circumstances. Indeed, psychotherapists have long recognized that behaviours classified as harmful typically carry some form of reward for the patient who therefore maintains them (Swerdlow et al., 2020). For

example, self-harm may provide short-term stress relief (Klonsky, 2007). Since such behaviours often arise from specific circumstances, any treatment is likely to be more effective if those same circumstances are explicitly taken into account. Adopting the patient's perspective and considering their particular situation reflects a more validating attitude and may yield greater motivation and compliance.

In general, it seems that beyond experiences of control and a belief in high agency, the capacity to flexibly arbitrate between strategies to adapt to current contextual factors may be essential. In recognition of this, American theologian Reinhold Niebuhr famously prayed: "God grant me the serenity to accept the things I cannot change, courage to change the things I can, and wisdom to know the difference" (Shapiro, 2014). A currently ongoing project aims at investigating whether flexibility in learning processes is positively linked to resilience (Meine et al., 2020).

5.5 Limitations and Future Directions

There are a number of limitations to the empirical studies described, which have already been considered in the respective discussion sections. Beyond study-specific issues, there are more general concerns that relate to translational science and research spanning the themes of stress, controllability, and resilience. In the following, three such difficulties and corresponding approaches to solutions or future directions are outlined.

5.5.1 "Mice Tell Lies" and Other Challenges of Translational Research

Like most large-scale research endeavours, translational projects face certain hurdles. Not all discoveries from the laboratory of basic research, hailed as promising, actually lead to new treatments, diagnostics, and prevention (Venniro et al., 2020). Termed the "valley of death" (Butler, 2008, p. 840), this disconnect may in part be caused by a lack of communication between basic and clinical scientists. It seems that, while animal researchers are rapidly deciphering disease mechanisms, it takes longer for those findings to be picked up in human research – which risks the possibility of progressing to applied research without having the full certainty that the findings translate well. In most cases, it takes around 17 years for discoveries from fundamental research to become incorporated into clinical practice (Morris et al., 2011).

The fact that, depending on the field of research, translations from animals to humans are expected to be incomplete further complicates the matter. For instance, in the context of mental disorders, with symptoms involving both neurocognitive and semantic factors, perfect

translation seems hardly possible (Aragona, 2017). Study 1 of this dissertation highlighted this difficulty: whereas human stress research places special focus on the psychological reaction, animal research is of course more concerned with behavioural read-outs. The promise of animal models to offer a clear-cut example allowing detailed delineation of disease mechanisms necessarily comes with the pitfall of over-simplification (Gururajan et al., 2019). Nonetheless, even without perfectly matching the human condition, animal models may have significant predictive validity (Venniro et al., 2020). They certainly provide an indispensable tool for studying mechanisms at a level we cannot easily (or non-invasively) get at in humans. However, there is always room for improvement. Bolker (2017) urges researchers to choose their models with care, keeping in mind known disparities between species. Furthermore, she encourages scientists to look beyond the tried and tested model and pursue complementary designs to effectively broaden the potential for translation. Gururajan et al. (2019) also point out that more precise wording, i.e., "animal models for studying depression" instead of "animal models of depression" (p. 687) can already make a difference.

Since translational research is often conducted collaboratively between academia and industry, projects may suffer from a clash of cultures. Whereas academics are largely incentivized to produce novel findings, companies charged with bringing research discoveries into the clinic or community focus more on whether data are reproducible, scalable, reimbursable, and commercially free to use (Schwartz & Macomber, 2017).

Moving forward, a good strategy for improvement would be to increase communication all around: between scientists of different disciplines, between researchers and stakeholders, between investors and policymakers as well as between doctors and patients. In order to improve communication, training at all levels should explicitly promote translational thinking so that projects may be planned collaboratively and comprehensively from the start (Vukotich, 2016).

5.5.2 A Developmental Perspective

Extensive literature from the field of reinforcement learning has established that the cumulative experience of action–outcome contingencies may yield a generalized belief in high or low agency, respectively (Moscarello & Hartley, 2017; Ly et al., 2019). Because such an internalized estimate of agency can drive subsequent behaviour, a deeper understanding of its development is relevant across disciplines. However, here the focus is on findings that can inform resilience research in particular. Research showing that high control beliefs prompt

more proactive coping strategies therefore seems exciting (Zimmer-Gembeck et al., 2016). Active coping is generally associated with better mental health outcomes than comparatively passive strategies that are thought to provide only temporary relief (Santiago & Wadsworth, 2009). This current state of knowledge has already sparked the development of promising interventions, as described earlier, and many more ideas are coming. Nevertheless, it appears useful to try to understand the mechanisms even better. To best address the question of how exactly high agency beliefs form and give rise to adaptive behaviour, longitudinal studies are necessary. Given that the constructs of generalized self-efficacy and locus of control are thought to be relatively stable, a closer look at how they develop during childhood and adolescence might provide answers.

Malhi et al. (2019) argue that adolescence, in particular, constitutes an ideal phase to investigate resilience processes because it is a period of transition characterized by increasing stress and susceptibility, but at the same time with great flexibility and potential for adaptive change. Resilience only fully emerges as a consequence of the system being tested and represents the outcome of improved or newly acquired skills that counteract adversity. Adolescence, as a shapeable make-or-break phase, thus represents the optimal window of opportunity. Although not much is known yet with regard to resilience, many studies have identified adolescence as the formative phase in which mental disorders emerge (Blakemore & Mills, 2014; Kessler et al., 2007; Thapar et al., 2012). However, much of the research focuses on dysfunctions in adolescence as a delayed consequence of adverse experiences made in early childhood (e.g., Dillon et al., 2009; Hanson et al., 2016).

In general, resilience research would benefit from integrating a developmental perspective – and adolescence may be taken as a starting point, but not as the sole time period of interest. In fact, a lifespan approach appears useful, considering that in old age, cognitive and physical decline again provoke broad changes (Grady, 2012) that affect mental health (Han et al., 2019; Laidlaw & Pachana, 2009). It is likely that during this time, resilience mechanisms are adjusted to account for diminishing resources and flexibility (Jopp & Smith, 2006). For example, older adults find they have less scope for instrumental control (Robinson & Lachman, 2017) and may therefore concentrate on self-regulatory strategies such as positive reappraisal. Indeed, subjective self-regulation has emerged as the most consistent predictor of health in old age (Reed et al., 2020). Furthermore, studies suggest that older adults tend to focus more on their emotions and are biased towards positive information (Carstensen et al., 2003; Charles & Piazza, 2009). Diehl and Hay (2010) also found evidence that younger adults may be more sensitive to perceiving low control in the context of interpersonal stressors. Despite that,

perceived control also continues to play an important role in older adults: higher levels were associated with lower hazard for mortality (Infurna et al., 2012).

It is quite conceivable that control beliefs evolve and fluctuate in a similar manner across individuals over the course of their development as they form during childhood, are pitted against overwhelming responsibility in adulthood, and then decrease in old age. Despite that, contextual factors, as previously discussed, will induce inter-individual variation and should not be neglected.

Overall, experiences in childhood have been shown to have a marked impact on later life functioning and mental health with adolescence potentially representing the phase when pre-determined dysfunctions start manifesting. By contrast, self-reported well-being has been described as elevated or even steadily increasing in later life (Stone et al., 2010), despite wide-spread decline in agency, cognitive functioning, and health. This apparent paradox makes a strong case for adopting a developmental perspective in the study of stressor controllability and resilience.

5.5.3 Beyond WEIRD Research

As suggested before, environmental aspects matter a great deal. In this regard it is lamentable that the majority of studies on human psychology and behaviour to date have been conducted by researchers from Western, educated, industrialized, rich and democratic (WEIRD) societies on just such participants (Henrich et al., 2010; Rad et al., 2018). It follows that stress research almost certainly captures primarily the mildly stressed and undersamples the severely stressed. The literature is therefore imbued with implicit biases that (mis)shape our understanding of research findings. For instance, reports linking poverty to psychopathology (Ridley et al., 2020), while certainly valid, lack nuance. Academia tends to dismiss features observed in psychological variables in people from less affluent and privileged backgrounds as deficiencies or impairments (Frankenhuis & Nettle, 2020). However, certain behaviours may simply reflect the different environmental demands. If reflexive responding is optimal in the absence of control (Dorfman & Gershman, 2019), and if poverty or low socioeconomic status is marked by uncontrollability (Evans et al., 2010; Lister, 2016), then it is surely adaptive to forego complex and costly strategies under such circumstances.

Overall, the role of systemic factors appears woefully understudied and merits closer attention in the future. It is important to note, however, that the lack of diverse and representative samples is generally not due to wilful neglect on the researchers' part, rather that

they frequently face obstacles in, e.g., recruitment (Robinson et al., 2016). More inclusive and therefore more representative investigations into stress and resilience are increasingly advocated for and pursued (Masten et al., 2021; Meili et al., 2019; Ungar, 2015b).

5.6 Conclusion

Stress represents a multifaceted construct that has been researched for decades but continues to grow in popularity as new questions arise. The view that stress has predominantly negative effects is certainly too narrow. In the words of Hans Selye: “Stress is not necessarily bad for you. It is also the spice of life, for any emotion, any activity causes stress” (Adams, 2016). As such, stress links to learning (Wirz et al., 2018), memory (Goldfarb et al., 2019), attention (Shields et al., 2019), health, and disease (Hammen, 2005; McLaughlin et al., 2020) and is itself influenced by many different factors (Sapolsky, 2015).

This dissertation has elaborated on the profound modulatory effect that control exerts over how stress is perceived and responded to. All in all, exposure to an adverse event that is beyond one's control is evidently associated with rather unfavourable outcomes, particularly when the stressor occurs frequently (Liu et al., 2015; Maier & Seligman, 2016; Soral et al., 2021). The experience of control, by contrast, has been shown to protect from future uncontrollable stress (Amat et al., 2010; Maier & Seligman, 2016). The process of registering, utilizing, and internalizing possibilities for consequential action in the face of adversity therefore bears great potential for mechanistic resilience research.

Further research on the formation of generalized control beliefs as a putative resilience mechanism could benefit from integrating a developmental perspective. Different phases across the lifespan typically afford different degrees of control with corresponding changes in agency beliefs (Robinson & Lachman, 2017). However, researchers should also not lose sight of contextual factors. Fostering a sense of agency can only be beneficial if the individual finds themself in an environment that holds opportunities for instrumental action (Troy et al., 2013, 2017). A significant but understudied proportion of the population is situated in less fortunate circumstances which necessitate a different approach. Future research on stress and controllability should aim at providing a more nuanced, inclusive picture. In this vein, interdisciplinary collaboration and communication need to be strengthened. The field of stressor controllability is deeply rooted in translational research, having emerged from animal studies that developed much-in-demand models for the development of psychopathology in humans. Although research is ongoing in both animal and human, concerted effort between

both groups is still expandable. In order to advance this agenda, researchers from different disciplines need to collaborate even more closely. After all, it is a truth universally acknowledged that science advances more rapidly and yields a more profound impact on society when researchers actively encourage and adhere to the principles of transparency, communication, and teamwork.

6. References

Abramson, L. Y., Seligman, M. E., & Teasdale, J. D. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology, 87*(1), 49–74. https://doi.org/10.1037/0021-843X.87.1.49

Adams, T. (2016, February 14). Is there too much stress on stress? *The Guardian*. https://www.theguardian.com/society/2016/feb/14/workplace-stress-hans-selye

Ajzen, I. (2002). Perceived Behavioral Control, Self-Efficacy, Locus of Control, and the Theory of Planned Behavior. *Journal of Applied Social Psychology*, *32*(4), 665–683. https://doi.org/10.1111/j.1559-1816.2002.tb00236.x

Algina, J., Keselman, H. J., & Penfield, R. D. (2005). An Alternative to Cohen's Standardized Mean Difference Effect Size: A Robust Parameter and Confidence Interval in the Two Independent Groups Case. *Psychological Methods*, *10*(3), 317-328. https://doi.org/10.1037/1082-989X.10.3.317

Alloy, L. B., Peterson, C., Abramson, L. Y., & Seligman, M. E. P. (1984). Attributional style and the generality of learned helplessness. *Journal of personality and social psychology*, *46*(3), 681-687. https://doi.org/10.1037/0022-3514.46.3.681

Amat, J., Aleksejev, R. M., Paul, E., Watkins, L. R., & Maier, S. F. (2010). Behavioral control over shock blocks behavioral and neurochemical effects of later social defeat. *Neuroscience*, *165*(4), 1031–1038. https://doi.org/10.1016/j.neuroscience.2009.11.005

Amat, J., Baratta, M. V., Paul, E., Bland, S. T., Watkins, L. R., & Maier, S. F. (2005). Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature Neuroscience*, *8*(3), 365–371. https://doi.org/10.1038/nn1399

Amat, J., Dolzani, S. D., Tilden, S., Christianson, J. P., Kubala, K. H., Bartholomay, K., … & Maier, S. F. (2016). Previous Ketamine Produces an Enduring Blockade of Neurochemical and Behavioral Effects of Uncontrollable Stress. *Journal of Neuroscience*, *36*(1), 153–161. https://doi.org/10.1523/JNEUROSCI.3114-15.2016

Amat, J., Matus-Amat, P., Watkins, L. R., & Maier, S. F. (1998). Escapable and inescapable stress differentially and selectively alter extracellular levels of 5-HT in the ventral hippocampus and dorsal periaqueductal gray of the rat. *Brain research*, *797*(1), 12-22. https://doi.org/10.1016/S0006-8993(98)00368-0

Amat, J., Paul, E., Watkins, L. R., & Maier, S. F. (2008). Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. *Neuroscience*, *154*(4), 1178–1186. https://doi.org/10.1016/j.neuroscience.2008.04.005

Amat, J., Paul, E., Zarza, C., Watkins, L. R., & Maier, S. F. (2006). Previous Experience with Behavioral Control over Stress Blocks the Behavioral and Dorsal Raphe Nucleus Activating Effects of Later Uncontrollable Stress: Role of the Ventral Medial Prefrontal Cortex. *Journal of Neuroscience*, *26*(51), 13264–13272. https://doi.org/10.1523/JNEUROSCI.3630-06.2006

American Psychiatric Association (Ed.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association.

