The Influence of Perceived Control on Appetitive and Aversive Decision Making

by

KAINAN (SALLY) WANG

A Dissertation submitted to the
Graduate School-Newark
Rutgers, The State University of New Jersey
In partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
Graduate Program in Behavioral and Neural Sciences
Written under the direction of Mauricio R. Delgado, PhD
and approved by:

Michael W. Cole, PhD

_____

Mauricio R. Delgado, PhD

_____

William W. Graves, PhD

_____

Catherine E. Myers, PhD

_____

Elizabeth M. Tricomi, PhD

_____

Newark, New Jersey

October, 2019

ABSTRACT OF THE DISSERTATION

The influence of perceived control on appetitive and aversive decision making

by KAINAN (SALLY) WANG

Dissertation Advisor:

Mauricio Delgado, PhD

The ability to perceive and exercise control over an outcome is both desirable and beneficial to our wellbeing. Organisms are biased to seek control in situations where rewards are available and such bias has been shown to recruit the ventromedial prefrontal cortex (vmPFC) and striatum. Moreover, when given control over potentially aversive outcomes, organisms increase behaviors to avoid those outcomes. These findings suggest that perceived control exerts behavioral influences in both appetitive and aversive environments. Yet, several questions remain unanswered. First, if an organism shows behavioral preference towards control in appetitive contexts, can we measure this bias and study the subjective value of control neurally? To find out, we employed the *Value of Control* (VoC) task where human participants were asked to make a series of binary choices between having control and no-control over a reward-seeking game. The mere presence of the control-option evoked activity in the striatum. Importantly, we extracted the positive subjective value of control and demonstrated that it was tracked in the vmPFC. Second, because control confers protective effects against behavioral passivity in aversive contexts, it remains

uncertain whether it is potent enough to reverse behavioral passivity following prolonged exposure to uncontrollability. To investigate this, we employed the *Control in Aversive Domain* (CAD) task to examine whether the introduction of controllability can rescue participants' behavior after persistent uncontrollability. We observed that even after developing behavioral passivity, instatement of control was able to restore avoidance behavior, and this behavioral reversal correlated with participants' vmPFC activity. Third, it is unknown whether exposure to acute stress can negatively impact participants' perception of control. To study this, we subjected participants to an acute stressor prior to implementing the VoC and CAD tasks. We found that exposure to acute stress did not significantly alter participants' subjective value of control but it did induce participants to exhibit greater behavioral responses towards uncontrollable aversive stimuli. Collectively, these studies show that perceived control can bias behavior via its rewarding values and protective effects. They also highlight the role of corticostriatal circuitry in encoding control, which has important implications in our understanding of psychopathologies associated with the loss of control.

Dedication

To Mum and Dad, for being the world to me.

To Grandma and Grandpa, for the unconditional love.

To Grandpa Zhou, for showing me the value of honor and integrity.

To the unnamed individual who came back to life twice in one month, for sustaining my belief in miracles.

Acknowledgement

I express my most sincere and heartfelt thanks to the individuals who have facilitated and influenced my graduate days in one way or another, science- or life-wise. First, I would like to thank my former mentors, Drs. James Tepper, Elizabeth Abercrombie, Joel Perlmutter, and Carlos Paladini, for helping to shape the very beginning of my science career. I also want to extend my thanks to Drs. Joan Morrell, Elizabeth Tricomi, Catherine Myers, William Graves and Michael Cole, for all the support both research-wise and career-wise throughout graduate school. All of you have helped me to grow my sense of control in both research and career-planning endeavors.

Second, I would like to thank several groups of individuals for being there with me from day one in graduate school. To Anna-Marie, for your continual presence since our first days in college and for bringing your parents to my defense (no pun intended!). To John, Vicky, Samar, Pinelopi, Hussein, Ahmet and Brynne, graduate school would not be the same flavor without any of you. Thanks for braving it with me through all the ups and downs. To Ivy, Stephanie, Jen, Patti, Debbie, Kathy, Scott, Michael and Joe, thanks for saving lives together and adding spices to my graduate school days! To Dave, Stephanie, Catherine, Heena and Noriya, thanks for being good colleagues but even better friends. I'm joining you as Delgado lab alumni! To Jamil, Maddy and Emily, thanks for sitting through my struggles at lab presentations and for all the insightful feedback and discussions.

Third, I would like to thank my family even though words are never enough to express my gratitude towards you. I can always rely on you for love and support at every stage of my life. And lastly and most importantly, lest I forget to thank the one individual who has shaped my graduate career the most—my dissertation advisor, Dr. Mauricio Delgado (aka M). By a stroke of luck, I joined your lab in my second year of graduate school. But it was the luckiest thing to have happened to me at Rutgers. Thank you for putting up with all my scientific and writing struggles. I can always count on you for encouragement and support in my endeavor to become an independent scientist and a rigorous thinker.

Table of contents

CHAPTER I: GENERAL INTRODUCTION ..... - 1 -

1.1 THE REWARDING NATURE OF PERCEIVED CONTROL ..... - 2 -
1.1.1 The motivational property of perceived control is driven by dopamine transmission ..... *- 3 -*
1.1.2 The affective property of perceived control is subserved by the striatum ..... *- 4 -*
1.2 THE PROTECTIVE NATURE OF PERCEIVED CONTROL ..... - 5 -
1.2.1 The neural mechanism of perceived control involves the vmPFC ..... *- 6 -*
1.3 PERCEIVED CONTROL IS NOT ALWAYS DESIRED ..... - 11 -
1.4 A CASE FOR THE SUBJECTIVE VALUE OF CONTROL ..... - 13 -
1.5 REMAINING QUESTIONS ..... - 15 -

CHAPTER II: AIM 1. CORTICOSTRIATAL CIRCUITS ENCODE THE SUBJECTIVE VALUE OF PERCEIVED CONTROL ..... - 19 -

2.1 INTRODUCTION ..... - 19 -
2.2 METHODS ..... - 21 -
2.2.1 Participants ..... *- 21 -*
2.2.2 Experimental design ..... *- 22 -*
2.2.2.1 The Value of Control task ..... - 23 -
2.2.2.1.1 Choice phase ..... - 23 -
2.2.2.1.2 Game phase ..... - 24 -
2.2.2.2 Training version of the task ..... - 25 -
2.2.2.3 Testing version of the task ..... - 26 -
2.2.2.3.1 Mixed condition ..... - 27 -
2.2.2.3.2 Baseline condition: (*Controllable* and *uncontrollable* trial types) ..... - 28 -
2.2.3 Neuroimaging data acquisition ..... *- 29 -*
2.2.4 FMRI preprocessing ..... *- 29 -*
2.2.5 Data analysis ..... *- 31 -*
2.2.5.1 Behavioral analyses of choices in the VoC task ..... - 31 -
2.2.5.1.1 Derivation of the subjective value of control ..... - 32 -
2.2.5.2 Neuroimaging analyses of value of control ..... - 34 -
2.2.5.2.1 Controllable and uncontrollable baseline trial types ..... - 35 -
2.2.5.2.2 Mixed condition ..... - 38 -
2.3 RESULTS ..... - 39 -
2.3.1 Behavioral results ..... *- 39 -*
2.3.1.1 Reaction time ..... - 43 -
2.3.2 Neuroimaging results ..... *- 44 -*
2.3.2.1 Neural correlates underlying the opportunity for control ..... - 44 -
2.3.2.2 Neural correlates of subjective value of SELF-choices ..... - 46 -
2.4 DISCUSSION ..... - 48 -

CHAPTER III: AIM 2. THE PROTECTIVE EFFECTS OF PERCEIVED CONTROL IN AVERSIVE DECISION MAKING ..... - 55 -

3.1 INTRODUCTION ..... - 55 -

3.2 METHODS ..... - 59 -
3.2.1 Participants ..... *- 59 -*
3.2.2 Experimental task and design ..... *- 60 -*
3.2.2.1 Trial structure ..... - 60 -
3.2.2.1.1 Cue phase ..... - 60 -
3.2.2.1.2 Tone phase ..... - 61 -
3.2.2.2 Run structure ..... - 62 -
3.2.2.2.1 Exposure phase ..... - 62 -
3.2.2.2.2 Uncontrollable and controllable runs ..... - 63 -
3.2.3 Neuroimaging data acquisition ..... *- 65 -*
3.2.4 FMRI preprocessing ..... *- 65 -*
3.2.5 Data analysis ..... *- 67 -*
3.2.5.1 Behavioral analysis of choices in the CAD task ..... - 67 -
3.2.5.1.1 Exposure runs ..... - 68 -
3.2.5.1.2 Uncontrollable and controllable runs ..... - 68 -
3.2.5.2 Neuroimaging analysis ..... - 69 -
3.2.5.2.1 Exposure runs ..... - 70 -
3.2.5.2.2 Uncontrollable and controllable runs ..... - 72 -
3.3 RESULTS ..... - 73 -
3.3.1 Behavioral results ..... *- 73 -*
3.3.1.1 Aversive vs neutral exposure runs ..... - 74 -
3.3.1.2 Aversive exposure vs uncontrollable runs ..... - 75 -
3.3.1.3 Uncontrollable vs controllable runs ..... - 77 -
3.3.2 Neuroimaging results ..... *- 79 -*
3.3.2.1 Exposure runs ..... - 79 -
3.3.2.2 Uncontrollable and controllable runs ..... - 79 -
3.4 DISCUSSION ..... - 83 -

CHAPTER IV: AIM 3. THE EFFECTS OF ACUTE STRESS ON THE SUBJECTIVE VALUE AND BEHAVIORAL IMPACTS OF PERCEIVED CONTROL ..... - 92 -

4.1 INTRODUCTION ..... - 92 -
4.2 METHODS ..... - 94 -
4.2.1 Participants ..... *- 94 -*
4.2.2 Experimental task and design ..... *- 96 -*
4.2.2.1 Acute stress manipulation ..... - 99 -
4.2.2.2 Salivary cortisol measurements ..... - 100 -
4.2.2.3 Skin conductance measurement ..... - 101 -
4.2.2.4 CAD task (behavioral version) ..... - 102 -
4.2.2.4.1 Uncontrollable phase ..... - 102 -
4.2.2.4.2 Controllable phase ..... - 103 -
4.2.3 Data analysis ..... *- 105 -*
4.2.3.1 Effect of acute stress on subjective value of control ..... - 105 -
4.2.3.2 Effect of acute stress on behavior in the CAD task ..... - 105 -
4.3 RESULTS ..... - 106 -
4.3.1 Acute stress induction via increases in physiological and subjective measures *- 106 -*
4.3.2 Acute stress did not significantly change the subjective value of control ..... *- 107 -*
4.3.3 Acute stress increased behavioral responses to uncontrollable aversive stimuli *- 109 -*
4.3.4 Acute stress did not significantly affect participants' SCRs in the uncontrollable condition ..... *- 111 -*

4.3.5 Participants' subjective value of control did not correlate with participants' behavior in the CAD task ..... - 114 -
4.3.6 Questionnaire results ..... - 114 -
4.4 Discussion ..... - 118 -

CHAPTER V: GENERAL DISCUSSION ..... - 126 -

5.1 Perceived Control can Bias Behavior ..... - 127 -
5.2 Perceived Control has Protective Effects ..... - 131 -
5.3 The Role of the Striatum and vmPFC in Mediating Perceived Control ..... - 134 -
5.4 Proposed candidates for the neural circuit of perceived control ..... - 138 -
5.5 Experimental Limitations ..... - 140 -
5.6 Remaining questions and future directions ..... - 142 -

REFERENCES ..... - 145 -

APPENDIX ..... - 174 -

Supplementary material for Chapter II ..... - 174 -
Sample size determination ..... - 174 -
Questionnaire results ..... - 174 -
Activation tables for all contrasts ..... - 175 -
Conjunction of controllable and uncontrollable ..... - 175 -
Controllable (SELF) – uncontrollable (COMP) ..... - 175 -
Uncontrollable (COMP) – controllable (SELF) ..... - 176 -
$Mixed_{SELF}$ – $Mixed_{COMP}$ with POE covariate ..... - 176 -
Additional behavioral experiment ..... - 176 -
Participants ..... - 177 -
Experimental design ..... - 177 -
Behavioral results ..... - 178 -

List of figures and tables

Figure 1.1 Key neural substrates of perceived control 15

Figure 2.1 *Value of Control* (VoC) task 25

Figure 2.2 Behavioral findings 42

Figure 2.3 Neural correlates for value of perceived control 47

Figure 3.1 Experimental timeline of Control in Aversive Domain (CAD) task 64

Figure 3.2 Subjective tone rating 74

Figure 3.3 Behavioral findings in the *exposure* runs 75

Figure 3.4 Behavioral findings in the *exposure* and *uncontrollable* runs 76

Figure 3.5 Behavioral findings in the *uncontrollable* and *controllable* runs 77

Figure 3.6 Behavioral findings in all aversive runs 79

Figure 3.7 Neural correlates for uncontrollable cues 81

Figure 3.8 Correlation of avoidance behavior and neural activity 83

Figure 4.1 Experimental timeline. 98

Figure 4.2 Control in Aversive Domain (CAD) task 104

Figure 4.3 Salivary cortisol levels 107

Figure 4.4 Changes in subjective value of control 108

Figure 4.5 Effect of acute stress on behavioral responses to uncontrollable and controllable conditions 110

Figure 4.6 Effect of acute stress on SCRs in response to uncontrollable and controllable conditions 113

Table 4.1 Questionnaire results 115-118

Chapter I: General introduction

Whenever we purchase an airline ticket, we are often presented with the choice of choosing our own seat or letting the airline computer assign one to us. Most of the time, when confronted with such choices, we tend to bias our behavior towards choosing our own seats. This is true even when we fly with the growing list of airlines who charge a fee for us to choose our own seats. In other words, we have a strong preference towards the option to exert control, even if it leads to incurring a cost to do so.