American Psychological Association, APA Working Group on Stress and Health Disparities. (2017). *Stress and health disparities: Contexts, mechanisms, and interventions among racial/ethnic minority and low-socioeconomic status populations.* https://www.apa.org/pi/health-disparities/resources/stress-report.pdf

American Psychological Association (2012). *Building your resilience*. Retrieved March 19, 2021, from https://www.apa.org/topics/resilience.

American Psychological Association (2020). *Stress in America™. A National Mental Health Crisis*. https://www.apa.org/news/press/releases/stress/2020/sia-mental-health-crisis.pdf

Aragona, M. (2017). The impact of translational neuroscience on revisiting psychiatric diagnosis: state of the art and conceptual analysis. *Balkan medical journal*, *34*(6), 487-492. https://dx.doi.org/10.4274%2Fbalkanmedj.2017.1190

Arnsten, A. F. T. (2015). Stress weakens prefrontal networks: Molecular insults to higher cognition. *Nature Neuroscience*, *18*(10), 1376–1385. https://doi.org/10.1038/nn.4087

Askelund, A. D., Schweizer, S., Goodyer, I. M., & van Harmelen, A. L. (2019). Positive memory specificity is associated with reduced vulnerability to depression. *Nature Human Behaviour*, *3*(3), 265-273. https://doi.org/10.1038/s41562-018-0504-3

Asselmann, E., Wittchen, H.-U., Lieb, R., & Beesdo-Baum, K. (2017). A 10-year prospective-longitudinal study of daily hassles and incident psychopathology among adolescents and young adults: Interactions with gender, perceived coping efficacy, and negative life events. *Social Psychiatry and Psychiatric Epidemiology*, *52*(11), 1353–1362. https://doi.org/10.1007/s00127-017-1436-3

Austin, C. P. (2018). Translating translation. *Nature Reviews Drug Discovery*, *17*(7), 455-456. https://doi.org/10.1038/nrd.2018.27

Bandettini, P. A. (2009). What's new in neuroimaging methods? *Annals of the New York Academy of Sciences*, *1156*, 260-293. https://doi.org/10.1111/j.1749-6632.2009.04420.x

Bandettini, P. A. (2012). Sewer pipe, wire, epoxy, and finger tapping: The start of fMRI at the Medical College of Wisconsin. *Neuroimage*, *62*(2), 620–631. https://doi.org/10.1016/j.neuroimage.2011.10.044

Bandler, R., & Depaulis, A. (1991). Midbrain periaqueductal gray control of defensive behavior in the cat and the rat. In *The midbrain periaqueductal gray matter* (pp. 175-198). Springer, Boston, MA.

Bandura, A. (1977). Self-efficacy: toward a unifying theory of behavioral change. *Psychological review*, *84*(2), 191-215. https://doi.org/10.1037/0033-295X.84.2.191

Bandura, A., Cioffi, D., Taylor, C. B., & Brouillard, M. E. (1988). Perceived self-efficacy in coping with cognitive stressors and opioid activation. *Journal of personality and social psychology*, *55*(3), 479-488. https://doi.org/10.1037/0022-3514.55.3.479

Baratta, M. V., Christianson, J. P., Gomez, D. M., Zarza, C. M., Amat, J., Masini, C. V., … & Maier, S. F. (2007). Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. *Neuroscience*, *146*(4), 1495–1503. https://doi.org/10.1016/j.neuroscience.2007.03.042

Baratta, M. V., Lucero, T. R., Amat, J., Watkins, L. R., & Maier, S. F. (2008). Role of the ventral medial prefrontal cortex in mediating behavioral control-induced reduction of later conditioned fear. *Learning & Memory*, *15*(2), 84–87. https://doi.org/10.1101/lm.800308

Baratta, M. V., Zarza, C. M., Gomez, D. M., Campeau, S., Watkins, L. R., & Maier, S. F. (2009). Selective activation of dorsal raphe nucleus-projecting neurons in the ventral medial prefrontal cortex by controllable stress. *European Journal of Neuroscience*, *30*(6), 1111–1116. https://doi.org/10.1111/j.1460-9568.2009.06867.x

Barr, D. J., Levy, R., Scheepers, C., & Tily, H. J. (2013). Random effects structure for confirmatory hypothesis testing: Keep it maximal. *Journal of Memory and Language*, *68*(3), 255-278. https://doi.org/10.1016/j.jml.2012.11.001

Bartlett, S. (1997). The significance of relocation for chronically poor families in the USA. *Environment and Urbanization*, *9*(1), 121-132. https://doi.org/10.1177%2F095624789700900101

Bauer, H., Pripfl, J., Lamm, C., Prainsack, C., & Taylor, N. (2003). Functional neuroanatomy of learned helplessness. *NeuroImage*, *20*(2), 927–939. https://doi.org/10.1016/S1053-8119(03)00363-X

Bennett, K. M., & Windle, G. (2015). The importance of not only individual, but also community and society factors in resilience in later life. *Behavioral and Brain Sciences*, *38*, E94. https://doi.org/10.1017/S0140525X14001459

Beste, C., Yildiz, A., Meissner, T. W., & Wolf, O. T. (2013). Stress improves task processing efficiency in dual-tasks. *Behavioural Brain Research*, *252*, 260–265. https://doi.org/10.1016/j.bbr.2013.06.013

Bhanji, J. P., Kim, E. S., & Delgado, M. R. (2016). Perceived control alters the effect of acute stress on persistence. *Journal of Experimental Psychology: General*, *145*(3), 356–365. https://doi.org/10.1037/xge0000137

Blakemore, S. J., & Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annual review of psychology*, *65*, 187-207. https://doi.org/10.1146/annurev-psych-010213-115202

Blumberg, R. S., Dittel, B., Hafler, D., Von Herrath, M., & Nestle, F. O. (2012). Unraveling the autoimmune translational research process layer by layer. *Nature medicine*, *18*(1), 35-41. https://doi.org/10.1038/nm.2632

Bobadilla-Suarez, S., Sunstein, C. R., & Sharot, T. (2017). The intrinsic value of choice: The propensity to under-delegate in the face of potential gains and losses. *Journal of Risk and Uncertainty*, *54*(3), 187–202. https://doi.org/10.1007/s11166-017-9259-x

Bolger, N., DeLongis, A., Kessler, R. C., & Schilling, E. A. (1989). Effects of daily stress on negative mood. *Journal of personality and social psychology*, *57*(5), 808-818. https://doi.org/10.1037/0022-3514.57.5.808

Bollini, A. M., Walker, E. F., Hamann, S., & Kestler, L. (2004). The influence of perceived control and locus of control on the cortisol and subjective responses to stress. *Biological Psychology*, *67*(3), 245–260. https://doi.org/10.1016/j.biopsycho.2003.11.002

Bolker, J. A. (2017). Animal models in translational research: Rosetta stone or stumbling block? *Bioessays*, *39*(12), 1700089. https://doi.org/10.1002/bies.201700089

Bonanno, G. A. (2004). Loss, Trauma, and Human Resilience: Have We Underestimated the Human Capacity to Thrive After Extremely Aversive Events? *American Psychologist*, *59*(1), 20-28. https://doi.org/10.1037/0003-066X.59.1.20

Bonanno, G. A., Galea, S., Bucciarelli, A., & Vlahov, D. (2006). Psychological Resilience After Disaster: New York City in the Aftermath of the September 11th Terrorist Attack. *Psychological Science*, *17*(3), 181–186. https://doi.org/10.1111/j.1467-9280.2006.01682.x

Bonanno, G. A., Mancini, A. D., Horton, J. L., Powell, T. M., LeardMann, C. A., Boyko, E. J., ... & Millennium Cohort Study Team. (2012). Trajectories of trauma symptoms and resilience in deployed US military service members: Prospective cohort study. *The British Journal of Psychiatry*, *200*(4), 317-323. https://doi.org/10.1192/bjp.bp.111.096552

Bonanno, G. A., Wortman, C. B., Lehman, D. R., Tweed, R. G., Haring, M., Sonnega, J., Carr, D., & Nesse, R. M. (2002). Resilience to loss and chronic grief: A prospective study from preloss to 18-months postloss. *Journal of Personality and Social Psychology*, *83*(5), 1150–1164. https://doi.org/10.1037/0022-3514.83.5.1150

Bongard, S. (1995). Mental effort during active and passive coping: A dual-task analysis. *Psychophysiology*, *32*(3), 242-248. https://doi.org/10.1111/j.1469-8986.1995.tb02960.x

Botvinick, M., & Braver, T. (2015). Motivation and Cognitive Control: From Behavior to Neural Mechanism. *Annual Review of Psychology*, *66*(1), 83–113. https://doi.org/10.1146/annurev-psych-010814-015044

Brachman, R. A., McGowan, J. C., Perusini, J. N., Lim, S. C., Pham, T. H., Faye, C., ... & Denny, C. A. (2016). Ketamine as a prophylactic against stress-induced depressive-like behavior. *Biological psychiatry*, *79*(9), 776-786. https://doi.org/10.1016/j.biopsych.2015.04.022

Bräscher, A.-K., Becker, S., Hoeppli, M.-E., & Schweinhardt, P. (2016). Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. *The Journal of Neuroscience*, *36*(18), 5013–5025. https://doi.org/10.1523/JNEUROSCI.1954-15.2016

Brauer, M., & Curtin, J. J. (2018). Linear mixed-effects models and the analysis of nonindependent data: A unified framework to analyze categorical and continuous independent variables that vary within-subjects and/or within-items. *Psychological Methods*, *23*(3), 389–411. https://doi.org/10.1037/met0000159

Brienza, J. P., & Grossmann, I. (2017). Social class and wise reasoning about interpersonal conflicts across regions, persons and situations. *Proceedings of the Royal Society B: Biological Sciences*, *284*(1869), 20171870. https://doi.org/10.1098/rspb.2017.1870

Brown, A. D., Kouri, N. A., Rahman, N., Joscelyne, A., Bryant, R. A., & Marmar, C. R. (2016). Enhancing self-efficacy improves episodic future thinking and social-decision making in combat veterans with posttraumatic stress disorder. *Psychiatry Research*, *242*, 19–25. https://doi.org/10.1016/j.psychres.2016.05.026

Brown, T. I., Gagnon, S. A., & Wagner, A. D. (2020). Stress Disrupts Human Hippocampal-Prefrontal Function during Prospective Spatial Navigation and Hinders Flexible Behavior. *Current Biology*, *30*(10), 1821-1833. https://doi.org/10.1016/j.cub.2020.03.006

Bryant, R. A., Waters, E., Gibbs, L., Gallagher, H. C., Pattison, P., Lusher, D., ... & Forbes, D. (2014). Psychological outcomes following the Victorian Black Saturday bushfires. *Australian & New Zealand Journal of Psychiatry*, *48*(7), 634-643. https://doi.org/10.1177/0004867414534476

Buckner, R. L. (1998). Event-related fMRI and the hemodynamic response. *Human brain mapping*, *6*(5-6), 373-377. https://doi.org/10.1002/(SICI)1097-0193(1998)6:5/6%3C373::AID-HBM8%3E3.0.CO;2-P

Bunge, S., & Kahn, I. (2009). Cognition: An Overview of Neuroimaging Techniques. In *Encyclopedia of Neuroscience* (Vol. 2, pp. 1063–1067). https://doi.org/10.1016/B978-008045046-9.00298-9

Butler, D. (2008). Translational research: crossing the valley of death. *Nature News*, *453*(7197), 840-842. https://doi.org/10.1038/453840a

Bzdok, D., & Meyer-Lindenberg, A. (2018). Machine Learning for Precision Psychiatry: Opportunities and Challenges. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(3), 223–230. https://doi.org/10.1016/j.bpsc.2017.11.007

Campbell, J., & Ehlert, U. (2012). Acute psychosocial stress: Does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology*, *37*(8), 1111–1134. https://doi.org/10.1016/j.psyneuen.2011.12.010

Cannon, W. B. (1929). *Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Research Into the Function of Emotional Excitement* (2nd ed.). New York: Appleton-Century-Crofts.

Carstensen, L. L., Fung, H. H., & Charles, S. T. (2003). Socioemotional selectivity theory and the regulation of emotion in the second half of life. *Motivation and emotion*, *27*(2), 103-123. https://doi.org/10.1023/A:1024569803230

Carver, C. S. (1998). Resilience and Thriving: Issues, Models, and Linkages. *Journal of Social Issues*, *54*(2), 245–266. https://doi.org/10.1111/j.1540-4560.1998.tb01217.x

Carver, C. S., Scheier, M. F., & Segerstrom, S. C. (2010). Optimism. *Clinical Psychology Review*, *30*(7), 879–889. https://doi.org/10.1016/j.cpr.2010.01.006

Charles, S. T., & Piazza, J. R. (2009). Age differences in affective well-being: Context matters. *Social and Personality Psychology Compass*, *3*(5), 711-724. https://doi.org/10.1111/j.1751-9004.2009.00202.x

Chmitorz, A., Kurth, K., Mey, L. K., Wenzel, M., Lieb, K., Tüscher, O., … & Kalisch, R. (2020a). Assessment of Microstressors in Adults: Questionnaire Development and Ecological Validation of the Mainz Inventory of Microstressors. *JMIR Mental Health*, *7*(2), e14566. https://doi.org/10.2196/14566

Chmitorz, A., Neumann, R. J., Kollmann, B., Ahrens, K. F., Öhlschläger, S., Goldbach, N., … & Reif, A. (2020b). Longitudinal determination of resilience in humans to identify mechanisms of resilience to modern-life stressors: The longitudinal resilience assessment (LORA) study. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-020-01159-2

Chourbaji, S., Zacher, C., Sanchis-Segura, C., Dormann, C., Vollmayr, B., & Gass, P. (2005). Learned helplessness: Validity and reliability of depressive-like states in mice. *Brain Research Protocols*, *16*(1–3), 70–78. https://doi.org/10.1016/j.brainresprot.2005.09.002

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374–381. https://doi.org/10.1038/nrendo.2009.106

Claro, S., Paunesku, D., & Dweck, C. S. (2016). Growth mindset tempers the effects of poverty on academic achievement. *Proceedings of the National Academy of Sciences of the United States of America, 113*(31), 8664-8668. https://doi.org/10.1073/pnas.1608207113

Cobb, S. (1976). Social support as a moderator of life stress. *Psychosomatic Medicine*, *38*(5), 300–314. https://doi.org/10.1097/00006842-197609000-00003

Coehoorn, C. J., Stuart-Hill, L. A., Abimbola, W., Neary, J. P., & Krigolson, O. E. (2020). Firefighter neural function and decision-making following rapid heat stress. *Fire Safety Journal*, *118*, 103240. https://doi.org/10.1016/j.firesaf.2020.103240

Cohen, J. (1973). Eta-Squared and partial eta-squared in fixed factor anova designs. *Educational and Psychological Measurement*, *33*, 107–112. https://doi.org/10.1177%2F001316447303300111

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale, NJ, USA: L. Erlbaum Associates.

Cohen, S., Gianaros, P. J., & Manuck, S. B. (2016). A Stage Model of Stress and Disease. *Perspectives on Psychological Science*, *11*(4), 456–463. https://doi.org/10.1177/1745691616646305

Cohen, S., Murphy, M. L. M., & Prather, A. A. (2019). Ten Surprising Facts About Stressful Life Events and Disease Risk. *Annual Review of Psychology*, *70*(1), 577–597. https://doi.org/10.1146/annurev-psych-010418-102857

Compas, B. E., Connor-Smith, J. K., Saltzman, H., Thomsen, A. H., & Wadsworth, M. E. (2001). Coping with stress during childhood and adolescence: Problems, progress, and potential in theory and research. *Psychological Bulletin*, *127*(1), 87-127. https://doi.org/10.1037/0033-2909.127.1.87

Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: The Connor-Davidson resilience scale (CD-RISC). *Depression and anxiety*, *18*(2), 76-82. https://doi.org/10.1002/da.10113

Conway, A. R. A., Kane, M. J., Bunting, M. F., Hambrick, D. Z., Wilhelm, O., Engle, R. W. (2005). Working memory span tasks: A methodological review and user's guide. *Psychonomic Bulletin & Review*, *12*, 769–786. https://doi.org/10.3758/BF03196772

Cremers, H., Keedy, S., & Coccaro, E. (2020). The development of an fMRI protocol to investigate vmPFC network functioning underlying the generalization of behavioral control. *Psychiatry Research: Neuroimaging*, *307*, 111197. https://doi.org/10.1016/j.pscychresns.2020.111197

Dale, A. M. (1999). Optimal experimental design for event-related fMRI. *Human brain mapping*, *8*(2-3), 109-114. https://doi.org/10.1002/(SICI)1097-0193(1999)8:2/3<109::AID-HBM7>3.0.CO;2-W

Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior*, *19*(4), 450–466. https://doi.org/10.1016/S0022-5371(80)90312-6

Datta, D., & Arnsten, A. F. T. (2019). Loss of Prefrontal Cortical Higher Cognition with Uncontrollable Stress: Molecular Mechanisms, Changes with Age, and Relevance to Treatment. *Brain Sciences*, *9*(5), 113. https://doi.org/10.3390/brainsci9050113

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual review of neuroscience*, *15*(1), 353-375. https://doi.org/10.1146/annurev.ne.15.030192.002033

Daw, N. D., Niv, Y., & Dayan, P. (2005). Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. *Nature neuroscience*, *8*(12), 1704-1711. https://doi.org/10.1038/nn1560

Daw, N. D., Gershman, S. J., Seymour, B., Dayan, P., & Dolan, R. J. (2011). Model-based influences on humans' choices and striatal prediction errors. *Neuron*, *69*(6), 1204-1215. https://doi.org/10.1016/j.neuron.2011.02.027

Deakin, J. W., & Graeff, F. G. (1991). 5-HT and mechanisms of defence. *Journal of psychopharmacology*, *5*(4), 305-315. https://doi.org/10.1177%2F026988119100500414

Degroote, C., Schwaninger, A., Heimgartner, N., Hedinger, P., Ehlert, U., & Wirtz, P. H. (2020). Acute Stress Improves Concentration Performance: Opposite Effects of Anxiety and Cortisol. *Experimental Psychology*, *67*(2), 88–98. https://doi.org/10.1027/1618-3169/a000481

Delgado, M. R., Beer, J. S., Fellows, L. K., Huettel, S. A., Platt, M. L., Quirk, G. J., & Schiller, D. (2016). Viewpoints: Dialogues on the functional role of the ventromedial prefrontal cortex. *Nature neuroscience*, *19*(12), 1545-1552. https://doi.org/10.1038/nn.4438

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, *31*(3), 968-980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Deuter, C. E., Kuehl, L. K., Blumenthal, T. D., Schulz, A., Oitzl, M. S., & Schachinger, H. (2012). Effects of Cold Pressor Stress on the Human Startle Response. *PLoS ONE*, *7*(11), e49866. https://doi.org/10.1371/journal.pone.0049866

Diehl, M., & Hay, E. L. (2010). Risk and resilience factors in coping with daily stress in adulthood: the role of age, self-concept incoherence, and personal control. *Developmental psychology*, *46*(5), 1132-1146. https://doi.org/10.1037/a0019937

Dickerson, S. S., & Kemeny, M. E. (2004). Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Diener, C., Struve, M., Balz, N., Kuehner, C., & Flor, H. (2009). Exposure to uncontrollable stress and the postimperative negative variation (PINV): Prior control matters. *Biological Psychology*, *80*(2), 189–195. https://doi.org/10.1016/j.biopsycho.2008.09.002

Dijkstra, M. T. M., Beersma, B., & Evers, A. (2011). Reducing conflict-related employee strain: The benefits of an internal locus of control and a problem-solving conflict management strategy. *Work & Stress*, *25*(2), 167–184. https://doi.org/10.1080/02678373.2011.593344

Dillon, D. G., Holmes, A. J., Birk, J. L., Brooks, N., Lyons-Ruth, K., & Pizzagalli, D. A. (2009). Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biological psychiatry*, *66*(3), 206-213. https://doi.org/10.1016/j.biopsych.2009.02.019

Dorfman, H. M., & Gershman, S. J. (2019). Controllability governs the balance between Pavlovian and instrumental action selection. *Nature Communications*, *10*(1), 1–8. https://doi.org/10.1038/s41467-019-13737-7

Drugan, R. C. (2001). Rodent Models of Depression: Learned Helplessness Using a Triadic Design in Rats. *Current Protocols in Neuroscience*, *14*(1), 8-10. https://doi.org/10.1002/0471142301.ns0810bs14

Duckworth, A. L. (2011). The significance of self-control. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 2639–2640. https://doi.org/10.1073/pnas.1019725108

Durodié, B., & Wainwright, D. (2019). Terrorism and post-traumatic stress disorder: A historical review. *The Lancet Psychiatry*, *6*(1), 61–71. https://doi.org/10.1016/S2215-0366(18)30335-3

Dulawa, S. C., & Hen, R. (2005). Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. *Neuroscience & Biobehavioral Reviews*, *29*(4-5), 771-783. https://doi.org/10.1016/j.neubiorev.2005.03.017

Eckenrode, J. (1984). Impact of chronic and acute stressors on daily reports of mood. *Journal of Personality and Social Psychology, 46*(4), 907–918. https://doi.org/10.1037/0022-3514.46.4.907

Egloff, B. (2015). Does a positive appraisal style work in all stressful situations and for all individuals? *Behavioral and Brain Sciences*, *38*, E100. https://doi.org/10.1017/S0140525X14001514

Ekstrom, A. (2010). How and when the fMRI BOLD signal relates to underlying neural activity: The danger in dissociation. *Brain Research Reviews*, *62*(2), 233–244. https://doi.org/10.1016/j.brainresrev.2009.12.004

Evans, G. W. (2004). The environment of childhood poverty. *American psychologist*, *59*(2), 77-92. https://doi.org/10.1037/0003-066X.59.2.77

Evans, G. W., Eckenrode, J., & Marcynyszyn, L. A. (2010). *Chaos and the macrosetting: The role of poverty and socioeconomic status.* In G. W. Evans & T. D. Wachs (Eds.), *Decade of behavior (science conference). Chaos and its influence on children's development: An ecological perspective* (p. 225–238). American Psychological Association. https://doi.org/10.1037/12057-014

Evans, G. W., & Kim, P. (2013). Childhood poverty, chronic stress, self-regulation, and coping. *Child development perspectives*, *7*(1), 43-48. https://doi.org/10.1111/cdep.12013

Fang, F. C., & Casadevall, A. (2010). Lost in Translation—Basic Science in the Era of Translational Research. *Infection and Immunity*, *78*(2), 563–566. https://doi.org/10.1128/IAI.01318-09

Fassett-Carman, A., Hankin, B. L., & Snyder, H. R. (2019). Appraisals of dependent stressor controllability and severity are associated with depression and anxiety symptoms in youth. *Anxiety, Stress, & Coping*, *32*(1), 32–49. https://doi.org/10.1080/10615806.2018.1532504

Feder, A., Fred-Torres, S., Southwick, S. M., & Charney, D. S. (2019). The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. *Biological Psychiatry*, *86*(6), 443–453. https://doi.org/10.1016/j.biopsych.2019.07.012

Fineberg, N. A., Chamberlain, S. R., Goudriaan, A. E., Stein, D. J., Vanderschuren, L. J., Gillan, C. M., ... & Potenza, M. N. (2014). New developments in human neurocognition: clinical, genetic and brain imaging correlates of impulsivity and compulsivity. *CNS spectrums*, *19*(1), 69-89. https://dx.doi.org/10.1017%2FS1092852913000801

Ford, B. Q., Lwi, S. J., Gentzler, A. L., Hankin, B., & Mauss, I. B. (2018). The cost of believing emotions are uncontrollable: Youths' beliefs about emotion predict emotion regulation and depressive symptoms. *Journal of Experimental Psychology: General*, *147*(8), 1170-1190. https://doi.org/10.1037/xge0000396

Fort, D. G., Herr, T. M., Shaw, P. L., Gutzman, K. E., & Starren, J. B. (2017). Mapping the evolving definitions of translational research. *Journal of Clinical and Translational Science*, *1*(1), 60–66. https://doi.org/10.1017/cts.2016.10

Frankenhuis, W. E., de Vries, S. A., Bianchi, J., & Ellis, B. J. (2019). Hidden talents in harsh conditions? A preregistered study of memory and reasoning about social dominance. *Developmental science*, *23*(4), e12835. https://doi.org/10.1111/desc.12835

Frankenhuis, W. E., & Nettle, D. (2020). The strengths of people in poverty. *Current Directions in Psychological Science*, *29*(1), 16-21. https://doi.org/10.1177/0963721419881154

Frankenhuis, W. E., Young, E. S., & Ellis, B. J. (2020). The hidden talents approach: Theoretical and methodological challenges. *Trends in cognitive sciences*, *24*(7), 569-581. https://doi.org/10.1016/j.tics.2020.03.007

Friedrich, M. J. (2017). Depression is the leading cause of disability around the world. *Jama*, *317*(15), 1517-1517. https://doi.org/10.1001/jama.2017.3826

Fullana, M. A., Zhu, X., Alonso, P., Cardoner, N., Real, E., López-Solà, C., … & Soriano-Mas, C. (2017). Basolateral amygdala-ventromedial prefrontal cortex connectivity predicts cognitive behavioural therapy outcome in adults with obsessive-compulsive disorder. *Journal of Psychiatry & Neuroscience: JPN*, *42*(6), 378–385. https://doi.org/10.1503/jpn.160215

Fuster, J. (2015). *The prefrontal cortex*. Academic Press.

Galatzer-Levy, I. R., Huang, S. H., & Bonanno, G. A. (2018). Trajectories of resilience and dysfunction following potential trauma: A review and statistical evaluation. *Clinical Psychology Review*, *63*, 41–55. https://doi.org/10.1016/j.cpr.2018.05.008

Geue, K., Strauß, B., Brähler, E. (2016). *Diagnostische Verfahren in der Psychotherapie*. Hogrefe: Göttingen.

Giles, G. E., Mahoney, C. R., Brunyé, T. T., Taylor, H. A., & Kanarek, R. B. (2014). Stress Effects on Mood, HPA Axis, and Autonomic Response: Comparison of Three Psychosocial Stress Paradigms. *PLoS ONE*, *9*(12), e113618. https://doi.org/10.1371/journal.pone.0113618

Gläscher, J., Daw, N., Dayan, P., & O'Doherty, J. P. (2010). States versus rewards: dissociable neural prediction error signals underlying model-based and model-free

reinforcement learning. *Neuron*, *66*(4), 585-595. https://doi.org/10.1016/j.neuron.2010.04.016

Godoy, L. D., Rossignoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & de Lima Umeoka, E. H. (2018). A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. *Frontiers in Behavioral Neuroscience*, *12*, 127. https://doi.org/10.3389/fnbeh.2018.00127

Goldfarb, E. V., Tompary, A., Davachi, L., & Phelps, E. A. (2019). Acute stress throughout the memory cycle: Diverging effects on associative and item memory. *Journal of Experimental Psychology: General*, *148*(1), 13-29. https://doi.org/10.1037/xge0000472

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491-505. https://doi.org/10.1038/nrn3256

Graeff, F. G., Guimarães, F. S., De Andrade, T. G. C. S., & Deakin, J. F. W. (1996). Role of 5-HT in stress, anxiety, and depression. *Pharmacology Biochemistry and Behavior*, *54*(1), 129–141. https://doi.org/10.1016/0091-3057(95)02135-3

Grahn, R. E., Will, M. J., Hammack, S. E., Maswood, S., McQueen, M. B., Watkins, L. R., & Maier, S. F. (1999). Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. *Brain research*, *826*(1), 35-43. https://doi.org/10.1016/S0006-8993(99)01208-1

Grant, H., & Dweck, C. S. (2003). Clarifying achievement goals and their impact. *Journal of personality and social psychology*, *85*(3), 541-553. https://doi.org/10.1037/0022-3514.85.3.541

Greiner, B. (2015). Subject pool recruitment procedures: Organizing experiments with ORSEE. *Journal of the Economic Science Association*, *1*, 114–125. https://doi.org/10.1007/s40881-015-0004-4

Grizzell, J. A., Clarity, T. T., Graham, N. B., Dulka, B. N., & Cooper, M. A. (2020). Activity of a vmPFC-DRN Pathway Corresponds With Resistance to Acute Social Defeat Stress. *Frontiers in Neural Circuits*, *14*, 50. https://doi.org/10.3389/fncir.2020.00050

Guitart-Masip, M., Huys, Q. J. M., Fuentemilla, L., Dayan, P., Duzel, E., & Dolan, R. J. (2012). Go and no-go learning in reward and punishment: Interactions between affect and effect. *Neuroimage*, *62–334*(1), 154–166. https://doi.org/10.1016/j.neuroimage.2012.04.024