By being able to pick our seats, we perceive a sense of control over the outcome rather than leaving it completely to chance and as such, we confer greater subjective value on our self-chosen seats. We reason that this subjective value accompanying the self-selected seat is subserved by the construct of perceived control. Perceived control is operationally defined as the ability, real or subjective, to manipulate and influence our environment to our advantage via the exercise of our behavior (Skinner 1996). Our sense of control over a particular context is dependent on whether we believe that the behaviors we exerted could act in our favor, whether it is trying to obtain a potential reward or to avoid an impending punishment.

Generalizing from the aforementioned airline example, we argue that if all else were equal, most people would gravitate towards exercising control (self-option) rather than ceding control to an external source (e.g., a computer program picks on your behalf). This argument is derived from decades of research in psychology from Julian Rotter's locus of control framework (Rotter

1966) to Albert Bandura's concept of self-efficacy (Bandura 1977) to Icek Ajzen's theory of planned behavior (Ajzen 1991). Collectively, these theories suggest that from an evolutionary perspective, control represents a need, and the ability to perceive and exercise control is necessary for our wellbeing (for review see Leotti et al 2010). Many studies subsequently expanded upon this idea to examine the influence of perceived control on our psychological health and behavior.

1.1 The rewarding nature of perceived control

The early efforts to empirically study perceived control revealed an important characteristic of perceived control: its desirability and the accompanying positive affect. Put differently, perceiving and exercising control can feel like a reward in and of itself (for review see Ly et al 2019). Indeed, by constraining the experimental definition of control to the ability to make choices, many studies have found that animals (Catania & Sagvolden 1980, Suzuki 1999) and humans (Bown et al 2003, Suzuki 1997) alike demonstrated a clear preference towards having choices over not having choices. More strikingly, the act of choosing itself, as a proxy for control, could increase the likability of an otherwise neutral cue (Lieberman et al 2001).

If there truly exists a behavioral preference for control, then control should generate approach behavior to bias our choices towards the control-conferring option, perhaps even at the expense of potentially incurring a cost (i.e., such as accepting a smaller reward in favor of exercising control). This can perhaps help to explain why airlines can profit from charging passengers to choose their seats—people are willing to incur a cost to choose (and have control). Therefore,

it may be argued that perceived control has underlying motivational and affective properties to drive organisms to seek out options and situations that allow them to perceive control.

1.1.1 The motivational property of perceived control is driven by dopamine transmission

If perceived control is indeed rewarding, it ought to carry incentive salience, described as a form of Pavlovian motivation that is captured by a state of 'wanting' (Berridge 2012, Berridge et al 2009). This state of 'wanting' often induces greater decision utility (i.e., motivating value of an outcome) compared to the predicted utility (i.e., expected value of that outcome; Berridge & Aldridge 2008). In simpler terms, one could still 'want' what one is expected to not to like. Going back to the airline example again, passengers want to choose their seats at the expense of paying the airline to do so (i.e., something they do not typically like). This motivation, which has been attributed to an increase in dopamine (DA) secretion and neurotransmission within the mesolimbic DA pathway (Berridge 2007), is tied to an organism's inherent tendency to explore and exert influence on one's environment in an effort to produce desired outcomes (White 1959). This behavioral tendency plays an important role to help fulfill the basic organismal drive to be competent.

If control carries motivational values that are attributed to incentive salience, then it is predicted that the detection of control in an external stimulus should reliably trigger DA release into the nucleus accumbens (NAcc), a substrate for ventral tegmental DA transmission in the mesolimbic DA pathway (Cabib & Puglisi-Allegra 1994). This was indeed the case when rodents

subjected to controllable shocks showed elevated DA levels in the NAcc, reliably triggering behaviors seeking control at the expense of energy expenditure and increased risks (Cabib & Puglisi-Allegra 2012). In addition, the release of DA, a neurotransmitter well-established in encoding reward prediction error (Ikemoto et al 2015), during the detection of control also hints at the reinforcing effects associated with exercising control. Indeed, the presence of free choice as a proxy for control was shown to amplify the positive reward prediction error in a reward-learning paradigm and provided a plausible explanation for the bias that human participants displayed for perceived control (Cockburn et al 2014). In short, the presence of control has motivational values that can elicit mesolimbic DA release into the NAcc to reinforce participants' preference for control.

1.1.2 The affective property of perceived control is subserved by the striatum

The motivational property of perceived control is intimately tied to its positive affective valence, which can be described as a 'liking' sensation (Berridge & Robinson 2003, Berridge et al 2009) that can elicit approach behavior (Schooler & Mauss 2010). This was suggested in previous studies that when people feel in control over their environment, they not only report increased sense of competence but also heightened feelings of happiness and pleasure (for review see Leotti et al 2010, Solomon & Rodin 1976). To probe the affective property of perceived control, many neuroimaging studies took advantage of the ability to choose as a proxy for perceiving control and presented human participants with cues that were either associated with choice or no-choice. Examinations of participants' neural responses to these cues revealed that they showed greater

ventral striatal activation in response to the choice cues compared to no-choice cues (Leotti & Delgado 2011, Leotti & Delgado 2014). In addition, participants also showed striatal activation in response to the increasing opportunity to choose (Fujiwara et al 2013). These findings are consistent with the notion that perceived control has an underlying motivational property and carries affective value. Nevertheless, it remains an open question as to whether the preference for control can be systematically measured in order to isolate the subjective value associated with perceived control and study its neural underpinnings.

1.2 The protective nature of perceived control

Another key characteristic of perceived control that emerged from the early studies is its protective effects against an aversive environment. This attribute of perceived control finds its root in the theory of learned helplessness (for review see Maier & Seligman 2016), which proposed that the lack of controllability over an aversive stimulus induces behavioral passivity, anxiety and learning deficits in rodents (Maier & Seligman 1976, Maier et al 1969, Seligman 1971, Seligman 1975). In contrast, the presence of controllability in an aversive stimulus was found to be protective against these negative effects and this protective effect has subsequently been established in many other species including cats (Seward & Humphrey 1967) and humans (Fosco & Geer 1971, Gatchel & Proctor 1976, Glass & Singer 1972, Hiroto 1974, Rodin & Langer 1977, Thornton & Jacobs 1971). In many of these human studies, researchers were able to convincingly show that when participants were given the ability to avoid or escape from an aversive stimulus (Hiroto 1974) or were granted control in the form of choices (Rodin & Langer 1977), they reported more positive emotions and enhanced self-

competence (Deci & Ryan 1987, Rodin 1986), resulting in improved overall sense of wellbeing. Interestingly, prior work also noted that stressor controllability was associated with blunted conditioned fear expression and improved fear recovery (Hartley et al 2014). This work is consistent with other findings showing that the presence of controllability rendered painful stimuli as less subjectively intense and more tolerable (Bräscher et al 2016, Müller 2012, Salomons et al 2004).

The view that perceived control has protective effects is further bolstered by clinical observations noting that impairments in our sense of control is commonly reported in many psychopathologies. For example, addiction often entails that patients lose psychological and behavioral control over drug-associated cues and outcomes, leading to their persistent drug intake and relapses (Bechara 2005). In addition, in major depressive disorder, one of the chief complaints in patients is the global lack of control in their lives (Glass & McKnight 1996). Furthermore, patients with anxiety-based disorders such as PTSD are more susceptible to episodic attacks when uncontrollable stressors are present (Frazier et al 2004). The unifying theme of losing or lack of control across these disparate disorders is striking, particularly considering the myriad of underlying neural mechanisms proposed for each disorder. As such, appreciating how and why perceived control can exert influences over our behaviors will greatly facilitate our understanding of these psychopathologies.

1.2.1 The neural mechanism of perceived control involves the vmPFC

It is well documented that perceiving and exercising control have protective effects against anxiety and behavioral passivity (Maier et al 2006). Building upon

an extensive literature examining the behavioral and emotional consequences of perceived control (for review see Skinner 1996), many early animal studies have attempted to shed light on the proposed neural circuitry mediating control. In particular, a line of rodent studies conducted to study the learned helplessness effect has delineated a neural mechanism for how the ventromedial prefrontal cortex (vmPFC in human literature or mPFCv in rodent literature) acts as the neural substrate for detecting control and mediates the physiological and physical responses towards external stressors (Maier & Seligman 2016, Maier & Watkins 2010).

Before we can try to understand the role of vmPFC in response to detecting control, we need to first appreciate the neural changes that occur in response to aversive stimuli and how these changes can drive behavioral outputs. When an animal is shocked (without the ability to escape), serotonergic neurons (5-HT) from the dorsal raphe nucleus (DRN) are consequently activated (Grahn et al 1999). This activation results in the extracellular accumulation of 5-HT within the DRN (Maswood et al 1998), which leads to the desensitization of inhibitory somatodendritic 5-HT_{1A} receptors within the DRN that lasts for days (Amat et al 1998, Greenwood et al 2003). Together, the accumulation of extracellular 5-HT and the ensuing upregulation of DRN 5-HT receptors induce exaggerated behavioral effects, such as increased anxiety and passivity, in response to external stressors. The causality between these neural changes and behavioral effects is evident because lesioning the DRN (Maier et al 1993) or applying selective pharmacological inhibition of 5-HT DRN neurons at time of

behavioral testing (Maier et al 1995) is sufficient to reverse the behavioral effects such as freezing induced by anxiety and passivity.

While the DRN is important in driving the exaggerated behavioral responses to aversive stimuli, this subcortical structure is unlikely to serve as the region to integrate sensory inputs (i.e., the DRN does not receive direct somatosensory inputs; Peyron et al 1997) or compute (i.e., the DRN is a brain stem structure that is not typically associated with higher-level cognitive functions; Abrams et al 2004) the degree of control associated with external stressors. Therefore, it is argued that the detection and computation of control is likely a cortical function and the DRN is a downstream target that receives instructions from the cortex. The cortical area that could subserve this function is likely the infralimbic (IL) and prelimbic (PL) regions of the vmPFC (Maier & Watkins 2010, Quirk & Beer 2006, Sierra-Mercado et al 2011), which provide the principal cortical inputs into the DRN via glutamatergic innervations onto γ-aminobutyric acid (GABA)-ergic interneurons of the DRN, thereby inhibiting DRN activity (Celada et al 2001, Hajós et al 1998, Jankowski & Sesack 2004). In terms of cross-species translation, the rodent vmPFC subregions of IL and PL regions map onto Brodmann's area 25 and 32 respectively (Gabbott et al 2005) and it is generally accepted that areas 25 and 32, along with areas 14 and 24, constitute the human vmPFC (Mackey & Petrides 2014, Öngür & Price 2000, Quirk & Beer 2006).

Taken together, the detection of control is hypothesized to be encoded by a neural network where the vmPFC integrates sensory information and projects

to downstream regions such as the DRN as well as the dorsolateral prefrontal cortex and striatum (Öngür & Price 2000) to drive control-seeking behaviors. This hypothesis is supported by a series of elegant experiments conducted in rodents showing that the vmPFC is activated to blunt downstream stress responses (i.e., heightened DRN activation and behavioral passivity) in response to the presence of control. In these studies, the researchers were able to convincingly show that the inactivation of the vmPFC via muscimol (GABA agonist) microinjection eliminated the protective effects of controllability in escapable shocks, rendering its behavioral outputs undifferentiable from inescapable shocks (Amat et al 2005). In contrast, activating the vmPFC via picrotoxin (GABA antagonist) microinjections induced the protective effects for inescapable shocks by inactivating DRN and diminishing behavioral effects such as anxiety and passivity, a dramatic reversal of learned helplessness (Maier et al 2006).

Although much of the focus has been placed on the vmPFC-DRN interaction during the detection of control, it is worth mentioning that the vmPFC also projects to other aversive-responsive structures. One such region of special interest is the amygdala, whose role in fear conditioning and anxiety is well-documented (for review see Duvarci & Pare 2014, Sotres-Bayon et al 2004). What is most relevant to the context of perceived control is the finding that vmPFC projections to the amygdala can inhibit amgydala responses to an already conditioned fear stimulus and its associated fear responses (Milad et al 2004, Quirk et al 2003, Rosenkranz et al 2003). This observation was further substantiated by results showing that when participants were engaged in the

emotional regulation of conditioned fear (i.e., a form of perceiving and exerting control over the conditioned fear responses), the vmPFC and the amygdala demonstrated an inverse relationship where greater vmPFC activity was coupled with lower amygdala activity (Delgado et al 2008). Therefore, we can infer that activation of the vmPFC can potentially inhibit the amygdala to reduce fear responses. But something needs to trigger the activation of vmPFC so that amygdala can be inhibited to dampen conditioned fear, and it is proposed that detection of control could assume such a role. It has indeed been shown that the controllability of an external stressor can retard fear conditioning and the development of freezing behavior in rodents (Maier et al 2006). Although more work is needed to clarify the vmPFC-amygdala relationship during experiences of control, the finding that perceiving and exerting control over aversive stimuli is associated with increased vmPFC activity and decreased amygdala activity supports the potential role of vmPFC-amygdala interactions in the neural mechanism subserving perceived control.

Putting it all together, the working neural model of perceived control involves the activation of vmPFC in response to controllable stressors, which subsequently triggers glutamatergic projections onto DRN GABAergic interneurons to inhibit stress-induced release of 5-HT. This model has been corroborated in human studies showing that post-traumatic stress disorder (PTSD) patients, who report uncontrollable emotional responses to external triggers, showed a dampening of vmPFC activity compared to healthy participants when exposed to emotional stimuli (Etkin & Wager 2007, Rauch et al

2006). However, we do not preclude the possibility that the vmPFC-DRN connection is not a direct one, but rather could be relayed by the amygdala. It has been shown for example, that the vmPFC projects to the central nucleus of the amygdala (McDonald et al 1996) and that the amygdala in turn projects to the DRN (Peyron et al 1997). Despite it being unlikely that the amygdala relay hub is a necessary component to the neural circuit underlying the detection of control, as previous studies reported that lesions in the amygdala had no effect on the failure to escape in response to uncontrollable stressor (Maier et al 1993), we cannot discount the amygdala as a player in the circuitry encoding control (Amat et al 2005). However, in view of the proposed neural circuit, we want to emphasize the critical role of the vmPFC in subserving perceived control.

1.3 Perceived control is not always desired

Whereas the act of choosing and the perceived ability to exercise control can be desirable and rewarding, there are certainly exceptions. For instance, it has been previously observed that both animals (Catania 1980, Hayes et al 1981) and humans (Chernev 2003, Iyengar & Lepper 2000, Sethi-Iyengar et al 2004) do not always prefer more over fewer choices. This phenomenon has garnered its own names called “ the paradox of choice” (Schwartz 2004, Vohs et al 2014) and “choice overload” (Chernev et al 2015, Scheibehenne et al 2010) where too many choices can be actually counterproductive on effective decision making. From this, we can infer that while choices can be effectively used as a proxy for control, the relationship between choice and control is not always a linear one where more choices equate to more control. This seemingly paradoxical relationship between the desire to exercise control and the negative effects of too

many choices can be partially reconciled by the notion that exercising control is cognitively effortful (Reed et al 2011), so there is a natural tendency for people to rely on default rules that forgo the act of choosing rather than participate in active choosing (Sunstein 2017). Even more so, with a greater choice set comes greater responsibility, where accountability for the decision increases with more choices (Chernev 2006, Ratner & Kahn 2002, Scheibehenne et al 2009).

In such cases when choosing becomes a burden, people are more willing to relinquish the ability to exercise control. It is thus evident that the desire for control and its positive subjective value have a ceiling where if exceeded, people are inclined to abandon the ability to perceive and exercise control. But it is important to note that even if people do defer decision making, they are still perceiving a certain degree of controllability by choosing not to choose. Hence, the rewarding value of the opportunity to exert control (by choosing a self or default option) is not completely lost in such contexts but is merely voluntarily diminished and these contexts certainly do not recapitulate situations where controllability is involuntarily removed by completely divorcing the contingency between action and outcome. In the latter situations, the absence of controllability is in conflict with the organism's subjective valuation of control and behavioral tendencies and this incongruency has been shown to negatively impact an organism's affective state and motivation, leading to the aforementioned phenomenon of learned helplessness. Taken together, these findings hint at a subjective value of control carrying affective and motivational properties that is highly malleable and context-dependent.

1.4 A case for the subjective value of control

While the vmPFC-DRN model sufficiently explains the behavioral differences between organisms subjected to either inescapable or escapable shocks, it fails to account for the individual differences that exist when two organisms show different levels of responses to the same uncontrollable stressor (e.g., why two soldiers who both experience the same war environment do not both develop post-traumatic stress disorder). In other words, it is likely that two organisms experiencing the same stimulus may not subjectively value control to the same degree and thus their vmPFC may be differentially recruited, resulting in differences in downstream behavioral and physiological outcomes. In addition, this vmPFC-DRN model also pares control down to an on/off switch whereas in most situations, control can be construed and valued differently depending on both the organism and the context. Therefore, we reason that there exists a subjective value for control, which can contribute to decision making and influence behavioral responses. This idea is gaining traction as recent efforts have started to use behavioral paradigms to probe people's willingness-to-pay for perceived control in economic decisions, which allows investigators to indirectly measure the weight or price tag of control in decision making. These studies have yielded "a control premium", which was described as the price that participants were prepared to pay in order to perceive and exert control (Bobadilla-Suarez et al 2017, Owens et al 2014).

If there is a way to isolate and quantify the subjective value of control in decisions, then the follow-up question would be to ask what brain regions compute and encode such values. As detailed above, the vmPFC is postulated to

detect control and serve as a top-down regulator on the stress responses generated by serotoninergic release from the DRN. Given its processing capability and widespread connections with other brain areas, the vmPFC perhaps could serve as the integrator of incoming sensory inputs to compute a "subjective value of control", consistent with its proposed role as the common currency arbitrator (Levy & Glimcher 2012). On the other hand, considering the motivational and affective properties of control, we propose that in addition to the vmPFC inhibition of DRN/5-HT, there is also an activation of the ventral striatum and mesolimbic dopamine pathway when control is detected. As such, vmPFC may be one of several, albeit very crucial, regions in the neural mechanism responsible for evaluating controllability in context. In other words, when control is present, there may be two concurrent neural systems that can detect control, the vmPFC-centric suppression of stress responses and the NAcc-centric stimulation of positive affect. It is likely that these two systems are not independent of each other in encoding control because there exist many communication pathways between the vmPFC and the striatum such as direct corticostriatal efferents and indirect ventral striatal projections to the cortex via ventral pallidum and the thalamus (Haber 2016). In fact, recent evidence does seem to suggest this crosstalk between the PL region of vmPFC and the striatum in rodents during the detection of control (Amat et al 2014). More importantly, these two systems have both been implicated in encoding subjective value of external stimuli (Chib et al 2009, McClure et al 2004, Ruff & Fehr 2014). Thus, it is proposed that the vmPFC and striatum could together comprise a neural

system to compute the “value of control” when control is detected in the external environment (Figure 1.1). However, the role of these neural regions in encoding the subjective value of perceived control remains to be studied.

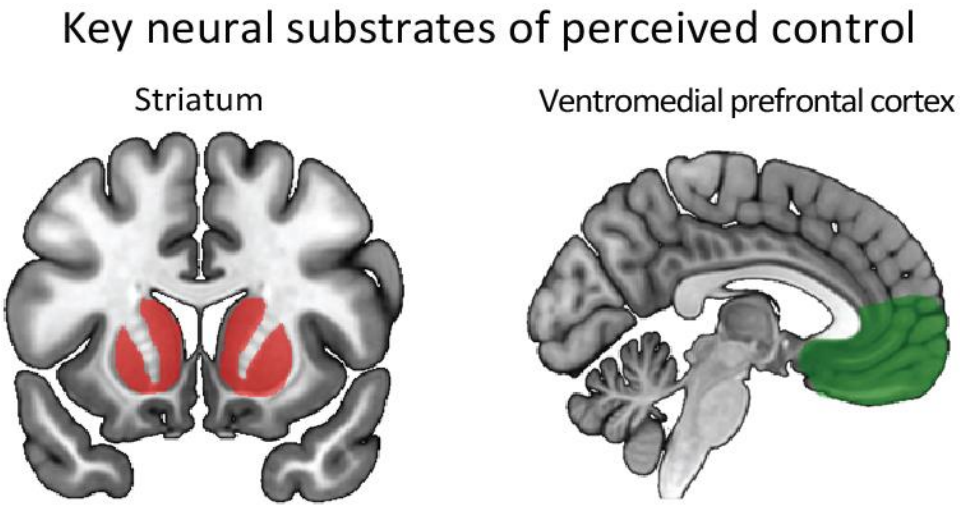


Figure 1.1. ***Key neural substrates of perceived control.*** Previous work has implicated the striatum and ventromedial prefrontal cortex (vmPFC) as important regions subserving the neural circuity of perceived control. This dissertation aims to investigate how these regions are involved in encoding the subjective value of control and protective effects conferred by control.

1.5 Remaining questions

Based on our assay of literature on perceived control, there remains several key questions to be tackled. First, can we isolate and study the subjective value of perceived control is decision making? And if so, how does the brain encode this subjective value? Second, given the protective effects of control in an aversive environment, can these protective effects be powerful enough to overcome prolonged exposure to uncontrollability in an aversive domain? Third, can

something as behaviorally-detrimental as acute stress (Smyth et al 2018) impact the subjective value and behavioral consequences of perceived control?

Here, we delineate a series of experiments to try and answer these questions relating to the neural basis and behavioral consequences of perceived control. In Aim 1, building on previous research showing that participants have an inherent behavioral bias towards seeking and exerting control, we sought to translate this bias into an experimental measure of the subjective value of control and investigate its neural underpinnings. Briefly, we devised a *Value of Control* (VoC) task where participants were asked to make a series of binary choices between an option conferring behavioral control and another that relinquishes control. By manipulating the reward expected value for each choice pair and examining participants' choice patterns, we were able to effectively capture participants' preference for control in a behaviorally-derived measure and study its neural underpinnings. We hypothesized that this subjective value of control is encoded in the vmPFC.

Next, in Aim 2, we were interested in examining the protective effects of perceived control. We expanded upon previous work demonstrating the protective effects of control against aversive stimuli to examine whether perceived control can be potent enough to not only prevent but reverse behavioral passivity in an aversive context. Instead of typical triadic design in learned helplessness paradigms, we created our Control in Aversive Domain (CAD) task to account for between-subject variability and individual differences in participants' behavioral responses to uncontrollable and controllable aversive

contexts. In the CAD task, participants were subjected to prolonged uncontrollability across different aversive contexts where they were predicted to develop behavioral passivity in the form of reduced avoidance behavior. We subsequently introduced control into a novel aversive context and tested our hypothesis that the detection of control was potent enough to rescue participants' avoidance behavior.

Finally, in aim 3, we set out to examine the effects of acute stress exposure on the subjective value and protective effects of perceived control. While it has been shown that uncontrollability can trigger a stress response in an organism (Bandura 1982, Bollini et al 2004, Hadad-Ophir et al 2017), it is unclear how a pre-existing stressed state can in turn influence the organism's valuation of control and its behavioral responses to controllability. This is an important consideration because acute stressors have been shown to have powerful negative effects on our decision-making strategies (Arnsten 2015, Maren & Holmes 2016, Porcelli & Delgado 2009) and can exacerbate negative affect (Bogdan & Pizzagalli 2006, Grillon et al 2007, Maier & Watkins 2005), leading to maladaptive behaviors such as those seen in drug relapse or depressive episodes (Hammen 2005, Pittenger & Duman 2008, Shaham et al 2003, Sinha 2001). In an attempt to answer these questions, we used the socially-evaluated cold-pressor manipulation to induce acute stress in participants in order to probe its behavioral effects in our VoC and CAD tasks. Together, the aims presented in this dissertation will serve to help deepen our understanding of the construct of

perceived control as well as strengthen our appreciation of its neural and behavioral underpinnings.