Gururajan, A., Kos, A., & Lopez, J. P. (2018). Preclinical stress research: Where are we headed? An early career investigator's perspective. *Stress*, *21*(5), 384–388. https://doi.org/10.1080/10253890.2018.1446519

Gururajan, A., Reif, A., Cryan, J. F., & Slattery, D. A. (2019). The future of rodent models in depression research. *Nature Reviews Neuroscience*, *20*(11), 686–701. https://doi.org/10.1038/s41583-019-0221-6

Hadad-Ophir, O., Ardi, Z., Brande-Eilat, N., Kehat, O., Anunu, R., & Richter-Levin, G. (2017). Exposure to prolonged controllable or uncontrollable stress affects GABAergic function in sub-regions of the hippocampus and the amygdala. *Neurobiology of Learning and Memory*, *138*, 271–280. https://doi.org/10.1016/j.nlm.2016.06.009

Haggard, P. (2017). Sense of agency in the human brain. *Nature Reviews Neuroscience*, *18*(4), 196–207. https://doi.org/10.1038/nrn.2017.14

Hammen, C. (2005). Stress and Depression. *Annual Review of Clinical Psychology*, *1*(1), 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Han, L. K., Verhoeven, J. E., Tyrka, A. R., Penninx, B. W., Wolkowitz, O. M., Månsson, K. N., ... & Picard, M. (2019). Accelerating research on biological aging and mental

health: Current challenges and future directions. *Psychoneuroendocrinology*, *106*, 293-311. https://doi.org/10.1016/j.psyneuen.2019.04.004

Hancock, L., & Bryant, R. A. (2018a). Perceived control and avoidance in posttraumatic stress. *European Journal of Psychotraumatology*, *9*(1), 1468708. https://doi.org/10.1080/20008198.2018.1468708

Hancock, L., & Bryant, R. A. (2018b). Posttraumatic stress, uncontrollability, and emotional distress tolerance. *Depression and Anxiety*, *35*(11), 1040–1047. https://doi.org/10.1002/da.22783

Hanson, J. L., Albert, D., Iselin, A. M. R., Carre, J. M., Dodge, K. A., & Hariri, A. R. (2016). Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Social cognitive and affective neuroscience*, *11*(3), 405-412. https://doi.org/10.1093/scan/nsv124

Hartley, C. A., Gorun, A., Reddan, M. C., Ramirez, F., & Phelps, E. A. (2014). Stressor controllability modulates fear extinction in humans. *Neurobiology of Learning and Memory*, *113*, 149–156. https://doi.org/10.1016/j.nlm.2013.12.003

Havranek, M. M., Bolliger, B., Roos, S., Pryce, C. R., Quednow, B. B., & Seifritz, E. (2016). Uncontrollable and unpredictable stress interacts with subclinical depression and anxiety scores in determining anxiety response. *Stress*, *19*(1), 53–62. https://doi.org/10.3109/10253890.2015.1117449

Hellhammer, J., & Schubert, M. (2012). The physiological response to Trier Social Stress Test relates to subjective measures of stress during but not before or after the test. *Psychoneuroendocrinology*, *37*(1), 119-124. https://doi.org/10.1016/j.psyneuen.2011.05.012

Henderson, R. K., Snyder, H. R., Gupta, T., & Banich, M. T. (2012). When Does Stress Help or Harm? The Effects of Stress Controllability and Subjective Stress Response on Stroop Performance. *Frontiers in Psychology*, *3*, 179. https://doi.org/10.3389/fpsyg.2012.00179

Henkel, V., Bussfeld, P., Möller, H. J., & Hegerl, U. (2002). Cognitive-behavioural theories of helplessness/hopelessness: valid models of depression? *European archives of psychiatry and clinical neuroscience*, *252*(5), 240-249. https://doi.org/10.1007/s00406-002-0389-y

Henn, F. A., & Vollmayr, B. (2005). Stress models of depression: Forming genetically vulnerable strains. *Neuroscience & Biobehavioral Reviews*, *29*(4), 799–804. https://doi.org/10.1016/j.neubiorev.2005.03.019

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world? *Behavioral and brain sciences*, *33*(2-3), 61-83. https://doi.org/10.1017/S0140525X0999152X

Hermans, E. J., & Fernández, G. (2015). Heterogeneity of cognitive-neurobiological determinants of resilience. *Behavioral and Brain Sciences*, *38*, E103. https://doi.org/10.1017/S0140525X14001769

Herten, N., Otto, T., Adolph, D., Pause, B. M., Kumsta, R., & Wolf, O. T. (2016). Enhanced startle responsivity 24 hours after acute stress exposure. *Behavioral Neuroscience*, *130*(5), 521–530. https://doi.org/10.1037/bne0000156

Hiroto, D. S. (1974). Locus of control and learned helplessness. *Journal of Experimental Psychology*, *102*(2), 187–193. https://doi.org/10.1037/h0035910

Hiroto, D. S., & Seligman, M. E. P. (1975). Generality of learned helplessness in man. *Journal of Personality and Social Psychology*, *31*(2), 311–327. https://doi.org/10.1037/h0076270

Hocking, G. (2003), 'Oxfam Great Britain and Sustainable Livelihoods in the UK', *Community Development Journal, 38*(3): 235–242. http://dx.doi.org/10.1093/cdj/38.3.235

Holm, S. A. (1979). Simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, *6*, 65–70.

Hooijmans, C. R., & Ritskes-Hoitinga, M. (2013). Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research. *PLOS Medicine*, *10*(7), e1001482. https://doi.org/10.1371/journal.pmed.1001482

Hopko, D. R., Armento, M. E., Robertson, S., Ryba, M. M., Carvalho, J. P., Colman, L. K., ... & Lejuez, C. W. (2011). Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: randomized trial. *Journal of consulting and clinical psychology*, *79*(6), 834-849. https://doi.org/10.1037/a0025450

Hopko, D. R., Lejuez, C. W., Ruggiero, K. J., & Eifert, G. H. (2003). Contemporary behavioral activation treatments for depression: Procedures, principles, and progress. *Clinical psychology review*, *23*(5), 699-717. https://doi.org/10.1016/S0272-7358(03)00070-9

Hostiuc, S., Moldoveanu, A., Dascălu, M. I., Unnthorsson, R., Jóhannesson, Ó. I., & Marcus, I. (2016). Translational research—the need of a new bioethics approach. *Journal of translational medicine*, *14*(1), 1-10. https://doi.org/10.1186/s12967-016-0773-4

Houtman, I., Cedillo, L., & Jettinghoff, K. (2007). *Raising awareness of stress at work in developing countries: A modern hazard in a traditional working environment: advice to employer and worker representatives*. World Health Organization (WHO).

Hovenkamp-Hermelink, J. H., Jeronimus, B. F., Spinhoven, P., Penninx, B. W., Schoevers, R. A., & Riese, H. (2019). Differential associations of locus of control with anxiety, depression and life-events: A five-wave, nine-year study to test stability and change. *Journal of affective disorders, 253*, 26-34. https://doi.org/10.1016/j.jad.2019.04.005

Huettel, S. A., Song, A. W., & McCarthy, G. (2014). *Functional magnetic resonance imaging* (3. ed). Sunderland, Mass: Sinauer.

Huys, Q. J. M., & Dayan, P. (2009). A Bayesian formulation of behavioral control. *Cognition*, *113*(3), 314–328. https://doi.org/10.1016/j.cognition.2009.01.008

Infurna, F. J., & Luthar, S. S. (2018). Re-evaluating the notion that resilience is commonplace: A review and distillation of directions for future research, practice, and policy. *Clinical Psychology Review*, *65*, 43–56. https://doi.org/10.1016/j.cpr.2018.07.003

Infurna, F. J., Ram, N., & Gerstorf, D. (2013). Level and change in perceived control predict 19-year mortality: Findings from the Americans' changing lives study. *Developmental Psychology*, *49*(10), 1833-1847. https://doi.org/10.1037/a0031041

Ioannidis, J. P. (2004). Materializing research promises: Opportunities, priorities and conflicts in translational medicine. *Journal of Translational Medicine*, *2*(1), 5. https://doi.org/10.1186/1479-5876-2-5

Ishimura, K., Takeuchi, Y., Fujiwara, K., Tominaga, M., Yoshioka, H., & Sawada, T. (1988). Quantitative analysis of the distribution of serotonin-immunoreactive cell bodies in the mouse brain. *Neuroscience Letters*, *91*(3), 265–270. https://doi.org/10.1016/0304-3940(88)90691-X

Jacobs, N., Myin-Germeys, I., Derom, C., Delespaul, P., Van Os, J., & Nicolson, N. A. (2007). A momentary assessment study of the relationship between affective and adrenocortical stress responses in daily life. *Biological psychology*, *74*(1), 60-66. https://doi.org/10.1016/j.biopsycho.2006.07.002

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., ... & Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for

depression. *Journal of consulting and clinical psychology*, *64*(2), 295-304. https://doi.org/10.1037/0022-006X.64.2.295

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Briggs, A. M. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789-1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience*, *10*(6), 459–466. https://doi.org/10.1038/nrn2632

Jopp, D., & Smith, J. (2006). Resources and life-management strategies as determinants of successful aging: On the protective effect of selection, optimization, and compensation. *Psychology and aging*, *21*(2), 253-265. https://doi.org/10.1037/0882-7974.21.2.253

Juslin, P. N. (2015). Resilience: Mediated by not one but many appraisal mechanisms. *Behavioral and Brain Sciences*, *38*, E106. https://doi.org/10.1017/S0140525X14001563

Kalisch, R., Baker, D. G., Basten, U., Boks, M. P., Bonanno, G. A., Brummelman, E., … Kleim, B. (2017). The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour*, *1*(11), 784–790. https://doi.org/10.1038/s41562-017-0200-8

Kalisch, R., Müller, M. B., & Tüscher, O. (2015). A conceptual framework for the neurobiological study of resilience. *Behavioral and Brain Sciences*, *38*, e92. https://doi.org/10.1017/S0140525X1400082X

Kanner, A. D., Coyne, J. C., Schaefer, C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, *4*(1), 1–39. https://doi.org/10.1007/BF00844845

Karatsoreos, I. N., & McEwen, B. S. (2013). Annual Research Review: The neurobiology and physiology of resilience and adaptation across the life course. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *54*(4), 337–347. https://doi.org/10.1111/jcpp.12054

Kassambara, A. (2019). *rstatix: Pipe-Friendly Framework for Basic Statistical Tests* (Version 0.5.0) [Computer Software Package]. https://CRAN.R-project.org/package=rstatix

Kerr, D. L., McLaren, D. G., Mathy, R. M., & Nitschke, J. B. (2012). Controllability Modulates the Anticipatory Response in the Human Ventromedial Prefrontal Cortex. *Frontiers in Psychology*, *3*, 557. https://doi.org/10.3389/fpsyg.2012.00557

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Current opinion in psychiatry*, *20*(4), 359-364. https://dx.doi.org/10.1097%2FYCO.0b013e32816ebc8c

Keynan, J. N., Cohen, A., Jackont, G., Green, N., Goldway, N., Davidov, A., … & Hendler, T. (2019). Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. *Nature Human Behaviour*, *3*(1), 63–73. https://doi.org/10.1038/s41562-018-0484-3

Kim, J. J., & Jung, M. W. (2006). Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. *Neuroscience & Biobehavioral Reviews*, *30*(2), 188–202. https://doi.org/10.1016/j.neubiorev.2005.06.005

Kim, Y., Woo, J., & Woo, M. (2017). Effects of Stress and Task Difficulty on Working Memory and Cortical Networking. *Perceptual and Motor Skills*, *124*(6), 1194–1210. https://doi.org/10.1177/0031512517732851

Kirschbaum, C., & Hellhammer, D. (1989). Response variability of salivary cortisol under psychological stimulation. *Journal of Clinical Chemistry and Clinical Biochemistry. Zeitschrift Fur Klinische Chemie Und Klinische Biochemie*, *27*(4), 237.

Klonsky, E. D. (2007). The functions of deliberate self-injury: A review of the evidence. *Clinical psychology review*, *27*(2), 226-239. https://doi.org/10.1016/j.cpr.2006.08.002

Kobasa, S. C., Maddi, S. R., & Kahn, S. (1982). Hardiness and health: A prospective study. *Journal of Personality and Social Psychology*, *42*(1), 168–177. https://doi.org/10.1037/0022-3514.42.1.168

Kool, W., Shenhav, A., & Botvinick, M. M. (2017). *Cognitive control as cost-benefit decision making.* In T. Egner (Ed.), *The Wiley handbook of cognitive control* (p. 167–189). Wiley Blackwell. https://doi.org/10.1002/9781118920497.ch10

Kranz, G. S., Hahn, A., Savli, M., & Lanzenberger, R. (2012). Challenges in the differentiation of midbrain raphe nuclei in neuroimaging research. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(29), E2000. https://doi.org/10.1073/pnas.1206247109

Krohne, H. W., Egloff, B., Kohlmann, C.-W., & Tausch, A. (1996). Untersuchungen mit einer deutschen Version der "Positive and Negative Affect Schedule" (PANAS). *Diagnostica, 42*(2), 139–156.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., … & Turner, R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, *89*(12), 5675–5679. https://doi.org/10.1073/pnas.89.12.5675

Laidlaw, K., & Pachana, N. A. (2009). Aging, mental health, and demographic change: Challenges for psychotherapists. *Professional Psychology: Research and Practice*, *40*(6), 601-608. https://doi.org/10.1037/a0017215

Langer, K., Hagedorn, B., Stock, L.-M., Otto, T., Wolf, O. T., & Jentsch, V. L. (2020). Acute stress improves the effectivity of cognitive emotion regulation in men. *Scientific Reports*, *10*(1), 11571. https://doi.org/10.1038/s41598-020-68137-5

Lazarus, R. S. & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer Publishing Company.

Laux, L., Hock, M., Bergner-Köther, R., Hodapp, V., Renner, K.H. (2013). *Stadi: State-Trait-Angst-Depressions-Inventar*. Göttingen: Hogrefe.