Chapter II: Aim 1. Corticostriatal circuits encode the subjective value of perceived control

2.1 Introduction

Our sense of control over an outcome hinges on our perceived ability to manipulate and influence the environment to our advantage. While the ability to exercise real objective control over an outcome can be behaviorally reinforcing, it is the perception or subjective belief in having control that serves a basic need and contributes to our general wellbeing in two important ways (White 1959). First, it has been demonstrated in both animals and humans alike that the perception of control has protective effects to blunt external stressors and can dampen depressive symptoms such as anxiety, passivity and helplessness (Abramson et al 1978, Maier & Seligman 1976, Thornton & Jacobs 1971). Second, fulfilling the sense of control can be rewarding in and of itself, suggesting that perceived control generates positive affect that can bias behaviors accordingly (Leotti & Delgado 2011, Leotti & Delgado 2014). Taken in conjunction with the pervasive manifestation of loss of control in psychopathologies (Bechara 2005, Frazier et al 2004, Glass & McKnight 1996), the significance of perceiving control as both desirable and valuable to an organism is notable.

From an evolutionary perspective, several prominent theories have proposed that organisms have an inherent need for control that biases them towards environments conferring the perception of control (Ajzen 1991, Bandura 1977, Rotter 1966). This is supported by the observation that organisms across

species show a clear preference to perform control-seeking behaviors (Bown et al 2003, Catania & Sagvolden 1980, Suzuki 1997, Suzuki 1999). One idea is that this preference for having the option to exert control is manifested as an affective signal that is processed in the brain's reward system (Ly et al 2019). Using choice as a proxy for control, for example, neuroimaging studies have reported that participants had greater ventral striatum activation in response to cues that were associated with an opportunity for choice compared to cues associated with no choice opportunity (Fujiwara et al 2013, Leotti & Delgado 2011, Leotti & Delgado 2014). The presence of controllability has also been linked to dopamine release in the nucleus accumbens (NAcc), providing a potential molecular-level account of perceived control and substantiating the observation of NAcc activation in neuroimaging experiments (Cabib & Puglisi-Allegra 2012, Cockburn et al 2014, Ikemoto et al 2015). Another complimentary idea is that the preference for control can help cope with external stressors, which is consistent with the theory of "learned helplessness" (for review see Maier & Seligman 2016). This line of work has implicated the ventromedial prefrontal cortex (vmPFC) as the neural substrate for detecting control and mediating the protective effects of control in response to external stressors (Amat et al 2005, Maier et al 2006, Maier & Watkins 2010).

Collectively, the aforementioned findings suggest that experimental conditions emphasizing a sense of perceived control over potential outcomes is not only desirable but also associated with regions involved in affective processing such as the striatum and the vmPFC (Bartra et al 2013, Delgado

2007, Haber & Knutson 2010). An intriguing question is whether perceived control itself carries a subjective value that changes how the potential reward is processed and in turn influences reward-seeking behaviors. Here, we test the possibility that the desirable quality of perceived control could artificially inflate the subjective value of the actual reward and trigger approach behavior, even to the extent of incurring a cost to have control—i.e., choosing a reward with an objectively smaller expected value.

In this paper, we implemented a two-alternative choice task to isolate the subjective value of control and study its neural correlates. Briefly, while undergoing functional magnetic resonance imaging (fMRI), human participants were instructed to make a series of binary choices between an option conferring behavioral control and another that relinquished control. By manipulating the reward magnitude for each choice pair and examining participants' choice patterns, we derived a subjective value for control and investigated its neural underpinnings. We hypothesized that participants would show behavioral bias towards exercising control and this preference would recruit regions such as the striatum and vmPFC.

2.2 Methods

2.2.1 Participants

31 right-handed individuals (11 Males and 20 Females) between the ages of 18 and 37 (Mean (M) = 23.3, standard deviation (SD) = 5.1) were recruited from the Rutgers University community for this study (see supplementary material for details on sample size determination). Participants were prescreened for any history of psychiatric and neurological illness. Participants were given monetary

compensation for their voluntary participation in the experiment. In addition, they could also earn up to $20 of bonus monetary reward based on task performance. All participants provided written informed consent in accordance with the experimental protocol approved by the Rutgers University Institutional Review Board. One participant did not complete the experiment due to equipment failure and was excluded from subsequent behavioral and neural analyses. Three additional participants completed the experiment but were excluded from subsequent analyses due to complications during scanning session (e.g., participants closed eyes in scanner or did not follow directions). Final data analysis was conducted on 27 participants (9 Males and 18 Females; M = 22.4, SD = 4.3).

2.2.2 Experimental design

The goal of the experiment was to quantify the behavioral and neural substrates of how much participants valued exercising control in a computer game for monetary reward. To probe this, we designed the *Value of Control* (VoC) task and evaluated participants' choice behavior when presented with a series of control/no-control choice pairs whose reward point magnitudes were manipulated.

Participants first underwent the training version of the VoC task in the lab, with the goal of familiarizing them with the experimental task. Second, they completed four paper questionnaires given in the same order: 1. Mini mood and anxiety symptom questionnaire (Clark & Watson 1995); 2. Behavioral inhibition system/ behavioral activation system (BIS/BAS) scale (Carver & White 1994); 3. Desirability of Control Scale (Burger & Cooper 1979); 4. Internal-External Locus

of Control (Rotter 2011). Third, participants performed the testing version of the VoC task in the fMRI scanner. All computerized tasks were coded and presented using MATLAB 2015a, The MathWorks, Inc., Natick, Massachusetts, United States and Psychtoolbox 3 (Brainard 1997). Next, we describe the VoC task in more detail, including the different experimental conditions, and highlight distinctions between the training and testing phases.

2.2.2.1 The Value of Control task

The *Value of Control* (VoC) task (Figure 2.1) was designed to measure an individual's subjective value attributed to exerting control. Each trial of the VoC Task was divided into two parts: *Choice* and *Game* phases. The key phase-of-interest was the *Choice* phase, which captured a decision between exerting control (SELF-option) or relinquishing control to a computer (COMP-option) in the subsequent *Game* phase. During the Game phase, a card game for monetary rewards was executed by either the participant or the computer. Participants played multiple trials where they either chose between SELF- or COMP-options (Experimental condition: Mixed) or options that only varied in terms of expected value (Experimental condition: Baseline). Each component of the VoC task is described next in more detail.

2.2.2.1.1 Choice phase

In the *Choice* phase, participants were presented with a binary choice between the SELF-option conferring behavioral control over a game and the COMP-option representing the ceding of gameplay to the computer. The two options were counterbalanced in terms of placement on the screen. For each option, we showed the participants the experimental points (0 to 20 points in increments of

2) that could be earned in the event of winning the game. Effectively, we manipulated the point magnitudes of each choice pair so that participants had to consider the reward value associated with seeking or deferring control. This two-alternative choice design permitted us to infer how participants subjectively valued control in terms of reward expected value.

The *Choice* phase lasted 4 seconds and was followed by a jittered 1 to 6-seconds fixation period (inter-stimulus interval [ISI]). A decision not captured within the 4-second *Choice* period was registered as a lapse for that trial and marked with a 6-second fixation period displaying the phrase “No Choice Detected!” to signal the end of that trial.

2.2.2.1.2 Game phase

The *Game* phase, which was adapted from Delgado et al (2000), consisted of a card-guessing game where participants were shown an unknown card hiding a number ranging from 1 to 9. The objective of the game was to guess whether the hidden number was higher or lower than the number 5 (which was omitted from the deck). Depending on how participants chose in the preceding *Choice* phase, they could either make the guess themselves (i.e., SELF-option chosen) or the computer would make the guess on their behalf (i.e., COMP-option chosen). Importantly, regardless of how the *Choice* phase was played, participants had to make a single button press during the *Game* phase, ensuring similar motor responses across trials.

Any correct guess made by either the participant or the computer would be rewarded with the associated points added to the participant’s point bank. Any incorrect guesses by the participant or the computer yielded no net gain or loss.

Experimental winning was resolved during debriefing when the participant's point bank was revealed and converted into monetary bonus. Each trial of the *Game* phase lasted for 2 seconds and was followed by a jittered 1 to 6-seconds inter-trial interval (ITI) showing a fixation cross to signal the end of each trial.

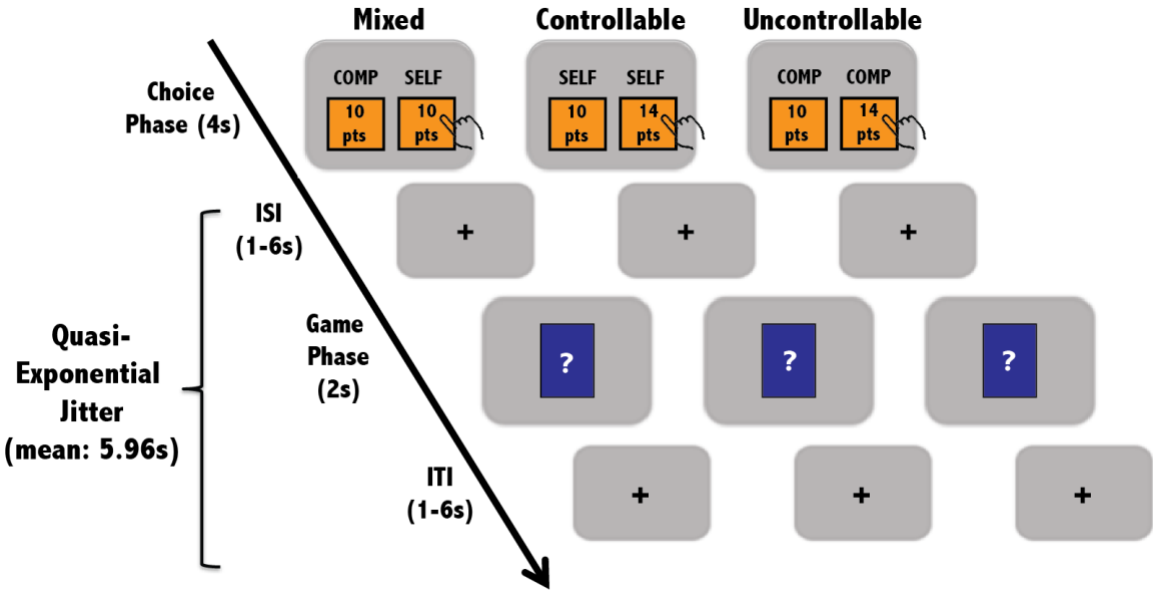


Figure 1.1 *Value of Control* (VoC) task. Each trial of the VoC task consisted of the *Choice* and *Game* phases. In the *Choice* phase, participants were presented with a pair of choices that differed based on the experimental condition. In the *Game* phase, depending on which option was previously chosen, either the participant (SELF-option) or the computer (COMP-option) would play the card-guessing game. Each trial ended after a quasi-exponential jitter period following the *Game* phase with no feedback provided for the game.

2.2.2.2 Training version of the task

Participants first performed the training version of the VoC task outside the fMRI scanner in order to learn the game. This session consisted of 20 forced-choice trials where participants were asked to direct their picks towards either the SELF-

or COMP-option (10 trials each). The placement of each option on the screen was counterbalanced across participants. The key distinction in this version of the task and the testing version was that during training, participants received feedback on the outcome of the card-guessing game after each trial. This allowed participants to experience outcomes resulting from both SELF- and COMP-options and to gage the rate of success in the game. Participants received feedback on the *Game* phase where they saw whether the preceding guess (made by the participant or the computer) was correct or incorrect. Importantly, success rates for SELF- and COMP-options were equivalent at 50% and point magnitude were matched at 10 points each. At the conclusion of this training phase, participants were probed about their understanding of the game, particularly the difference between the SELF- and COMP-choices. We did not explicitly ask participants about the contingencies for the options to avoid potential instructional bias.

2.2.2.3 Testing version of the task

After training, participants performed the testing version of the VoC task consisting of four runs of 22 trials lasting 220 seconds per run. Unlike the training version of the task, participants did not experience feedback on the card-guessing game following each *Game* phase. In other words, while doing the task in the scanner, participants were never informed of the outcome of any guesses made by either the participant or the computer. Instead, participants' performance and point totals were revealed to them during the debriefing session at the conclusion of the experiment. This was done to minimize the opportunity to learn and to prevent potential feedback bias on ensuing trials. In all trials

following gameplay by either the participant or the computer, an ITI ensued directly after the *Game* phase and the trial would start again with the *Choice* phase. Participants were also not shown whether the computer picked higher or lower in the *Game* phase on trials where the COMP-option was chosen.

There were two experimental conditions: *mixed* and baseline (i.e., *controllable* and *uncontrollable*; Figure 2.1). Specifically, runs 1 and 3 were *mixed* condition trials whereas runs 2 and 4 were a balanced combination of *controllable* and *uncontrollable* baseline trials. This run order was consistent across all participants. The two conditions differed only in the types of binary choices presented to the participant during the *Choice* phase.

2.2.2.3.1 Mixed condition

In *mixed* condition trials, the participant was presented with a choice between SELF- and COMP-options. The SELF-option was fixed at 10 points on all trials whereas the COMP-option had a balanced distribution of 0 to 20 points in intervals of 2 points (an additional behavioral experiment where the COMP-option was fixed at 10 points while the SELF-option varied between 0 and 20 points yields similar results and is included in the supplementary material). This manipulation resulted in the COMP-option having a larger reward magnitude than the SELF-option in half the trials and a smaller reward magnitude in the remaining half of the trials. If participants chose the SELF-option, they were instructed to play the card-guessing game and take a gamble between two buttons: one signaling that the card number would be higher than five and the other one signaling lower than five. In contrast, if participants chose the COMP-option, they were asked to defer gameplay to the computer and instead press a

designated button to move on to the next trial. It is important to note that gameplay occurs regardless of whether SELF- or COMP-option was chosen; but the only difference is who (i.e., participant or computer) had behavioral control over the gameplay.

2.2.2.3.2 Baseline condition: (*Controllable* and *uncontrollable* trial types)

The *controllable* and *uncontrollable* trial types collectively served as the baseline conditions for the experiment. In contrast to the *mixed* condition, the two baseline trial types each featured only one type of choice (either all SELF or all COMP). For example, during the *controllable* trials, the participant was shown a series of choice pairs featuring two SELF-options. On the other hand, the *uncontrollable* trials gave participants a series of choice pairs with two COMP-options. In effect, the *controllable* and *uncontrollable* trials each encompassed sets of choice pair that differed only in its associated point magnitude but not along the dimension of controllability. It is important to note that the point magnitudes for the choice pairs in the baseline condition were matched to those in the *mixed* condition.

The baseline condition (i.e., *controllable* and *uncontrollable* trial types) served two purposes. First, these trials provided us with a behavioral measure of whether the participant understood the task and was paying attention to the information presented during the *Choice* phase (i.e., option type and point magnitude). Since each pair of options only differed in its point magnitude, the participant should pick the option with the higher point magnitude. Second, these trials served as a reference to which we could compare the choice pattern in the *mixed* condition. In the baseline condition, the participant made choices along the dimension of expected value; in contrast, in the *mixed* condition, the participant

chose along both the dimensions of expected value and controllability. By comparing the choice patterns across the conditions, we can infer any difference driven by the influence of controllability in the decisions.

2.2.3 Neuroimaging data acquisition

Images were collected using a 3T Siemens MAGNETOM Trio scanner with the 12-channel head at the Rutgers University Brain Imaging Center (RUBIC). High-resolution structural images encompassing the whole brain were acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR): 1900 ms; echo time (TE): 2.52 ms; matrix 256 x 256; field of view (FOV): 256 mm; voxel size 1.0 x 1.0 x 1.0 mm; 176 slices; flip angle: 9°). The blood-oxygenation-level-dependent (BOLD) functional images were obtained using a single-shot T_2*-weighted echo-planar imaging (EPI) sequence (TR: 2000 ms; TE: 25 ms; matrix 64 x 64; FOV: 192 mm; voxel size 3.0 x 3.0 x 3.0 mm; 35 slices (0% gap); flip angle: 90°). In addition, B_0 field maps (TR: 400 ms; TE_1: 5.19 ms; TE_2: 7.65 ms; matrix 64 x 64; FOV: 192 mm; voxel size 3.0 x 3.0 x 3.0 mm; 35 slices (0% gap); flip angle: 60°) were collected prior to the functional images to correct for geometric distortion in the functional images.

2.2.4 FMRI preprocessing

The neuroimaging data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12; Ashburner 2012). First, we defined the origin of each image to align with the anterior and posterior commissure plane (Ardekani & Bachman 2009). After we motion-corrected each time series to its first volume, we then performed spatial unwarping to minimize geometric distortions due to susceptibility artifacts (Andersson et al 2001, Hutton

et al 2002). Next, we coregistered the mean functional image to the anatomical scan and normalized the anatomical using the unified segmentation model (Ashburner & Friston 2005). The normalized anatomical was subsequently used to reslice the functional data to standard stereotaxic space defined by the Montreal Neurological Institute (MNI). We applied a spatial smoothing at full-width half-maximum of 6mm to the normalized functional data.

To minimize the impact of head motion on the neuroimaging data, we applied additional preprocessing steps using tools from FSL (FMRIB Software Library version 5.0.4; http://www.fmrib.ox.ac.uk/fsl; Smith et al 2004). We detected motion spikes using the FSL tools *fsl_motion_outliers*. The motion spikes were evaluated with two metrics: 1) root-mean-square (RMS) intensity difference of each volume relative to the reference volume obtained from the first time point; and 2) frame-wise displacements calculated as the mean RMS change in rotation/translation parameters relative to the same reference volume. We subjected the metric values within a run to a boxplot threshold (75^{th} percentile plus 1.5 times the interquartile range) and labeled volumes as spikes, which were subsequently removed via regression (Power et al 2015, Satterthwaite et al 2013). Across all participants, this method removed 5.8% of volumes (range: 1.0 to 11.4%). After the removal of motion spikes, no participants exhibited extreme average volume-to-volume head motion (M = 0.06mm; range: 0.03 to 0.14mm) or maximum volume-to-volume head motion (M = 0.12mm; range: 0.05 to 0.31mm). Following the removal of motion spikes, we extracted brain material from the functional images (Smith 2002) and normalized

the entire 4D dataset using a single scaling factor (grand-mean intensity scaling). We also passed the images through the SUSAN (Smallest Univalue Segment Assimilating Nucleus) noise reduction filter, part of the FSL software package, using a 2mm kernel (Smith & Brady 1997). This step allowed us to achieve greater signal-to-noise ratio while preserving the image structure. Lastly, we applied a high-pass temporal filter with a 100-second cutoff (Gaussian-weighted least-squares straight line fitting, with sigma = 50s) to remove low frequency drift in the MR signal. Applying the temporal filter after the removal of motion spikes helps to minimize ringing artifacts (Carp 2013, Satterthwaite et al 2013, Weissenbacher et al 2009).

2.2.5 Data analysis

2.2.5.1 Behavioral analyses of choices in the VoC task

We were interested in participants' choice behavior during the *Choice* phase when they were asked to pick between each choice pair. We first looked at whether participants showed any bias towards one of the two choices in each condition (i.e., *mixed* and *baseline*). For both conditions, we manipulated the reward magnitude of the choice pairs where across all trials, the two options had evenly-matched expected value, resulting in a hypothesized choice proportion of 0.5 for each option (i.e., they would pick each option 50% of the time). Therefore, within each condition, we compared participants' choice proportions for the two options using a one-sample *t*-test against the hypothesized mean of 0.5 to investigate whether they showed a significant bias towards one of the two options. We used a paired *t*-test to test whether participants' choice behavior differed in the two baseline trial types (i.e., *controllable* and *uncontrollable*).

Next, we used the participants' trial-by-trial data in each condition to fit their choice behavior onto a logistic regression. By doing so, we would be able to derive at which choice pairing in *mixed* condition was the participant equally likely to choose either SELF- or COMP-option. The derivation of this point of equivalence (POE) provides an experimental measure of the subjective value that participants attributed to exerting control. Further details on the derivation of this POE is described in the following section. Upon deriving this POE value, we used *t*-tests to compare the POE for the *mixed* and baseline conditions to the hypothesized mean of 0 and a paired *t*-test to compare POE in the *mixed* and baseline conditions.

Finally, we examined participants' RT during the *Choice* phase by running a 3 x 2 ANOVA looking at the interaction between the effect of trial type (*mixed*, *controllable*, *uncontrollable*) and run sequence (first vs second run). The RT analysis allowed us to rule out differences in decisional uncertainty as a potential explanation for any choice pattern variations.

2.2.5.1.1 Derivation of the subjective value of control

To compare the two options, we first computed the expected value for both options as

$$EV_{SELF} = p_{SELF} \times V_{SELF}$$

$$EV_{COMP} = p_{COMP} \times V_{COMP}$$

where p is the objective success probability and *V* is the point magnitude rewarded. Probability (p) was deterministically set at .5 for both options based on the training phase feedback. The *V* for the COMP-option ranged from 0 to 20 points in increments of 2 while the *V* for the SELF-option was fixed at 10 points.

To probe participants' choices, we fitted their trial-by-trial data onto a logistic regression. Each choice pair presented during the *Choice* phase was coded by the expected value difference between the two options and this difference (i.e., EV_{COMP} minus EV_{SELF}) served as the independent variable in our analysis. Using this EV difference and employing maximum likelihood estimation, we fitted the trial-by-trial choice data of each participant to a single logistic function of the form (Berkson 1944, Davidson & MacKinnon 2004, Press & Wilson 1978, Reed & Berkson 1929).

$$p_{SELF} = \frac{1}{1 + e^{\gamma(EV_{COMP} - EV_{SELF})}}$$

where p_{SELF} is the probability that the participant chose the SELF-option, EV_{COMP} and EV_{SELF} were the EV of the COMP- and SELF- options, respectively, and γ is the slope of the logistic function (which was negative in this case), or equivalently the noise parameter.

Once data has been logistically regressed, we were interested in identifying the EV pairing where participants showed a behavioral indifference between SELF- and COMP-options. This point of indifference, or point of equivalence (POE), would shed light on participants' subjective valuation of the two options. To derive this POE for each individual participant, we analyzed each participant's regressed behavioral data while setting the participant's p_{SELF} to 0.5 using the inverse of the logistic function

$$\frac{p_{SELF}}{1 - p_{SELF}} = e^{\beta_0 + \beta_1 x}$$

where p_{SELF} is the probability of a SELF-choice, β_0 is the coefficient of the constant term, and β_1 is the coefficient of the predictor or independent variable.

The term *x* represents POE- the difference in value between the two options (EV_{COMP}-EV_{SELF}) for each participant where the participant was equally likely (i.e., p_{SELF} = 0.5) to choose either option.

$$POE = \frac{\ln(1) - \beta_0}{\beta_1}$$

It is important to note that at the POE, EV_{SELF} and EV_{COMP} are not necessarily equivalent in terms of their *EV* but they are equated based on participants' choices. Therefore, this translated into a subjective value for the SELF-option (SV_{SELF})

$$SV_{SELF} = EV_{SELF} + POE$$

that took into account both the EV_{SELF}, which was the objective expected value of the SELF-option, and the POE, which was the intrinsic value for control.

2.2.5.2 Neuroimaging analyses of value of control

Neuroimaging analyses were carried out with FSL FEAT (FMRI Expert Analysis Tool) Version 6.0 (Smith et al 2004). All of the general linear models (GLM) described below included a regressor of no-interest for the *Game* phase with the duration set to two seconds and an intensity of one. In addition, all models also included a nuisance regressor for any lapse trial with the duration set to ten seconds and an intensity of one. Note that all linear regressors will have an intensity set to one. All task regressors-of-interest in the GLMs were convolved with the canonical hemodynamic response function and incorporated temporal derivatives and temporal filtering.

For each participant, the data were combined across two runs in the second-level analysis utilizing a fixed-effects model. At the group-level analysis,

we performed a mixed-effects one-sample *t*-tests using FEAT's FLAME 1 + 2, which first fits the model using Bayesian modelling for mixed-effects variance estimation before processing all voxels that were close to threshold using the Metropolis-Hastings Markov Chain Monte Carlo sampling to obtain a more precise estimation of the mixed-effect variance (Woolrich et al 2004). Unless stated otherwise, for all z-statistics images discussed, we thresholded and corrected for multiple comparisons across the whole brain using a false-discovery rate-corrected voxel-extent threshold of $p < 0.05$ (Lieberman & Cunningham 2009, Worsley 2001). We used MRIcroN and MRIcroGL to create the statistical overlay images (https://www.mccauslandcenter.sc.edu/crnl/tools; Rorden et al 2007). We had specific hypotheses for each planned contrast that are described in more details in the following sections. All other findings were exploratory and are reported in the supplementary material under "Activation tables for all contrasts" (see supplementary material).