Leder, J., Häusser, J. A., & Mojzisch, A. (2013). Stress and strategic decision-making in the beauty contest game. *Psychoneuroendocrinology*, *38*(9), 1503–1511. https://doi.org/10.1016/j.psyneuen.2012.12.016

Lefcourt, H. M. (1982) *Locus of Control: Current Trends in Theory and Research*. Lawrence Erlbaum Associates.

Leiner, D. (2019). SoSci Survey (Version 3.1.06) [Computer Software]. SoSci Survey GmbH. http://www.soscisurvey.com.

Lenth, R.V. (2016). Least-Squares means: The r package lsmeans. *Journal of Statistical Software*, *69*, 1–33. http://dx.doi.org/10.18637/jss.v069.i01

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*, *30*(10), 939–946. https://doi.org/10.1016/j.psyneuen.2005.03.013

Lieberman, H. R., Thompson, L. A., Caruso, C. M., Niro, P. J., Mahoney, C. R., McClung, J. P., & Caron, G. R. (2015). The catecholamine neurotransmitter precursor tyrosine increases anger during exposure to severe psychological stress. *Psychopharmacology*, *232*(5), 943–951. https://doi.org/10.1007/s00213-014-3727-7

Limbachia, C., Morrow, K., Khibovska, A., Meyer, C., Padmala, S., & Pessoa, L. (2021). Controllability over stressor decreases responses in key threat-related brain areas. *Communications Biology*, *4*(1), 1-11. https://doi.org/10.1038/s42003-020-01537-5

Lister, R. (2015). 'To count for nothing': Poverty beyond the statistics. *Journal of the British Academy*, *3*, 139-165. https://doi.org/10.5871/jba/003.139

Liu, R. T., Kleiman, E. M., Nestor, B. A., & Cheek, S. M. (2015). The Hopelessness Theory of Depression: A Quarter-Century in Review. *Clinical Psychology: Science and Practice*, *22*(4), 345–365. https://doi.org/10.1111/cpsp.12125

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–878. https://doi.org/10.1038/nature06976

Lowe, S. R., Sampson, L., Gruebner, O., & Galea, S. (2015). Psychological Resilience after Hurricane Sandy: The Influence of Individual- and Community-Level Factors on Mental Health after a Large-Scale Natural Disaster. *PLOS ONE*, *10*(5), e0125761. https://doi.org/10.1371/journal.pone.0125761

Lucas, M., Ilin, Y., Anunu, R., Kehat, O., Xu, L., Desmedt, A., & Richter-Levin, G. (2014). Long-term effects of controllability or the lack of it on coping abilities and stress resilience in the rat. *Stress*, *17*(5), 423–430. https://doi.org/10.3109/10253890.2014.930430

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209–237. https://doi.org/10.1016/j.bandc.2007.02.007

Lupien, S. J., Juster, R.-P., Raymond, C., & Marin, M.-F. (2018). The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. *Frontiers in Neuroendocrinology*, *49*, 91–105. https://doi.org/10.1016/j.yfrne.2018.02.001

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Luyten, L., Boddez, Y., & Hermans, D. (2015). Positive appraisal style: The mental immune system? *Behavioral and Brain Sciences*, *38*, E112. https://doi.org/10.1017/S0140525X14001629

Ly, V., Roijendijk, L., Hazebroek, H., Tonnaer, C., & Hagenaars, M. A. (2017). Incident experience predicts freezing-like responses in firefighters. *PLOS ONE*, *12*(10), e0186648. https://doi.org/10.1371/journal.pone.0186648

Ly, V., Wang, K. S., Bhanji, J., & Delgado, M. R. (2019). A Reward-Based Framework of Perceived Control. *Frontiers in Neuroscience*, *13*, 65. https://doi.org/10.3389/fnins.2019.00065

Mace, F. C., & Critchfield, T. S. (2010). Translational Research in Behavior Analysis: Historical Traditions and Imperative for the Future. *Journal of the Experimental Analysis of Behavior*, *93*(3), 293–312. https://doi.org/10.1901/jeab.2010.93-293

Maddi, S. (2013). Personal Hardiness as the Basis for Resilience. In S. R. Maddi (Ed.), *Hardiness: Turning Stressful Circumstances into Resilient Growth* (pp. 7–17). Springer Netherlands. https://doi.org/10.1007/978-94-007-5222-1_2

Maier, S. F., & Seligman, M. E. P. (2016). Learned helplessness at fifty: Insights from neuroscience. *Psychological Review*, *123*(4), 349-367. https://doi.org/10.1037/rev0000033

Maier, S. F., & Watkins, L. R. (2005). Stressor controllability and learned helplessness: The roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor.

Neuroscience & Biobehavioral Reviews, *29*(4–5), 829–841. https://doi.org/10.1016/j.neubiorev.2005.03.021

Maier, S. F., & Watkins, L. R. (2010). Role of the medial prefrontal cortex in coping and resilience. *Brain Research*, *1355*, 52–60. https://doi.org/10.1016/j.brainres.2010.08.039

Mair, P., & Wilcox, R. (2020). Robust statistical methods in R using the WRS2 package. *Behavior Research Methods*, *52*(2), 464–488. https://doi.org/10.3758/s13428-019-01246-w

Mak, I. W., Evaniew, N., & Ghert, M. (2014). Lost in translation: animal models and clinical trials in cancer treatment. *American journal of translational research*, *6*(2), 114-118.

Malhi, G. S., Das, P., Bell, E., Mattingly, G., & Mannie, Z. (2019). Modelling resilience in adolescence and adversity: A novel framework to inform research and practice. *Translational Psychiatry*, *9*, 316. https://doi.org/10.1038/s41398-019-0651-y

Malik, M. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use: Task force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology. *Annals of Noninvasive Electrocardiology*, *1*(2), 151-181. https://doi.org/10.1111/j.1542-474X.1996.tb00275.x

Mancini, A. D. (2019). When acute adversity improves psychological health: A social–contextual framework. *Psychological Review*, *126*(4), 486–505. https://doi.org/10.1037/rev0000144

Marantz, P. R., Keller, M. J., & Meagher, E. A. (2020). A counterpoint to "training the translational workforce: Expanding beyond translational research to include translational science". *Journal of Clinical and Translational Science*, *4*(4), 363–364. https://doi.org/10.1017/cts.2020.32

Marsh, S., Dobson, R., & Maddison, R. (2020). The relationship between household chaos and child, parent, and family outcomes: a systematic scoping review. *BMC public health*, *20*, 513. https://doi.org/10.1186/s12889-020-08587-8

Masten, A. S. (2007). Resilience in developing systems: Progress and promise as the fourth wave rises. *Development and Psychopathology*, *19*(3), 921–930. https://doi.org/10.1017/S0954579407000442

Masten, A. S. (2018). Resilience Theory and Research on Children and Families: Past, Present, and Promise. *Journal of Family Theory & Review*, *10*(1), 12–31. https://doi.org/10.1111/jftr.12255

Masten, A. S., Lucke, C. M., Nelson, K. M., & Stallworthy, I. C. (2021). Resilience in Development and Psychopathology: Multisystem Perspectives. *Annual Review of Clinical Psychology*, *17*(1), annurev-clinpsy-081219-120307. https://doi.org/10.1146/annurev-clinpsy-081219-120307

Matveychuk, D., Thomas, R. K., Swainson, J., Khullar, A., MacKay, M.-A., Baker, G. B., & Dursun, S. M. (2020). Ketamine as an antidepressant: Overview of its mechanisms of action and potential predictive biomarkers. *Therapeutic Advances in Psychopharmacology*, *10*, 1-21. https://doi.org/10.1177/2045125320916657

Mayeli, A., Misaki, M., Zotev, V., Tsuchiyagaito, A., Al Zoubi, O., Phillips, R., … & Bodurka, J. (2019). Self-regulation of ventromedial prefrontal cortex activation using real-time fMRI neurofeedback—Influence of default mode network. *Human Brain Mapping*, *41*(2), 342–352. https://doi.org/10.1002/hbm.24805

McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research*, *886*(1-2), 172–189. https://doi.org/10.1016/S0006-8993(00)02950-4

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators.

European Journal of Pharmacology, *583*(2–3), 174–185. https://doi.org/10.1016/j.ejphar.2007.11.071

McEwen, B. S., & Akil, H. (2020). Revisiting the Stress Concept: Implications for Affective Disorders. *Journal of Neuroscience*, *40*(1), 12–21. https://doi.org/10.1523/JNEUROSCI.0733-19.2019

McEwen, B. S., & Stellar, E. (1993). Stress and the individual: Mechanisms leading to disease. *Archives of internal medicine*, *153*(18), 2093-2101. https://doi.org/10.1001/archinte.1993.00410180039004

McLaughlin, K. A., Colich, N. L., Rodman, A. M., & Weissman, D. G. (2020). Mechanisms linking childhood trauma exposure and psychopathology: A transdiagnostic model of risk and resilience. *BMC Medicine*, *18*, 96. https://doi.org/10.1186/s12916-020-01561-6

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standardapproaches. *Neuroimage*, *61*(4), 1277-1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Meili, I., Heim, E., & Maercker, A. (2019). Culturally shared metaphors expand contemporary concepts of resilience and post-traumatic growth: Contrasting an indigenous Brazilian community and a Swiss rural community. *Medical humanities*, *45*(4), 335-345. http://dx.doi.org/10.1136/medhum-2018-011450

Meine, L. E., Heeg, A.-C., Schueler, K., Wessa, M. (2019, August 19-22). *Overcoming learned helplessness: can experience of control over a stressor immunize against uncontrollable stress?* [Conference Session]. 3rd CRC 1193 PhD & Postdoc Retreat, Hirschegg, Austria.

Meine, L. E., Raab, H. A., Wessa, M., & Hartley, C. A. (2020, September 23-25). *Linking flexibility in learning processes to stress history and resilience.* [Poster Presentation]. 6th International Symposium on Resilience Research, Mainz, Germany.

Merriam-Webster. (n.d.). Resilient. In *Merriam-Webster.com dictionary*. Retrieved January 5, 2021, from https://www.merriam-webster.com/dictionary/resilient

Meteyard, L., & Davies, R. A. I. (2020). Best practice guidance for linear mixed-effects models in psychological science. *Journal of Memory and Language*, *112*, 104092. https://doi.org/10.1016/j.jml.2020.104092

Miller, W. R., & Seligman, M. E. P. (1975). Depression and learned helplessness in man. *Journal of Abnormal Psychology*, *84*(3), 228-238. https://doi.org/10.1037/h0076720

Miller-Graff, L. E., & Howell, K. H. (2015). Posttraumatic stress symptom trajectories among children exposed to violence. *Journal of Traumatic Stress*, *28*(1), 17-24. https://doi.org/10.1002/jts.21989

Mkrtchian, A., Aylward, J., Dayan, P., Roiser, J. P., & Robinson, O. J. (2017). Modeling Avoidance in Mood and Anxiety Disorders Using Reinforcement Learning. *Biological Psychiatry*, *82*(7), 532–539. https://doi.org/10.1016/j.biopsych.2017.01.017

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H.,… & Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 2693–2698. https://doi.org/10.1073/pnas.1010076108

Morris, Z. S., Wooding, S., & Grant, J. (2011). The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of the Royal Society of Medicine*, *104*(12), 510-520. https://doi.org/10.1258%2Fjrsm.2011.110180

Moscarello, J. M., & Hartley, C. A. (2017). Agency and the Calibration of Motivated Behavior. *Trends in Cognitive Sciences*, *21*(10), 725–735. https://doi.org/10.1016/j.tics.2017.06.008

Náfrádi, L., Nakamoto, K., & Schulz, P. J. (2017). Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLOS ONE*, *12*(10), e0186458. https://doi.org/10.1371/journal.pone.0186458

Nederhof, E. (2015). Phenotypic programming as a distal cause of resilience. *Behavioral and Brain Sciences*, *38*, E115. https://doi.org/10.1017/S0140525X14001654

Nicholson, A. A., Rabellino, D., Densmore, M., Frewen, P. A., Paret, C., Kluetsch, R., … & Lanius, R. A. (2017). The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala downregulation via real-time fMRI neurofeedback. *Human Brain Mapping*, *38*(1), 541–560. https://doi.org/10.1002/hbm.23402

Ogawa, S., Lee, T. M., Nayak, A. S., & Glynn, P. (1990a). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic resonance in medicine*, *14*(1), 68-78. https://doi.org/10.1002/mrm.1910140108

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990b). *Brain magnetic resonance imaging with contrast dependent on blood oxygenation*. *87*(24), 9868-9872. https://doi.org/10.1073/pnas.87.24.9868

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America*, *89*(13), 5951–5955. https://doi.org/10.1073/pnas.89.13.5951

Orem, T. R., Wheelock, M. D., Goodman, A. M., Harnett, N. G., Wood, K. H., Gossett, E. W., … & Knight, D. C. (2019). Amygdala and prefrontal cortex activity varies with individual differences in the emotional response to psychosocial stress. *Behavioral Neuroscience*, *133*(2), 203-211. https://doi.org/10.1037/bne0000305

Orgaz, C., Estevez, A., & Matute, H. (2013). Pathological gamblers are more vulnerable to the illusion of control in a standard associative learning task. *Frontiers in Psychology*, *4*, 306. https://doi.org/10.3389/fpsyg.2013.00306

Osório, C., Probert, T., Jones, E., Young, A. H., & Robbins, I. (2017). Adapting to Stress: Understanding the Neurobiology of Resilience. *Behavioral Medicine*, *43*(4), 307–322. https://doi.org/10.1080/08964289.2016.1170661

Otto, A. R., Raio, C. M., Chiang, A., Phelps, E. A., & Daw, N. D. (2013). Working-memory capacity protects model-based learning from stress. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(52), 20941–20946. https://doi.org/10.1073/pnas.1312011110

Ousdal, O. T., Huys, Q. J., Milde, A. M., Craven, A. R., Ersland, L., Endestad, T., ... & Dolan, R. J. (2018). The impact of traumatic stress on Pavlovian biases. *Psychological Medicine*, *48*(2), 327–336. https://doi.org/10.1017/S003329171700174X

Overmier, J. B., & Seligman, M. E. P. (1967). Effects of inescapable shock upon subsequent escape and avoidance responding. *Journal of Comparative and Physiological Psychology*, *63*(1), 28–33. https://doi.org/10.1037/h0024166

Ozbay, F., Johnson, D. C., Dimoulas, E., Morgan, C. A., Charney, D., & Southwick, S. (2007). Social Support and Resilience to Stress. *Psychiatry (Edgmont)*, *4*(5), 35–40.