2.2.5.2.1 Controllable and uncontrollable baseline trial types

In the *controllable* (two SELF-options) and *uncontrollable* (two COMP-options) trials, participants were asked to choose between two options that differed only in their reward magnitudes but not along the dimension of controllability. Therefore, we conducted a conjunction analysis on the *controllable* and *uncontrollable* trials to analyze regions associated with reward magnitude recruited by both trial types while controlling for the interaction effect between the trial types (Price & Friston 1997). We hypothesized that this analysis would yield canonical value regions such as the orbitofrontal cortex (OFC; Padoa-Schioppa & Assad 2006, Rangel et al 2008, Saez et al 2017, Schoenbaum et al 2011), vmPFC (Grabenhorst & Rolls

2011, Knutson et al 2005, Wang et al 2016), striatum (Barkley-Levenson & Galván 2014, Hare et al 2008, Jocham et al 2011, Strait et al 2015) and anterior cingulate cortex (ACC; Hyman et al 2017, Kennerley et al 2011, Kolling et al 2016, Rushworth et al 2012, Shenhav et al 2016b). In particular, prior studies that have implicated these regions (i.e., OFC, vmPFC, striatum and ACC) in encoding the magnitude associated with potential reward have done so using both human fMRI work (Diekhof et al 2012, Knutson et al 2005) and animal electrophysiological recordings (Hamid et al 2015, Padoa-Schioppa & Assad 2006).

To carry out the conjunction analysis, we performed a parametric general linear model (GLM) and created participant-specific design matrices containing the following task regressors: (1) a parametric regressor encoding *controllable* (SELF) choices with the duration corresponding to the duration of the *Choice* phase and the parametric modulation set to the higher EV of each choice pair; (2) a parametric regressor encoding *uncontrollable* (COMP) choices with the duration corresponding to the duration of the *Choice* phase and the parametric modulation set to the higher EV of each choice pair. This model also included a regressor of no-interest for the *Game* phase with the duration set to two seconds and an intensity of one, and a nuisance regressor for any lapse trial with the duration set to ten seconds and an intensity of one. To obtain conjunction activation, we masked regressor (1) with regressor (2).

In addition to the conjunction analysis, we did a second analysis by contrasting the *controllable* and the *uncontrollable* trials to probe neural systems

involved in encoding the opportunity for control during gameplay. Based on previous studies from our lab showing that cues associated with control (i.e., having choices) in contrast to cues associated with no control (i.e., no choices) recruited reward-processing regions such as the striatum (Leotti & Delgado 2011, Leotti & Delgado 2014), we hypothesized that the contrast of *controllable* - *uncontrollable* trials would reveal activation in the striatum and that this predicted activation would be related to participants' inherent preference for control as measured by their Locus of Control score. In addition, our hypothesis on striatal activation was also drawn from previous experiments showing that the presence of controllability in the external environment was associated with dopamine release into the NAcc (Cabib & Puglisi-Allegra 2012, Cockburn et al 2014, Ikemoto et al 2015).

For the second analysis, we built a GLM by creating participant-specific design matrices containing a linear regressor encoding *controllable* (all SELF) choices with the duration corresponding to the duration of the *Choice* phase and the intensity set to one as well as a linear regressor encoding *uncontrollable* (all COMP) choices with the duration corresponding to the duration of the *Choice* phase and the intensity set to one. This model also included a regressor of no-interest for the *Game* phase with the duration set to two seconds and an intensity of one, and a nuisance regressor for any lapse trial with the duration set to ten seconds and an intensity of one. Our group-level contrasts included *controllable* minus *uncontrollable* choices and vice versa.

2.2.5.2.2 Mixed condition

We reasoned that in the *mixed* trials, participants were choosing between each choice pair by assigning a subjective value to the SELF-option. This subjective value had to encompass both expected value computation and the subjective valuation of control. We effectively isolated this subjective valuation of control in our POE measure (for additional details, see section on “Derivation of the subjective value of control”). By leveraging this POE measure, we could examine whether the subjective value of control was encoded by neural regions associated with the computation of affective value such as the vmPFC (Bartra et al 2013, Delgado et al 2016, Delgado 2007, Haber & Knutson 2010, Roy et al 2012). We had a particular hypothesis on the vmPFC as a potential region for encoding the POE measure for two reasons. First, prior studies collectively suggested that the vmPFC could serve as the region responsible for representing the subjective values associated with choices across different types of reward (Levy & Glimcher 2012). Second, the vmPFC has been suggested to be necessary for the behavioral bias that animals show towards detecting and exercising control (Amat et al 2005, Maier et al 2006, Maier & Watkins 2010).

We performed a GLM analysis with participant-specific design matrices containing the following regressors for the *mixed* condition: (1) a linear regressor encoding the SELF-choices with the duration corresponding to the duration of the *Choice* phase and an intensity of one; (2) a linear regressor encoding the COMP-choices with the duration corresponding to the duration of the *Choice* phase and an intensity of one. This model also included a regressor of no-interest for the *Game* phase with the duration set to two seconds and an intensity of one, and a

nuisance regressor for any lapse trial with the duration set to ten seconds and an intensity of one. At the group-level analysis, we added the participant-specific POE into the GLM as a covariate and performed a mixed-effects one-sample *t*-tests on the contrast between SELF-choices and COMP-choices (i.e., SELF-choices – COMP-choices).

2.3 Results

2.3.1 Behavioral results

The analysis focused on participants' behavior in the *Choice* phase of the VoC task because how they picked between the binary options would inform on how much perceived control contributed to decision making. Therefore, we probed participants choice pattern by first examining whether they showed any bias towards one of the two options. In the *mixed* condition, participants showed a preference for the SELF-option by choosing it 57.1% of the time (Figure 2.2a; $t(26) = 3.55$, $p = 0.0015$). In contrast, participants showed no bias towards either option in each choice pair in the *controllable* and *uncontrollable* trial types—i.e., they chose COMP1 51% of the time in *uncontrollable* trials ($t(26) = 0.73$, $p = 0.47$] and SELF1 51% in *controllable* trials (Figure 2.2b; $t(26) = 1.00$, $p = 0.32$). Because the point magnitude for each choice pair in all the mixed and baseline conditions were matched, the bias shown for the SELF-option in the *mixed* condition suggested that participants subjectively inflated the value of said option over its expected value.

For the baseline condition, participants picked the option carrying the higher EV 88% (SD: 4.6) of the time in the *controllable* trials and 87% (SD: 4.8) of the time in the *uncontrollable* trials, suggesting that they overwhelmingly

deferred to the choice with the higher EV in the baseline condition. Given that there was no statistical difference in participants' choice pattern between the *controllable* and *uncontrollable* trials ($t(10) = 0.19$, $p = 0.85$), we combined the two baseline trial types in subsequent analyses.

To examine how much controllability contributed to decision making during the *Choice* phase, we performed a logistic regression analysis on participants' trial-by-trial data to extract individual participant's POE. If controllability did not contribute to decision making, participants' POE should be 0 to indicate that participants were equally likely to choose either option when there was no expected value difference between the choice pair. In other words, the behavioral equivalence derived from participants' choice pattern was established from the reward expected value of the choice pairs. Based on participants' choice bias from the previous analysis, we predicted that the POEs for the combined baseline condition would be close to 0 whereas the POEs extracted from the *mixed* condition would be significantly different from 0. We tested this hypothesis using a one-sample *t*-test against the predicted mean of 0.

For the pooled baseline condition data (i.e., *controllable* and *uncontrollable*), the regression analysis revealed a mean participant POE of 0.16 (Figure 2.2c, solid line; SD = 1, Range = -2.27 to 2.98), and this was found to not be significantly different from the expected POE of 0 ($t(26) = 0.83$, $p = 0.41$), suggesting that participants chose based on EV. In contrast, for the *mixed* condition, the regression analysis yielded an average participant POE of 3.06 (Figure 2.2c, dashed line; SD = 6.8, Range = -2.02 to 33.44), with a beta value of

-0.41 and odds ratio of 0.67 ($z = -17.82$, $p < 0.001$). This mean POE in the *mixed* condition was significantly different from the expected POE of 0 ($t(26) = 2.33$, $p = 0.028$), suggesting that EV was not the only factor influencing the choices. Comparing the *mixed* and baseline conditions, we found that the POEs across participants were significantly different ($t(26) = 2.16$, $p = 0.04$).

Taken together, the extracted POEs for the *mixed* condition could be interpreted as the SELF-option carrying an average of 30% increase in value compared to the COMP-option, suggesting that participants placed a higher subjective value on the SELF-option. This 30% increase for the SELF-option was derived from the mean POE measure (POE = 3.06) where a 10-point SELF-option was found to be behaviorally-equivalent to a 13-point COMP-option. This increase in the value of the SELF-option was only observed when participants were asked to choose between a SELF- and a COMP-option but not when two SELF-options (i.e., *controllable* trial type) were presented to participants. Collectively, our behavioral analyses revealed that in the *mixed* condition, participants were making their decisions based on both reward magnitude and the presence of controllability over gameplay. Specifically, exactly how much controllability contributed in terms of reward value to the decision was effectively captured by POE measure.

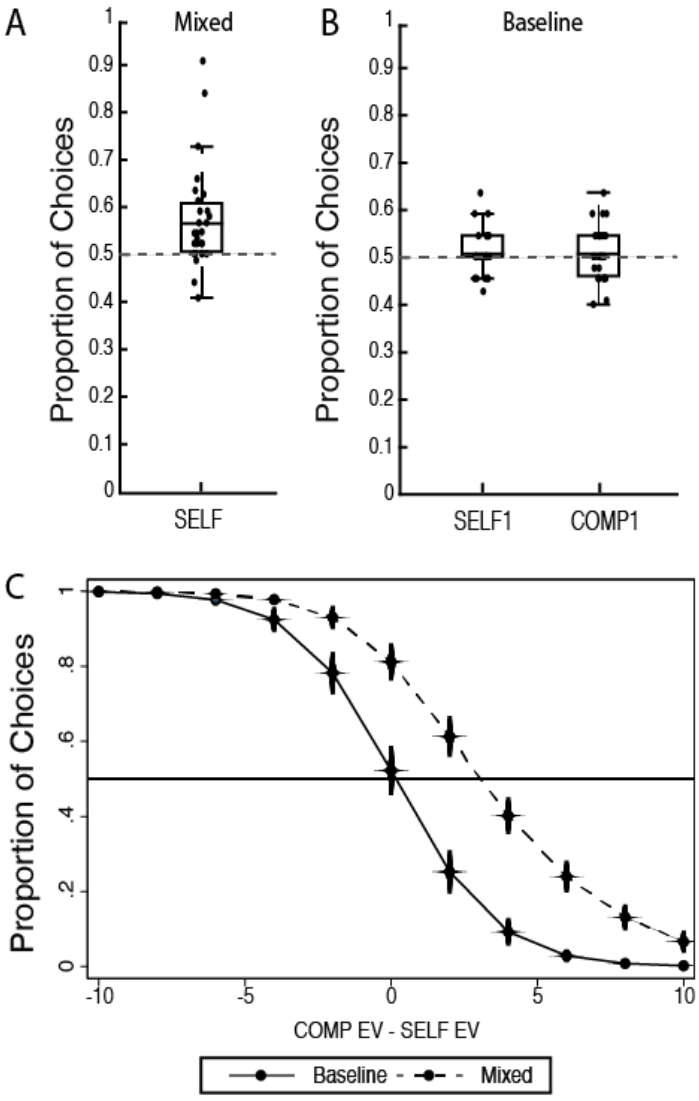


Figure 2.2 Behavioral findings. We compared participants' choice proportion for one of the two options (i.e., SELF in *mixed*, SELF1 in *controllable*, COMP1 in *uncontrollable*) against the hypothesized mean of 0.5. **(A)** In the *mixed* condition, participants showed a significant bias towards the SELF-option. **(B)** In contrast, in the two baseline trial types, participants did not show a significant bias towards either option in each choice pair. Note that SELF1 for the *controllable* trials indicated one of the two SELF-options presented to participants whereas COMP1 indicated one of the two COMP options in the *uncontrollable* trials. In

addition, we found no significant difference in the choice bias and pattern between the two baseline trial types. **(C)** Regression analysis conducted on participants' choice patterns revealed that the POE for the *mixed* condition was significantly greater than 0 (POE = 3.06) in contrast to the POE of 0.16 for the baseline condition. The x-axis indicated the reward expected value difference between each choice pair such that in the *mixed* condition, x-axis less than 0 indicated a larger SELF EV compared to COMP EV and vice versa for x-axis greater than 0. The y-axis indicated the proportion of choices which for the *mixed* condition would be proportion of SELF-choices and for the baseline condition would be proportion of fixed choices. The horizontal line indicated a choice proportion of 0.5 and intersections with the curved lines represent the POE for each condition.