Padilla, A. M., Padilla, C., Ketterer, T., & Giacalone, D. (1970). Inescapable shocks and subsequent escape/avoidance conditioning in goldfish, Carassius auratus. *Psychonomic Science*, *20*(5), 295–296. https://doi.org/10.3758/BF03329075

Panzarella, C., Alloy, L. B., & Whitehouse, W. G. (2006). Expanded hopelessness theory of depression: On the mechanisms by which social support protects against depression. *Cognitive Therapy and Research*, *30*(3), 307-333. https://doi.org/10.1007/s10608-006-9048-3

Paschke, L. M., Dörfel, D., Steimke, R., Trempler, I., Magrabi, A., Ludwig, V. U., ... & Walter, H. (2016). Individual differences in self-reported self-control predict successful emotion regulation. *Social Cognitive and Affective Neuroscience*, *11*(8), 1193–1204. https://doi.org/10.1093/scan/nsw036

Pedrotti, M., Mirzaei, M. A., Tedesco, A., Chardonnet, J.-R., Mérienne, F., Benedetto, S., & Baccino, T. (2014). Automatic Stress Classification With Pupil Diameter Analysis. *International Journal of Human–Computer Interaction*, *30*(3), 220–236. https://doi.org/10.1080/10447318.2013.848320

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., ... & Lindeløv, J. K. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior research methods*, *51*(1), 195-203. https://doi.org/10.3758/s13428-018-01193-y

Petermann, F. (2012). *WAIS-IV. Wechsler Adult Intelligence Scale–Fourth Edition. Deutschsprachige Adaptation der WAIS-IV von D. Wechsler.* Pearson Assessment. https://www.pearsonclinical.de/pub/media/wysiwyg/Pearson_DE/WAIS_IV_Manual_1.pdf.

Petscher, Y., Terry, N. P., Gaab, N., & Hart, S. (2020). *Widening the Lens of Translational Science through Team Science*. PsyArXiv. https://doi.org/10.31234/osf.io/a8xs6

Peyron, C., Petit, J. M., Rampon, C., Jouvet, M., & Luppi, P. H. (1997). Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience*, *82*(2), 443-468. https://doi.org/10.1016/S0306-4522(97)00268-6

Pogge, T., & Wisor, S. (2016). Measuring poverty: A proposal. *The Oxford handbook of well-being and public policy*, 645-676.

Poldrack, R. A., Nichols, T., & Mumford, J. (2011). *Handbook of Functional MRI Data Analysis*. Cambridge University Press. https://doi.org/10.1017/CBO9780511895029

Potter, T. C. S., Bryce, N. V., & Hartley, C. A. (2017). Cognitive components underpinning the development of model-based learning. *Developmental Cognitive Neuroscience*, *25*, 272–280. https://doi.org/10.1016/j.dcn.2016.10.005

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., ... & Lupien, S. (2008). Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological psychiatry*, *63*(2), 234-240. https://doi.org/10.1016/j.biopsych.2007.04.041

Pryce, C. R., Azzinnari, D., Spinelli, S., Seifritz, E., Tegethoff, M., & Meinlschmidt, G. (2011). Helplessness: A systematic translational review of theory and evidence for its relevance to understanding and treating depression. *Pharmacology & Therapeutics*, *132*(3), 242–267. https://doi.org/10.1016/j.pharmthera.2011.06.006

R Core Team. (2019). *R: A Language and Environment for Statistical Computing* (Version 3.6.2) [Computer Software]. R Foundation for Statistical Computing.

Raab, H. A., & Hartley, C. A. (2020). Adolescents exhibit reduced Pavlovian biases on instrumental learning. *Scientific Reports*, *10*(1), 15770. https://doi.org/10.1038/s41598-020-72628-w

Rad, M. S., Martingano, A. J., & Ginges, J. (2018). Toward a psychology of Homo sapiens: Making psychological science more representative of the human population. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(45), 11401-11405. https://doi.org/10.1073/pnas.1721165115

Radenbach, C., Reiter, A. M. F., Engert, V., Sjoerds, Z., Villringer, A., Heinze, H.-J., ... & Schlagenhauf, F. (2015). The interaction of acute and chronic stress impairs model-based behavioral control. *Psychoneuroendocrinology*, *53*, 268–280. https://doi.org/10.1016/j.psyneuen.2014.12.017

Reed, R. G., Combs, H. L., Segerstrom, S. C., Donnellan, M. B., & Visser, B. (2020). The Structure of Self-Regulation and Its Psychological and Physical Health Correlates in Older Adults. *Collabra: Psychology*, *6*(1), 23. https://doi.org/10.1525/collabra.297

Ren, J., Friedmann, D., Xiong, J., Liu, C. D., Ferguson, B. R., Weerakkody, T., ... & Luo, L. (2018). Anatomically Defined and Functionally Distinct Dorsal Raphe Serotonin Sub-systems. *Cell*, *175*(2), 472-487.e20. https://doi.org/10.1016/j.cell.2018.07.043

Reznik, S. J., Nusslock, R., Pornpattananangkul, N., Abramson, L. Y., Coan, J. A., & Harmon-Jones, E. (2017). Laboratory-induced learned helplessness attenuates approach motivation as indexed by posterior versus frontal theta activity. *Cognitive, Affective, & Behavioral Neuroscience*, *17*(4), 904-916. https://doi.org/10.3758/s13415-017-0521-0

Richter-Levin, G., Stork, O., & Schmidt, M. V. (2019). Animal models of PTSD: a challenge to be met. *Molecular psychiatry*, *24*(8), 1135-1156. https://doi.org/10.1038/s41380-018-0272-5

Ridley, M., Rao, G., Schilbach, F., & Patel, V. (2020). Poverty, depression, and anxiety: Causal evidence and mechanisms. *Science*, *370*(6522), eaay0214. https://doi.org/10.1126/science.aay0214

Robinson, L., Adair, P., Coffey, M., Harris, R., & Burnside, G. (2016). Identifying the participant characteristics that predict recruitment and retention of participants to randomised controlled trials involving children: a systematic review. *Trials*, *17*, 294. https://doi.org/10.1186/s13063-016-1415-0

Robinson, A. M. (2018). Let's Talk about Stress: History of Stress Research. *Review of General Psychology*, *22*(3), 334–342. https://doi.org/10.1037/gpr0000137

Robinson, S. A., & Lachman, M. E. (2017). Perceived control and aging: A mini-review and directions for future research. *Gerontology*, *63*(5), 435-442. https://doi.org/10.1159/000468540

Roddenberry, A., & Renk, K. (2010). Locus of Control and Self-Efficacy: Potential Mediators of Stress, Illness, and Utilization of Health Services in College Students. *Child Psychiatry & Human Development*, *41*(4), 353–370. https://doi.org/10.1007/s10578-010-0173-6

Rohleder, N., Wolf, J. M., & Kirschbaum, C. (2003). Glucocorticoid sensitivity in humans-interindividual differences and acute stress effects. *Stress*, *6*(3), 207–222. https://doi.org/10.1080/1025389031000153658

Rolls, E. T., Huang, C. C., Lin, C. P., Feng, J., & Joliot, M. (2020). Automated anatomical labelling atlas 3. *NeuroImage, 206*, 116189. https://doi.org/10.1016/j.neuroimage.2019.116189

Rotter, J. B. (1966) Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs: General and Applied, 80*(1), 1-28. https://doi.org/10.1037/h0092976

Rozeske, R. R., Evans, A. K., Frank, M. G., Watkins, L. R., Lowry, C. A., & Maier, S. F. (2011). Uncontrollable, But Not Controllable, Stress Desensitizes 5-HT1A Receptors in the Dorsal Raphe Nucleus. *Journal of Neuroscience*, *31*(40), 14107–14115. https://doi.org/10.1523/JNEUROSCI.3095-11.2011

Russo, S. J., Murrough, J. W., Han, M.-H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. *Nature Neuroscience*, *15*(11), 1475–1484. https://doi.org/10.1038/nn.3234

Sabroe, I., Dockrell, D. H., Vogel, S. N., Renshaw, S. A., Whyte, M. K., & Dower, S. K. (2007). Identifying and hurdling obstacles to translational research. *Nature Reviews Immunology*, *7*(1), 77-82. https://doi.org/10.1038/nri1999

Salomons, T. V., Nusslock, R., Detloff, A., Johnstone, T., & Davidson, R. J. (2015). Neural Emotion Regulation Circuitry Underlying Anxiolytic Effects of Perceived Control over Pain. *Journal of Cognitive Neuroscience*, *27*(2), 222–233. https://doi.org/10.1162/jocn_a_00702

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., ... & for the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. (2017). A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*, *74*(4), 399–405. https://doi.org/10.1001/jamapsychiatry.2017.0080

Sandi, C. (2013). Stress and cognition. *WIREs Cognitive Science*, *4*(3), 245–261. https://doi.org/10.1002/wcs.1222

Sandner, M., Lois, G., Streit, F., Zeier, P., Kirsch, P., Wüst, S., & Wessa, M. (2020). Investigating individual stress reactivity: High hair cortisol predicts lower acute stress responses. *Psychoneuroendocrinology*, *118*, 104660. https://doi.org/10.1016/j.psyneuen.2020.104660

Santiago, C. D., & Wadsworth, M. E. (2009). Coping with family conflict: What's helpful and what's not for low-income adolescents. *Journal of Child and Family Studies*, *18*(2), 192-202. https://doi.org/10.1007/s10826-008-9219-9

Sapolsky, R. M. (2015). Stress and the brain: Individual variability and the inverted-U. *Nature Neuroscience*, *18*(10), 1344–1346. https://doi.org/10.1038/nn.4109

Schäfer, A., & Vagedes, J. (2013). How accurate is pulse rate variability as an estimate of heart rate variability?: A review on studies comparing photoplethysmographic technology with an electrocardiogram. *International journal of cardiology*, *166*(1), 15-29. https://doi.org/10.1016/j.ijcard.2012.03.119

Schönfeld, P., Preusser, F., & Margraf, J. (2017). Costs and benefits of self-efficacy: Differences of the stress response and clinical implications. *Neuroscience & Biobehavioral Reviews*, *75*, 40–52. https://doi.org/10.1016/j.neubiorev.2017.01.031

Schultze-Lutter, F., Schimmelmann, B. G., & Schmidt, S. J. (2016). Resilience, risk, mental health and well-being: Associations and conceptual differences. *European Child & Adolescent Psychiatry*, *25*(5), 459–466. https://doi.org/10.1007/s00787-016-0851-4

Schwabe, L., & Wolf, O. T. (2009). Stress Prompts Habit Behavior in Humans. *Journal of Neuroscience*, *29*(22), 7191–7198. https://doi.org/10.1523/JNEUROSCI.0979-09.2009

Schwabe, L., & Wolf, O. T. (2013). Stress and multiple memory systems: From 'thinking' to 'doing'. *Trends in Cognitive Sciences*, *17*(2), 60–68. https://doi.org/10.1016/j.tics.2012.12.001

Schwartz, J., & Macomber, C. (2017). So, you think you have an idea: A practical risk reduction-conceptual model for academic translational research. *Bioengineering*, *4*(2), 29. https://doi.org/10.3390/bioengineering4020029

Schwind, J. S., Norman, S. A., Brown, R., Frances, R. H., Koss, E., Karmacharya, D., & Santangelo, S. L. (2019). Association Between Earthquake Exposures and Mental Health Outcomes in Phulpingdanda Village After the 2015 Nepal Earthquakes. *Community Mental Health Journal*, *55*(7), 1103–1113. https://doi.org/10.1007/s10597-019-00404-w

Seligman, M. E. P., & Maier, S. F. (1967). Failure to escape traumatic shock. *Journal of Experimental Psychology*, *74*(1), 1–9. https://doi.org/10.1037/h0024514

Seligman, M. E. P. (1972). Learned Helplessness. *Annual Review of Medicine*, *23*(1), 407–412. https://doi.org/10.1146/annurev.me.23.020172.002203

Shapiro, F. R. (2014, April 28). Who Wrote the Serenity Prayer? *Chronicle of Higher Education.* https://www.chronicle.com/article/who-wrote-the-serenity-prayer/

Shields, G. S., Doty, D., Shields, R. H., Gower, G., Slavich, G. M., & Yonelinas, A. P. (2017). Recent life stress exposure is associated with poorer long-term memory, working memory, and self-reported memory. *Stress*, *20*(6), 598–607. https://doi.org/10.1080/10253890.2017.1380620

Shields, G. S., Rivers, A. M., Ramey, M. M., Trainor, B. C., & Yonelinas, A. P. (2019). Mild acute stress improves response speed without impairing accuracy or interference control in two selective attention tasks: Implications for theories of stress and cognition. *Psychoneuroendocrinology*, *108*, 78–86. https://doi.org/10.1016/j.psyneuen.2019.06.001

Shields, G. S., Sazma, M. A., & Yonelinas, A. P. (2016). The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. *Neuroscience & Biobehavioral Reviews*, *68*, 651–668. https://doi.org/10.1016/j.neubiorev.2016.06.038

Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: A systematic review. *The Lancet. Psychiatry*, *5*(1), 65–78. https://doi.org/10.1016/S2215-0366(17)30272-9

Singer, T., Seymour, B., O'doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, *303*(5661), 1157-1162. https://doi.org/10.1126/science.1093535

Singmann, H., Bolker, B., Westfall, J., Aust, F., Ben-Shachar, M. S. (2020). *afex: Analysis of Factorial Experiments* (Version 0.26-0) [Computer Software Package]. https://CRAN.R-project.org/package=afex.