2.3.1.1 Reaction time

We also quantified participants' reaction time (RT) during the *Choice* phase across trial types (*mixed*- M = 1.13, SD = 0.23; *Controllable*- M = 1.1; SD = 0.16; *Uncontrollable*- M = 1.08; SD = 0.14). We found that participants' RT did not differ across trial types ($F(2,156) = 0.78$, $p = 0.4580$) and run sequence ($F(1,156) = 0.73$, $p = 0.3930$). We also did not find a significant interaction between trial types and run sequence ($F(2,156) = 0.04$, $p = 0.9608$). Similarly, participants did not differ significantly in their SELF- and COMP-choice RTs during the *controllable* and *uncontrollable* trials respectively ($t(26) = -1.44$, $p = 0.16$). Reaction time between the SELF- and COMP-choices in the *mixed* condition was marginally significant ($t(26) = 1.71$ p = 0.099), with slower RTs for the SELF-choices.

2.3.2 Neuroimaging results

As detailed in the behavioral results section, participants' choice behavior demonstrated that, in the *controllable* and *uncontrollable* trials, they overwhelmingly picked the option with the higher reward magnitude, suggesting that their choices were driven by the reward expected value. Therefore, we hypothesized that our parametric analysis of these two trial types should yield activation in canonical value-encoding regions such as the OFC, ACC, striatum and vmPFC (Bartra et al 2013, Rangel & Hare 2010). After correcting for whole-brain multiple comparisons, the conjunction analysis revealed activation in the ventral striatum (peak *z*-stats = 3.6 at $MNI_{x, y, z}$ = -20, 16, -4, $p_{FDR\ voxel\text{-}corrected}$ < 0.01, 71 voxels), ACC (peak *z*-stats = 5.5 at $MNI_{x, y, z}$ = 3, 11, 43, $p_{FDR\ voxel\text{-}corrected}$ < 0.01, 2041 voxels) and OFC (peak *z*-stats = 3.5 at $MNI_{x, y, z}$ = 37, 22, -12, $p_{FDR\ voxel\text{-}corrected}$ < 0.01, 38 voxels).

2.3.2.1 Neural correlates underlying the opportunity for control

Although participants' choice behaviors were similar in the two baseline trial types, we argued that the two trial types were different on the basis that participants made only SELF-choices in the *controllable* trials and only COMP-choices in the *uncontrollable* trials. Therefore, we directly contrasted the *controllable* and *uncontrollable* responses across the two trial types to identify regions whose activation changed according to the presence of control, or more aptly, the opportunity to exert control. Our whole-brain analysis identified the ventral striatum, particularly the nucleus accumbens (Figure 2.3a; peak *z*-stats = 3.9 at $MNI_{x, y, z}$ = -6, 6, -8, $p_{FDR\ voxel\text{-}corrected}$ < 0.05, 16 voxels) and anterior midcingulate cortex (aMCC; Figure 2.3a; peak *z*-stats = 4.2 at $MNI_{x, y, z}$ = -2, 10,

43, $p_{FDR\ voxel\text{-}corrected} < 0.01$, 127 voxels) exhibiting greater responses to the *controllable* SELF-choices relative to the *uncontrollable* COMP-choices but not the reverse contrast.

Based on our a priori hypothesis regarding the ventral striatum, we tested whether the activity in this region could be related to participants' inherent preference for control by conducting a *post hoc* analysis comparing the striatal responses to the participants' Locus of Control (LOC) scores (M = 5.82, SD = 2.00, normally distributed using skewness and kurtosis test for normality [p = 0.44]) obtained using a questionnaire at the start of the experiment (all other questionnaire results are reported in the supplementary material under section titled "Questionnaire results"). In particular, the Internal-External Locus of Control scale has been a longstanding subjective scale to measure individual differences in how people generally perceive both the presence and the significance of having control in their lives (Lefcourt 2014). The LOC concept centers on the differences in perception of control across individuals where someone with a more internal locus of control is more likely to have stronger beliefs for perceiving control in his or her life that is captured in a lower LOC score (Rotter 2011). Using an anatomical striatal mask, we extracted each participant's contrast of parameter estimate for the striatal activation and found that this measure correlated negatively with participants' LOC scores (Figure. 3b; r = -0.392, p = 0.043). This suggested that participants with stronger striatal activation in response to the opportunity for control have a more internal locus of control (i.e.,

they believed in themselves and preferred more control) represented by a lower LOC score (Rotter 2011, Rotter 1966).

2.3.2.2 Neural correlates of subjective value of SELF-choices

From the regression analysis, we showed that in the *mixed* condition participants showed a clear bias towards the option conferring control (i.e., SELF-option). This led to the derivation of the POE measure, which was the experimental measure for the subjective value of control. Using this measure as a parametric covariate added to our GLM, we tested for regions that tracked this POE measure when participants selectively chose the SELF-option over the COMP-option. We found that in the contrast of SELF-choices minus COMP-choices, the parametric modulation of the POE covariate yielded activation in the vmPFC cortex (Figure 2.3c; peak *z*-stats = 3.8 at $MNI_{x, y, z}$ = -6, 32, -14, $p_{FDR\ voxel\text{-}corrected} <$ 0.05, 12 voxels), potentially suggesting that a higher subjective value of control, as captured by the POE measure, is encoded in participants' vmPFC BOLD signals.

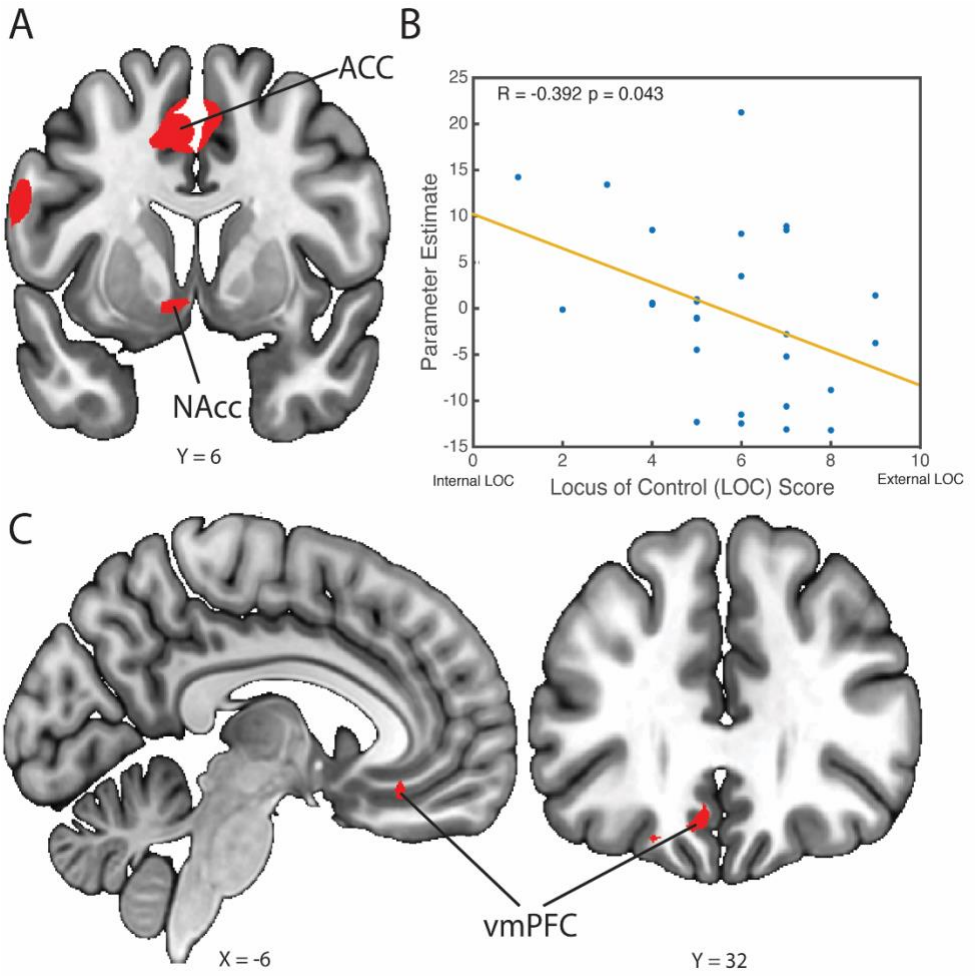


Figure 2.3 Neural correlates for value of perceived control. (A) To identify brain regions that were recruited in the *controllable* trials, we conducted a parametric model by contrasting the two baseline trial types (*controllable* – *uncontrollable*). After correcting for whole-brain voxel-based multiple comparisons, we found that the NAcc and ACC showed stronger activation during the *controllable* trials relative to the *uncontrollable* trials. **(B)** A negative correlation between NAcc activity and each participant's LOC score was observed, with higher striatal activation corresponding to more internal LOC and greater subjective preference for control. **(C)** To identify brain regions whose

activation tracked increasing subjective value of control represented by participants' POE measure, we performed a GLM of the *mixed* condition and added a subject-level POE covariate to parametrically modulate the contrast of SELF-choices – COMP-choices. After correcting for multiple comparisons across the whole brain, we found that the vmPFC responded to increasing POE measure.

2.4 Discussion

In this study, we examined the neural basis of subjective value of perceived control and how it impacts decision making. We found that perceiving control over a potential reward resulted in participants inflating the value of the associated outcome by 30%. This value inflation was sufficient to make the option conferring control desirable even at a cost to participants, which was consistent with previous experiments showing that the general partiality towards control translated into a "control premium" (Bobadilla-Suarez et al 2017, Owens et al 2014). Importantly, we were able to extend these findings by quantifying the subjective value of perceived control embedded within reward-seeking behaviors highlighting that control bears desirable qualities. Critically, the vmPFC computed and tracked this subjective value of control within the reward-seeking decision.

There were two baseline trial types (i.e., *controllable* and *uncontrollable*) that served as our experimental reference for the behavioral analyses in the condition of interest (i.e., *mixed*). We leveraged the differences in the two baseline conditions where control was always presented in one (i.e., *controllable* trials) and always absent in the other (i.e., *uncontrollable* trials) to find that the ventral striatum (i.e., NAcc) and the aMCC were engaged when there was an

opportunity for control in the *controllable* trials. In line with previous research concluding that perceived control may have inherent affective properties that makes it subjectively desirable (for review see Leotti et al 2010), our current experiment strengthened this argument by presenting evidence that the opportunity for control in the environment recruited key reward-processing regions such as the ventral striatum (Apicella et al 1991, Delgado 2007, Wang et al 2016). We also observed activation in the aMCC in response to the controllable compared to the uncontrollable trials. This observation is consistent with a previous experiment where aMCC is more engaged during free compared to forced motor choice (Hoffstaedter et al 2012) and with animal studies showing that neurons in the aMCC respond to anticipated reward-related motor behaviors (Akkal et al 2002, Shima & Tanji 1998).

The striatal activation in response to the opportunity for control was tied to how much the participants subjectively preferred exercising control as a function of their Locus of Control (LOC) score. The LOC scale has previously been applied in experimental settings to demonstrate that those with a more internal locus were oriented towards behaviors and activities meeting their higher expectancy of control (Dembroski et al 1984, Hashimoto & Fukuhara 2004, Joe 1971). Extending from these findings, a participant with a lower LOC score (i.e., more internal locus of control) would be predicted to have a greater inclination for having control (Rotter 2011) and as such, we observed that this translated into stronger striatal activity when control was present in the *controllable* trials. While this observation is associated with a typical neuroimaging sample size (N = 27), it

is important to replicate this individual difference effect in future studies. Taken together, the striatum was recruited when there was an opportunity for control in the environment and the strength of its activation was related to the individual's inherent preference for control.

Turning to the *mixed* condition and our experimental measure of the subjective value of control (i.e., POE), we found that the vmPFC served as the neural correlate subserving the computation of how much perceived control influenced decision making. That is, vmPFC was recruited to encode a higher subjective value of control as captured by the POE measure. This suggests that beyond the vmPFC's involvement when an organism perceives and chooses to exercise control in the environment (Amat et al 2005, Christianson et al 2009, Maier et al 2006), the vmPFC may also have a more fine-tuned role to engage in computing how much the organism actually desired control. Accordingly, individuals who showed greater behavioral bias towards seeking control (i.e., stronger desire for control) also had a higher subjective value of control that was tracked by greater vmPFC activation. The vmPFC has been implicated in encoding a "common currency" for the valuation of choices made between different rewards (for review see Bartra et al 2013, Knutson et al 2005, Levy & Glimcher 2012, Roy et al 2012), and the observation that vmPFC tracks the subjective value of control lends support to the idea that perceiving and exercising control has positive affective properties to make it valuable.