Singmann, H., & Kellen, D. (2019). An Introduction to Mixed Models for Experimental Psychology. In D. Spieler & E. Schumacher (Eds.), *New Methods in Cognitive Psychology* (1st ed., pp. 4–31). Routledge. https://doi.org/10.4324/9780429318405-2

Smeets, T., van Ruitenbeek, P., Hartogsveld, B., & Quaedflieg, C. W. E. M. (2019). Stress-induced reliance on habitual behavior is moderated by cortisol reactivity. *Brain and Cognition*, *133*, 60–71. https://doi.org/10.1016/j.bandc.2018.05.005

Smith, B. W., Dalen, J., Wiggins, K., Tooley, E., Christopher, P., & Bernard, J. (2008). The brief resilience scale: Assessing the ability to bounce back. *International Journal of Behavioral Medicine*, *15*(3), 194–200. https://doi.org/10.1080/10705500802222972

Soares, J. M., Magalhães, R., Moreira, P. S., Sousa, A., Ganz, E., Sampaio, A., ... & Sousa, N. (2016). A Hitchhiker's Guide to Functional Magnetic Resonance Imaging. *Frontiers in Neuroscience*, *10*, 515. https://doi.org/10.3389/fnins.2016.00515

Soral, W., Kofta, M., & Bukowski, M. (2020). Helplessness experience and intentional (un-) binding: Control deprivation disrupts the implicit sense of agency. *Journal of Experimental Psychology: General, 150*(2), 289-305. https://doi.org/10.1037/xge0000791

Sperr, E. (2016). *PubMed by Year* [Computer Software]. http://esperr.github.io/pubmed-by-year/

Steffen, A., Thom, J., Jacobi, F., Holstiege, J., & Bätzing, J. (2020). Trends in prevalence of depression in Germany between 2009 and 2017 based on nationwide ambulatory claims data. *Journal of Affective Disorders*, *271*, 239-247. https://doi.org/10.1016/j.jad.2020.03.082

Steptoe, A., & Poole, L. (2016). Control and Stress. In *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 73–80). Elsevier. https://doi.org/10.1016/B978-0-12-800951-2.00008-X

Stone, A. A., Schwartz, J. E., Broderick, J. E., & Deaton, A. (2010). A snapshot of the age distribution of psychological well-being in the United States. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(22), 9985-9990. https://doi.org/10.1073/pnas.1003744107

Swainson, J., McGirr, A., Blier, P., Brietzke, E., Richard-Devantoy, S., Ravindran, N., ... & Lam, R. W. (2020). The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder: Recommandations Du Groupe De Travail Du Réseau Canadien Pour Les Traitements De L'humeur Et De L'anxiété (Canmat) Concernant L'utilisation De La Kétamine Racémique Chez Les Adultes Souffrant De Trouble Dépressif Majeur. *The Canadian Journal of Psychiatry*, 0706743720970860. https://doi.org/10.1177/0706743720970860

Swerdlow, B. A., Pearlstein, J. G., Sandel, D. B., Mauss, I. B., & Johnson, S. L. (2020). Maladaptive behavior and affect regulation: A functionalist perspective. *Emotion*, *20*(1), 75-79. https://doi.org/10.1037/emo0000660

Szabo, S., Tache, Y., & Somogyi, A. (2012). The legacy of Hans Selye and the origins of stress research: A retrospective 75 years after his landmark brief "Letter" to the Editor# of Nature. *Stress*, *15*(5), 472–478. https://doi.org/10.3109/10253890.2012.710919

Tang, X., Upadyaya, K., & Salmela-Aro, K. (2021). School burnout and psychosocial problems among adolescents: Grit as a resilience factor. *Journal of Adolescence*, *86*, 77–89. https://doi.org/10.1016/j.adolescence.2020.12.002

Taylor, J. J., Neitzke, D. J., Khouri, G., Borckardt, J. J., Acierno, R., Tuerk, P. W., ... & George, M. S. (2014). A pilot study to investigate the induction and manipulation of learned helplessness in healthy adults. *Psychiatry Research*, *219*(3), 631–637. https://doi.org/10.1016/j.psychres.2014.05.045

Techniker Krankenkasse (2016). *Entspann dich, Deutschland. TK-Stressstudie.* Hamburg: Techniker Krankenkasse.

Tedeschi, R. G., Park, C. L., & Calhoun, L. G. (1998). *Posttraumatic Growth: Positive Changes in the Aftermath of Crisis*. Routledge.

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence. *The Lancet*, *379*(9820), 1056-1067. https://doi.org/10.1016/S0140-6736(11)60871-4

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews*, *36*(2), 747–756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thornton, J. W., & Jacobs, P. D. (1971). Learned helplessness in human subjects. *Journal of Experimental Psychology*, *87*(3), 367–372. https://doi.org/10.1037/h0030529

Tice, D. M., & Bratslavsky, E. (2000). Giving in to Feel Good: The Place of Emotion Regulation in the Context of General Self-Control. *Psychological Inquiry*, *11*(3), 149–159. https://doi.org/10.1207/S15327965PLI1103_03

Tielemans, N. S., Schepers, V. P., Visser-Meily, J. M., Post, M. W., & van Heugten, C. M. (2015). Associations of Proactive Coping and Self-Efficacy With Psychosocial Outcomes in Individuals After Stroke. *Archives of Physical Medicine and Rehabilitation*, *96*(8), 1484–1491. https://doi.org/10.1016/j.apmr.2015.04.009

Tomczak, M., Tomczak, E. (2014). The need to report effect size estimates revisited. An overview of some recommended measures of effect size. *Trends in Sport Sciences*, *1*, 19–25.

Trapp, S., O'Doherty, J. P., & Schwabe, L. (2018). Stressful Events as Teaching Signals for the Brain. *Trends in Cognitive Sciences*, *22*(6), 475–478. https://doi.org/10.1016/j.tics.2018.03.007

Travis, J., Kaszycki, A., Geden, M., & Bunde, J. (2020). Some stress is good stress: The challenge-hindrance framework, academic self-efficacy, and academic outcomes. *Journal of Educational Psychology*, *112*(8), 1632–1643. https://doi.org/10.1037/edu0000478

Troy, A. S. (2015). Reappraisal and resilience to stress: Context must be considered. *Behavioral and Brain Sciences*, *38*, E123. https://doi.org/10.1017/S0140525X1400171X

Troy, A. S., Ford, B. Q., McRae, K., Zarolia, P., & Mauss, I. B. (2017). Change the things you can: Emotion regulation is more beneficial for people from lower than from higher socioeconomic status. *Emotion*, *17*(1), 141-154. https://doi.org/10.1037/emo0000210

Troy, A. S., Shallcross, A. J., & Mauss, I. B. (2013). A person-by-situation approach to emotion regulation: Cognitive reappraisal can either help or hurt, depending on the context. *Psychological science*, *24*(12), 2505-2514. https://doi.org/10.1177%2F0956797613496434

Trujillo, K. A., & Iñiguez, S. D. (2020). Ketamine beyond anesthesia: Antidepressant effects and abuse potential. *Behavioural Brain Research*, *394*, 112841. https://doi.org/10.1016/j.bbr.2020.112841

Ungar, M. (2015a). Social ecological complexity and resilience processes. *Behavioral and Brain Sciences*, *38*, E124. https://doi.org/10.1017/S0140525X14001721

Ungar, M. (2015b). Resilience and culture: The diversity of protective processes and positive adaptation. In *Youth resilience and culture* (pp. 37-48). Springer, Dordrecht.

United Nations (2021). *Ending Poverty*. Retrieved March 19, 2021, from https://www.un.org/en/global-issues/ending-poverty

van Harmelen, A.-L., Kievit, R. A., Ioannidis, K., Neufeld, S., Jones, P. B., Bullmore, E., ... & Goodyer, I. (2017). Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychological Medicine*, *47*(13), 2312–2322. https://doi.org/10.1017/S0033291717000836

van Oort, J., Tendolkar, I., Hermans, E. J., Mulders, P. C., Beckmann, C. F., Schene, A. H., ... & van Eijndhoven, P. F. (2017). How the brain connects in response to acute stress: A review at the human brain systems level. *Neuroscience & Biobehavioral Reviews*, *83*, 281–297. https://doi.org/10.1016/j.neubiorev.2017.10.015

van Rossum, G., & Drake, F. L. (2010). *The Python Library Reference* (Version 2.7) [Computer Software]. The Python Software Foundation. www.python.org

Veer, I. M., Riepenhausen, A., Zerban, M., Wackerhagen, C., Puhlmann, L. M. C., Engen, H. ... & Kalisch, R. (2021). Psycho-social factors associated with mental resilience in the Corona lockdown. *Translational Psychiatry*, *11*, 67. https://doi.org/10.1038/s41398-020-01150-4

Venniro, M., Banks, M. L., Heilig, M., Epstein, D. H., & Shaham, Y. (2020). Improving translation of animal models of addiction and relapse by reverse translation. *Nature Reviews Neuroscience*, *21*(11), 625–643. https://doi.org/10.1038/s41583-020-0378-z

Vollmayr, B., & Gass, P. (2013). Learned helplessness: Unique features and translational value of a cognitive depression model. *Cell and Tissue Research*, *354*(1), 171–178. https://doi.org/10.1007/s00441-013-1654-2

Volpicelli, J., Balaraman, G., Hahn, J., Wallace, H., & Bux, D. (1999). The Role of Uncontrollable Trauma in the Development of PTSD and Alcohol Addiction. *Alcohol Research & Health*, *23*(4), 256–262.

von der Malsburg, T. (2015). *Py-Span.-Task–A Software for Testing Working Memory Span* [Computer Software]. https://github.com/tmalsburg/py-span-task

Voon, V., Reiter, A., Sebold, M., & Groman, S. (2017). Model-Based Control in Dimensional Psychiatry. *Biological Psychiatry, 82*(6), 391–400. https://doi.org/10.1016/j.biopsych.2017.04.006

Vukotich Jr, C. J. (2016). Challenges of T3 and T4 Translational Research. *Journal of Research Practice*, *12*(2), P2.

Wadsworth, M. E. (2015). Development of Maladaptive Coping: A Functional Adaptation to Chronic, Uncontrollable Stress. *Child Development Perspectives*, *9*(2), 96–100. https://doi.org/10.1111/cdep.12112

Wadsworth, M. E., Broderick, A. V., Loughlin-Presnal, J. E., Bendezu, J. J., Joos, C. M., Ahlkvist, J. A., ... & McDonald, A. (2019). Co-activation of SAM and HPA responses to acute stress: A review of the literature and test of differential associations with preadolescents' internalizing and externalizing. *Developmental Psychobiology*, *61*(7), 1079–1093. https://doi.org/10.1002/dev.21866

Wagnild, G. M., & Young, H. M. (1993). Development and psychometric evaluation of the resilience scale. *Journal of Nursing Measurement, 1,* 165–178.

Wang, K. S., & Delgado, M. R. (2021). The Protective Effects of Perceived Control During Repeated Exposure to Aversive Stimuli. *Frontiers in Neuroscience*, *15*, 625816. https://doi.org/10.3389/fnins.2021.625816

Wanke, N., & Schwabe, L. (2019). Subjective Uncontrollability over Aversive Events Reduces Working Memory Performance and Related Large-Scale Network Interactions. *Cerebral Cortex, 30*(5), 3116-3129. https://doi.org/10.1093/cercor/bhz298

Wanke, N., & Schwabe, L. (2020). Dissociable neural signatures of passive extinction and instrumental control over threatening events. *Social Cognitive and Affective Neuroscience*, *15*(6), 625–634. https://doi.org/10.1093/scan/nsaa074

Weiss, J. M., Goodman, P. A., Losito, B. G., Corrigan, S., Charry, J. M., & Bailey, W. H. (1981). Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. *Brain Research Reviews*, *3*(2), 167-205. https://doi.org/10.1016/0165-0173(81)90005-9

Wichman, C., Smith, L. M., & Yu, F. (2020). A framework for clinical and translational research in the era of rigor and reproducibility. *Journal of Clinical and Translational Science*, 1-10. https://doi.org/10.1017/cts.2020.523

Wilkinson, S. T., Toprak, M., Turner, M. S., Levine, S. P., Katz, R. B., & Sanacora, G. (2017). A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders. *The American Journal of Psychiatry*, *174*(7), 695–696. https://doi.org/10.1176/appi.ajp.2017.17020239

Wirz, L., Bogdanov, M., & Schwabe, L. (2018). Habits under stress: mechanistic insights across different types of learning. *Current opinion in behavioral sciences*, *20*, 9-16. https://doi.org/10.1016/j.cobeha.2017.08.009

Wolff, B. C., Wadsworth, M. E., & Santiago, C. D. (2010). Family poverty, stress, and coping. In R. J. R. Levesque (Ed.), Encyclopedia of adolescence (pp. 941–951). New York, NY: Springer.

Wood, K. H., Wheelock, M. D., Shumen, J. R., Bowen, K. H., Ver Hoef, L. W., & Knight, D. C. (2015). Controllability modulates the neural response to predictable but not unpredictable threat in humans. *NeuroImage*, *119*, 371–381. https://doi.org/10.1016/j.neuroimage.2015.06.086

Woolf, S. H. (2008). The Meaning of Translational Research and Why It Matters. *JAMA*, *299*(2), 211-213. https://doi.org/10.1001/jama.2007.26

Worley, N. B., Hill, M. N., & Christianson, J. P. (2018). Prefrontal endocannabinoids, stress controllability and resilience: A hypothesis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *85*, 180–188. https://doi.org/10.1016/j.pnpbp.2017.04.004

Yin, X., Guven, N., & Dietis, N. (2016). Stress-based animal models of depression: Do we actually know what we are doing? *Brain research*, *1652*, 30-42. https://doi.org/10.1016/j.brainres.2016.09.027

Yon, D., Bunce, C., & Press, C. (2020). Illusions of control without delusions of grandeur. *Cognition*, *205*, 104429. https://doi.org/10.1016/j.cognition.2020.104429

Yuen, E. Y., Liu, W., Karatsoreos, I. N., Feng, J., McEwen, B. S., & Yan, Z. (2009). Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(33), 14075–14079. https://doi.org/10.1073/pnas.0906791106

Yurgil, K. A., Barkauskas, D. A., & Baker, D. G. (2021). Deployment and psychological correlates of suicide ideation: a prospective, longitudinal study of risk and resilience among combat veterans. *Military medicine*, *186*(1-2), e58-e66. https://doi.org/10.1093/milmed/usaa450

Zahniser, E., & Conley, C. S. (2018). Interactions of emotion regulation and perceived stress in predicting emerging adults' subsequent internalizing symptoms. *Motivation and Emotion*, *42*(5), 763–773. https://doi.org/10.1007/s11031-018-9696-0

Zannas, A. S., & West, A. E. (2014). Epigenetics and the regulation of stress vulnerability and resilience. *Neuroscience*, *264*, 157–170. https://doi.org/10.1016/j.neuroscience.2013.12.003

Zimmer-Gembeck, M. J., Van Petegem, S., & Skinner, E. A. (2016). Emotion, controllability and orientation towards stress as correlates of children's coping with interpersonal stress. *Motivation and Emotion*, *40*(1), 178-191. https://doi.org/10.1007/s11031-015-9520-z

Zimmermann, P., & Fimm, B. (2002). Testbatterie zur Aufmerksamkeitsprüfung (TAP) (Version 1.7). Psytest.

Zlomuzica, A., Preusser, F., Schneider, S., & Margraf, J. (2015). Increased perceived self-efficacy facilitates the extinction of fear in healthy participants. *Frontiers in Behavioral Neuroscience, 9*, 270. https://doi.org/10.3389/fnbeh.2015.00270

Zweerings, J., Sarkheil, P., Keller, M., Dyck, M., Klasen, M., Becker, B., ... & Mathiak, K. (2020). Rt-fMRI neurofeedback-guided cognitive reappraisal training modulates amygdala responsivity in posttraumatic stress disorder. *NeuroImage: Clinical*, *28*, 102483. https://doi.org/10.1016/j.nicl.2020.102483

7. Acknowledgements

I am deeply grateful for the support of many people who have helped me in many different ways to carry out my research and make the absolute most of these past few years.

First of all, I must thank my supervisor, [redacted], who supported me throughout the process, always greeted my ideas with enthusiasm, and gave me great freedom to explore my interests. I appreciate the trust she has placed in me and have benefitted greatly from being allowed to work independently and take responsibility. At the same time, I continue to value her guidance and advice as an experienced, imaginative, engaging, and considerate mentor.

I thank [redacted], who actively helped me expand my network by tirelessly promoting talks, seminars, and conferences and inviting me to join the international resilience alliance. These events have provided stimulating discussions and wonderful opportunities for exchange with colleagues from around the world, which I especially cherish during the current pandemic-imposed lockdown. I would also like to thank [redacted], who supplied me with helpful insights into the secret workings of academia and whose approachable, kind, and delightfully sarcastic manner further ignited my passion for teaching. I thank both [redacted] and [redacted] for their readiness to serve as examination committee members.

I would also like to thank [redacted] and her whole group for teaching me new ways to conduct cutting-edge, transparent, and slightly faster-paced, "NYC-style" research, which I will forever try to emulate.

I am grateful to my colleagues, [redacted] and [redacted] for showing me the ropes and highlighting the intricacies of efficient collaboration, respectively. Special thanks go to my colleagues, [redacted], [redacted], and [redacted] for practical and emotional support as well as the many fun lunch parties. I also thank [redacted], the "partner-in-crime" I needed to get through the stressful bits, especially towards the end of this dissertation project. A like-minded aspiring researcher and night-owl, she was always happy to discuss meta-science and delve into the nitty-gritty of neuroimaging, data analysis, and coding with me.

I thank [redacted] who helped me with all the administrative details, enjoyed following my progress and celebrated my successes. In the same vein, I sincerely thank the many students who helped with recruitment, data acquisition, data preparation, and any and all issues around project organization: [redacted]

[redacted]. We did not all work together at the same time, but each team made for a great group feeling. Their commitment, attention to detail, and flexibility enabled me to pursue so many different projects, there was not room enough to include them all in this dissertation. I now feel equipped with invaluable leadership skills that I am excited to put to the test soon.

A big thank you goes to all the participants who voluntarily and good-naturedly underwent the rather uncomfortable experiments and provided the data for my projects.

Even though she was not involved in my dissertation research, I would also like to thank [redacted] for being a wonderful mentor to me. Her success, curiosity, modesty, and amiable manner continue to inspire me.

Lastly, I would not have come this far without the support of my family and friends. I warmly thank my friend, [redacted], for proofreading the bulk of this dissertation, my uncle, [redacted], for many helpful discussions, and my mother, [redacted], for practical advice on issues that required diplomatic sensitivity. I also thank my father, my siblings, and all the rest of my family for always showing a keen interest and cheering me on. In particular, I thank my husband, [redacted], and my sister, [redacted]. As a fellow psychologist and avid research follower, she has been my constant brainstorming buddy, ad hoc reviewer, test participant, motivational coach, etc. I am counting on her to always be ready to give her opinion on pressing matters, such as whether the subtle reference to Jane Austen in the last sentence of this dissertation is perhaps a little too much. In times of stress, my husband has patiently borne all my "too-much-to-do-and-no-time" rants. He did candidly remind me that, after all, I chose this for myself. At the same time, he remains my earnest supporter and I am incredibly thankful for his love and understanding. Que o nosso futuro traga muito mais aventuras! ☺

8. Erklärung

gemäß § 6 Absatz 2 g) und gemäß § 6 Absatz 2 h) der Promotionsordnung der Fachbereiche 02, 05, 06, 07, 09 und 10 vom 04. April 2016

Name (ggf. Geburtsname): Meine

Vorname: Laura Elisabeth

Hiermit erkläre ich, dass ich die eingereichte Dissertation selbständig, ohne fremde Hilfe verfasst und mit keinen anderen als den darin angegebenen Hilfsmitteln angefertigt habe, dass die wörtlichen oder dem Inhalt nach aus fremden Arbeiten entnommenen Stellen, Zeichnungen, Skizzen, bildlichen Darstellungen und dergleichen als solche genau kenntlich gemacht sind.

Von der Ordnung zur Sicherung guter wissenschaftlicher Praxis in Forschung und Lehre und zum Verfahren zum Umgang mit wissenschaftlichem Fehlverhalten habe ich Kenntnis genommen.

Bei einer publikationsbasierten Promotion:
Meine Erklärung bezieht sich auf Schriften, die ich als alleiniger Autor bzw. Autorin eingereicht habe oder bei Ko-Autorenschaft auf jene Teile, für die ich mich verantwortlich zeichne.

Ich habe keine Hilfe von kommerziellen Promotionsberatern in Anspruch genommen.

31.03.2021 _____

Datum Unterschrift

9. Curriculum Vitae

Name: Laura Elisabeth Meine
Geburtsdatum: 11.01.1991
Geburtsort: Hannover
Nationalität: Deutsch
Familienstand: Verheiratet

AKADEMISCHER HINTERGRUND

Sep 2021	Promotion in Psychologie an der Johannes Gutenberg-Universität Mainz; Titel der Dissertation: „The Modulatory Effect of Control on Stress Responding – A Translational Perspective with Implications for Resilience Research“
Mai 2017 – Jun 2021	Wissenschaftliche Mitarbeiterin in der Abteilung Klinische Psychologie und Neuropsychologie, Psychologisches Institut, Johannes Gutenberg-Universität Mainz
Okt 2019 – Mär 2020	Forschungsaufenthalt Department of Psychology, New York University, New York, NY, USA Betreuer: Prof. Dr. [redacted]
Mai 2017	M. Sc. in Social, Cognitive and Affective Neuroscience (SCAN) Freie Universität Berlin, 6. Fachsemester <u>Prüfungsfächer:</u> SCAN, Clinical SCAN, Statistical Methods, Applied Programming, Learning, Memory and Decision-making, Language, Music and Emotion, Advanced Neurocognitive Methods, Research Experience (Internship) <u>Hochschullehrer*innen:</u> Univ.-Prof. Dr. [redacted], Prof. Dr. [redacted], Prof. Dr. [redacted], Univ.-Prof. Dr. [redacted], Prof. Dr. [redacted], Univ.-Prof. Dr. [redacted]
Sep 2012 – Mai 2013	Auslandsstudium am Trinity College Dublin, Irland, unterstützt durch ein DAAD PROMOS Stipendium
Jun 2014	B. Sc. in Psychologie Universität Hildesheim, 8. Fachsemester <u>Prüfungsfächer:</u> Einführung in die Psychologie, Forschungsmethoden I+II, Allgemeine Psychologie I+II, Sozialpsychologie, Einführung in die Pädagogik, Studium Generale I+II, Psychologische Diagnostik

I+II, Wissenschaftliche Praxis, Entwicklungspsychologie, Pädagogische Psychologie I+II, Klinische Psychologie I+II, Praktikum, Differentielle und Persönlichkeitspsychologie

Hochschullehrer*innen:
Prof. Dr. [redacted], Dr. [redacted], Dr. [redacted], Prof. Dr. [redacted], Prof. Dr. [redacted], apl. Prof. Dr. [redacted], Prof. Dr. [redacted], Dr. [redacted], Prof. Dr. [redacted], Prof. Dr. [redacted]

PUBLIKATIONEN

Meine, L. E., [redacted], [redacted], [redacted], [redacted], [redacted]. (2021). *Look after yourself: Students consistently showing high resilience engaged in more self-care and proved more resilient during the COVID-19 pandemic.* [Manuscript under review]. Institute of Psychology, Johannes Gutenberg University Mainz.

Meine, L. E., [redacted], [redacted], [redacted], & [redacted] (2021). *Reward and memory interactions in middle childhood and evidence for income-related differences* [Manuscript in preparation]. Institute of Psychology, Goethe University Frankfurt.

[redacted], **Meine, L. E.**, & [redacted] (2021). It's worth the trouble: stressor exposure is related to increased cognitive reappraisal ability. *Stress and Health*, 1-8. https://doi.org/10.1002/smi.3101

Meine, L. E., [redacted], [redacted], & [redacted] (2021). Don't stress, it's under control: neural correlates of stressor controllability in humans. *bioRxiv*. https://doi.org/10.1101/2021.03.30.437657

Meine, L. E.[*], [redacted][*], [redacted], [redacted], & [redacted] (2020). A translational paradigm to study the effects of uncontrollable stress in humans. *International journal of molecular sciences*, *21*(17), 6010. https://doi.org/10.3390/ijms21176010
[*]Both authors contributed equally to this work.

KONFERENZBEITRÄGE

Meine, L. E., [redacted], [redacted], [redacted], [redacted], [redacted] (2021, September). *Look after yourself: Students consistently showing high resilience engaged in more self-care and proved more resilient during the COVID-19 pandemic.* Poster at the 7th International Symposium on Resilience Research, Mainz, DE. (online)

Meine, L. E. [redacted], [redacted], [redacted] (2021, September). *Don't stress, it's under control: neural correlates of stressor controllability in humans.* Poster at the ZNZ Symposium 2021 - Neuroscience Center Zurich, Zürich, CH.

Meine, L. E. [redacted], [redacted], [redacted] (2021, May). *Don't stress, it's under control: neural correlates of stressor controllability in humans.* Poster at the 38th Symposium of the Division of Clinical Psychology and Psychotherapy of the DGPs, Mannheim, DE. (online)

Meine, L. E., [redacted], [redacted], [redacted] (2020, November). *Don't stress, it's under control: neural correlates of stressor controllability in humans.* Talk at Leibniz Institute for Resilience Research – Seminar Series, Mainz, DE. (online)

Meine, L. E., [redacted], [redacted], [redacted] (2020, September). *Linking flexibility in learning processes to stress history and resilience.* Poster at the 6th International Symposium on Resilience Research, Mainz, DE. (online)

Meine, L. E., [redacted], [redacted], [redacted], [redacted] (2019). *Income-related differences in reward anticipation-mediated memory enhancement in children*. Talk at Neuroscience 2019 – Society for Neuroscience 50th annual meeting, Chicago, US.

Meine, L. E., [redacted], [redacted], [redacted] (2019, September). *Why trust is fine but control is better – neural correlates of stressor controllability in humans.* Poster at the 5th International Symposium on Resilience Research, Mainz, DE.

Meine, L. E., [redacted], [redacted], [redacted] (2019, September). *Overcoming learned helplessness: can experience of control over a stressor immunized against uncontrollable stress?* Poster at the 5th International Symposium on Resilience Research, Mainz, DE.

Meine, L. E., [redacted], [redacted], [redacted] (2019, August). *Overcoming learned helplessness: can experience of control over a stressor immunize against uncontrollable stress?* Talk at the 3rd CRC 1193 PhD & Postdoc Retreat, Hirschegg, AT.

Meine, L. E., [redacted], [redacted] (2019, June). *A translational study to investigate the effects of stressor controllability in humans.* Poster at the 45th Conference "Psychologie und Gehirn", Dresden, DE.

Meine, L. E., & [redacted], [redacted] (2018). *Neurobiological correlates of stressor controllability in humans.* Poster at the 4th International Symposium on Resilience Research, Mainz, DE.

[redacted], & **Meine, L. E.**, [redacted] (2018). *It's all about control: a translational study of two resilience mechanisms.* Poster at the 4th International Symposium on Resilience Research, Mainz, DE.

Meine, L. E., & [redacted], [redacted], [redacted] (2018). *Interindividual differences promoting stress resilience.* Poster at the 48th Annual Meeting of the International Society of Psychoneuroendocrinology, Irvine, US.

[redacted] & **Meine, L. E.**, [redacted], [redacted] (2018). *Translating the learned*

helplessness paradigm to study potential resilience mechanisms in humans. Poster at the 48th Annual Meeting of the International Society of Psychoneuroendocrinology, Irvine, US.

Meine, L. E. & [redacted], [redacted], [redacted] (2018). *Making lemonade out of lemons: interindividual differences promoting stress resilience*. Poster at the 11th FENS Forum of Neuroscience, Berlin, DE.

[redacted] & **Meine, L. E:**, [redacted], [redacted] (2018). *Will they fail to escape? Translating the shuttlebox paradigm to humans*. Poster at the 11th FENS Forum of Neuroscience, Berlin, DE.

Meine, L. E., & [redacted] (2018). *Our novel translational stress paradigm - a basis for human research on stress immunization*. Talk at the 1st CRC 1193 Science Day, Leinsweiler, DE.

Meine, L. E., [redacted], [redacted], [redacted] (2017). *Studying the effects of stressor controllability in humans using a novel paradigm adapted from animal research.* Selected Young Investigator Talk and Poster at the 3rd International Symposium on Resilience Research, Mainz, DE.

Meine, L. E., [redacted], [redacted], [redacted], [redacted] (2017). *Differential effects of hair cortisol and cumulative risk on reward anticipation-mediated memory enhancement in children.* Poster at the 47th Annual Meeting of the International Society of Psychoneuroendocrinology, Zürich, CH.

[redacted], **Meine, L. E.**, [redacted], [redacted], [redacted], [redacted] (2017). *Chronic stress and reward anticipation-mediated memory enhancement in children*. Poster at the 59th Conference of Experimental Psychologists (TeaP), Dresden, DE.