Taken together with the observation that the striatum was involved in encoding the opportunity for control, we argue that participants' inherent

behavioral bias towards seeking and retaining control was sustained by the rewarding and motivating nature of perceived control. Our current finding expands upon prior animal studies (Amat et al 2005, Maier & Watkins 2010) to suggest that the role of vmPFC in subserving control was contingent on how much positive value the organism attributed to seeking control in the decision-making process. The perception of control is not a binary on/off switch but rather, its contribution to adaptive behaviors is dependent on how it is subjectively valued. This graded-value feature of control allows for the possibility of circumstances where control is voluntarily relinquished (Sunstein 2017) or even not desired (Iyengar & Lepper 2000, Schwartz 2004). We postulate that one of the driving forces potentially subserving this inherent preference for control is the value of information (Bordia et al 2004, Tricomi & Fiez 2012), even if useless (Eliaz & Schotter 2010), which can lower uncertainty (Behrens et al 2007). By having agency over the gameplay, participants could subjectively interpret that they have more information on the game and hence contribute to their bias towards the SELF-option.

In the *mixed* condition of our task, participants had to evaluate both the reward value and the anticipated effort cost associated with choosing either option before they reach an optimizing decision to retain or forgo control. According to the expected value of control theory (Shenhav et al 2013), the higher-level integration of control-related reward and cost computation is subserved by the dorsal anterior cingulate cortex (dACC) while lower-level direct representation of affective value of control is associated with regions such as

ventral PFC and striatum. As such, our current findings aligned with this framework by showing that the ventral striatum encoded the affective signal associated with presence of control in the baseline *controllable* trials and that vmPFC tracked the value of control exertion in the *mixed* condition. It would be worthwhile for future research to also manipulate task demands (e.g., increasing or decreasing task difficulty) so as to not only replicate the striatum and vmPFC observation of encoding reward-related value signals associated with perceived control, but also the involvement of dACC in higher-level integration of reward and cost signals for action selection.

Another potential interpretation of our findings is that participants' SELF-option choices were driven by the belief in the probability of success for a particular option. However, we note that all participants in our experiment first underwent a training version of the task where they experienced feedback for both options that was deterministically set at 50% correct. Therefore, they started the game under the belief that both SELF- and COMP-options could result in successful and unsuccessful outcomes. In addition, in a prior study by our group, it was found that the opportunity for choice as a proxy for perceived control elicited different subjective ratings and neural activations compared to an option that conferred a belief of higher success probability (Leotti & Delgado 2011). Nevertheless, in our current paradigm, because we only manipulated reward expected value via varying the reward magnitude, future studies should separately vary the probability and magnitude component of reward expected value so as to tease apart whether each component exert differential influence

on the subjective value of control. In a similar vein, given the possibility that the value of reward can potentially interact with the subjective value of control, future studies should investigate any contextual effects related to varying the size of the overall reward at stake.

Yet another potential interpretation of participants' choice bias is that they picked the control-conferring option in order to stay engaged in the scanner. However, a motor response was required for both options in the choice phase and their subsequent game phase and reaction time data was not different across the conditions. Further, participants' post-experimental debriefing suggested that they were engaged in the task while in the scanner. Accordingly, we argue that the bias that participants showed towards the control-conferring option was most likely driven by their inherent preference for perceiving and exercising control. This notion of staying engaged in the scanner begets the possibility that arousal represents another potential driver of SELF-choices during the task. Control can be perceived as both rewarding and inherently desired, and that perceiving control has been tied to both increased (e.g., Ramsey & Etcheverry 2013) and decreased arousal (e.g., Gallagher et al 2014). Thus, an interesting future direction may be to more directly assess arousal via measures such as skin conductance or pupil size in order to gain insights into how arousal influences participants' choice behavior in the VoC task.

In conclusion, we found that participants showed a clear preference towards exerting control that was captured as the subjective value of control embedded in the reward expected value. This behavioral bias was subserved by

the ventral striatum mediating the opportunity for control in the environment and the vmPFC tracking this subjective value of control (i.e., POE). These findings collectively suggest that the computation of the value of perceived control in decision making is rooted within corticostriatal circuitry typically associated with reward-related processing and valuation. This is important to consider given the prevalence of the loss of control in many psychopathologies such as addiction, post-traumatic stress disorder and depression (Bechara 2005, Frazier et al 2004, Glass & McKnight 1996). Indeed, the perceived loss of control is a hallmark of disorders like addiction where loss of behavioral control to resist the addicted substance are observed (for review see Everitt & Robbins 2016, Koob & Volkow 2016). Ultimately, measuring the subjective valuation of control and understanding its source can help to both reconcile changes reported in diseased states and also to inform us on questions regarding the inherent preference for control. The gained knowledge of the relationship between perceived control and adaptive behavior can foster development of better treatment plans and methods to predict susceptibility to psychopathologies.

Chapter III: Aim 2. The protective effects of perceived control in aversive decision making

3.1 Introduction

Our sense of control is governed by our perceived ability to influence the environment. This ability to perceive and exercise control serves an important role to help maintain and support a healthy psychological and physical state. Therefore, it is not surprising that when animals and humans alike are faced with a situation where controllability is diminished or altogether absent, such as the dissociation of behavior and outcome, they are prone to develop behavioral passivity and heightened anxiety (Rodin 1986, Ryan & Deci 2000, Wallston et al 1987). When an organism is made to persistently endure an uncontrollable environment, one major consequence is the reduced behavioral responses towards trying to avoid or escape from future stressors, an effect also known as learned helplessness (for review see Maier & Seligman 2016).

Because organisms presented with controllable stressors do not typically experience behavioral passivity like those given uncontrollable stressors, it is argued that endowing an organism with behavioral control or enhancing the perception of control over the stressors can blunt against the development of learned helplessness. In other words, the detection of controllability, where an organism believes that its behavior can reliably bring about desired outcomes, can confer protective effects against behavioral passivity in an aversive environment. This perception of control is often associated with an increased sense of competence and stronger intrinsic motivation to learn to avoid or escape

from future aversive stimuli (Feather & Volkmer 1988, Holmes & Jackson 1975, Maier & Seligman 1976, Quaglieri 1980, Taub & Dollinger 1975, Trusty & Macan 1995). Prior work exploring the benefits of perceived controllability have found that both animals and humans will work harder and longer to obtain rewards or to avoid stressors when they detect that the environment is controllable (Bhanji et al 2016, Bongard 1995). Examining the protective effects of perceived control in humans, researchers showed that when participants were given the ability to avoid or escape from an aversive stimulus (Hiroto 1974) or were granted control in the form of choices (Rodin & Langer 1977), they reported stronger positive emotions and enhanced self-competence, resulting in improved overall sense of wellbeing (Deci & Ryan 1987, Rodin 1986).

Classic learned helplessness paradigms employ a triadic design where three separate groups of participants undergo the same schedule of events and each group respectively receive controllable, uncontrollable and no stressor before facing the same novel test phase (for review see Maier & Seligman 2016). With this between-subject design, it precluded the consideration of individual differences associated with both the behavioral effects of stressor controllability and participants' behavioral differences between uncontrollable and controllable conditions (Costello 1978, Lubow et al 1981). For instance, a participant with a strong sense of control might test strongly (i.e., showing above-average performance in the test phase) irrespective of whether the participant was subjected to controllable or uncontrollable treatment. Moreover, a participant who is less affected by the aversive stimuli might show low behavioral motivation in

the test phase regardless of group assignment in the treatment phase. Therefore, it is of interest to study participants' behavioral responses to controllability in a within-participant design in order to account for these individual differences.

In addition, previous findings suggested that healthy individuals have a behavioral bias towards seeking and exercising control even when control is merely subjective rather than objective (for review see Leotti et al 2010, Ly et al 2019). In other words, participants' natural behavioral tendency is to perform control-seeking actions and this includes the willingness to take on a cost to do so (e.g., accepting a smaller reward or energy expenditure related to performing an action). The question remains as to whether this is true even after exposure to prolonged uncontrollability across different aversive contexts—in other words, are the protective effects conferred by control potent enough to not only prevent but reverse behavioral passivity? In order to consider both the between-subject variability and to answer the question on the potency of control's protective effects, we built upon previous learned helplessness paradigms (Hiroto 1974) to design our Control in Aversive Domain (CAD) task. We predict that the presence of controllability after prolonged exposure to uncontrollability would be potent enough to reverse their behavioral passivity and rescue avoidance behavior towards aversive stimuli.

In addition to behavioral differences, we were also interested in examining neural differences between controllable and uncontrollable aversive contexts. Previous research largely implicated the ventromedial prefrontal cortex (vmPFC; Amat et al 2005, Christianson et al 2009) and the striatum (Leotti & Delgado

2011, Leotti & Delgado 2014) in the perception of control. In particular, we previously found that the vmPFC was important in encoding the subjective value of perceived control (Wang & Delgado 2019). As such, if perceived control were to have protective effects over behavior, then the organism must be able to detect and subjectively value perceived control in the given context. Therefore, we hypothesize that the vmPFC is involved in mediating the participants' behavioral change between the controllable and uncontrollable context. Investigating this could help shed light on the brain-behavior relationship between the neural detection of controllability and its associated behavioral responses.

To test our hypotheses, we implemented the CAD task in a functional magnetic resonance imaging (fMRI) scanner. The CAD task consisted of three different phases (i.e., *exposure, uncontrollable and controllable*). In the *exposure* phase, we tested participants' avoidance responses towards two cues paired with either an aversive (i.e., stressor; 4000 Hz) or a neutral (i.e., 500 Hz) tone. Both types of cues were presented in an uncontrollable context where participants had no behavioral control to successfully avoid the tones. The main goal of this phase was to expose participants to uncontrollability and to test for behavioral differences between aversive and neutral cues. In the *uncontrollable* and *controllable* phases, we investigated participants' behavioral responses towards a novel uncontrollable and a novel controllable aversive context respectively. The purpose of the *uncontrollable* phase was to investigate behavioral changes after prolonged exposure to uncontrollability and probe its

neural correlates whereas in the *controllable* phase, we set out to test the protective effects of controllability against behavioral passivity and examine its neural underpinnings.

3.2 Methods

3.2.1 Participants

31 right-handed individuals (11 Males and 20 Females) between the ages of 18 and 37 (Mean (M) = 23.3, standard deviation (SD) = 5.1) were recruited from the Rutgers University community. Participants were prescreened for any history of psychiatric and neurological illness. They were given monetary compensation for their voluntary participation in the experiment. All participants provided written informed consent in accordance with the experimental protocol approved by the Rutgers University Institutional Review Board. Three participants did not complete the experiment due to equipment failure and were excluded from subsequent behavioral and neural analyses. Two additional participants completed the experiments but were excluded from subsequent analyses due to complications (e.g., experienced phobia) during the scanning session. Four participants were excluded based on the criteria that they had >50% lapse trials in at least one experimental run. The final participant count was 22 (8 Males and 14 Females; M = 23.3, SD = 4.58). Despite the exclusions, the final participant count was consistent with the desired sample size of 19, obtained from a power analysis for paired *t*-test conducted using G*Power (version 3.1; Faul et al 2007) according to the guidelines established by Cohen (alpha = 0.05, power = 0.9, effect size = 0.8; 1992).

3.2.2 Experimental task and design

We adapted the classic learned helplessness paradigm implemented in both animals (Maier & Seligman 1976) and humans (Hiroto 1974) to design our Control in Aversive Domain (CAD) task and test the hypothesis that controllability can confer protective advantages on avoidance behavior across aversive contexts.

Prior to beginning the task, all participants were asked to listen to and rate the aversiveness of two tones on a Likert scale of 1 to 7. The two tones were respectively an unpleasant but not harmful tone (4000 Hz) and a neutral tone (500 Hz). Importantly, the amplitude (i.e., loudness) of the tones were matched but they differed on their frequency (i.e., pitch). The presentation of the tones was counterbalanced across participants.

After the initial tone ratings, participants were subsequently instructed on the task. They were informed that each tone could be randomly paired to four different visual cues represented by colored (i.e., red, blue, green, yellow) shapes (i.e., triangle, circle, square). Each cue-tone pairing remained consistent throughout the entire experiment.

3.2.2.1 Trial structure

Each trial consisted of a cue phase and a tone phase, each presented for 4s (Figure 3.1).

3.2.2.1.1 Cue phase

During the cue phase with a fixed duration of 4s, participants were presented with one of four colored cues and were told that they had to either press the AVOID or GIVE-UP button. The AVOID button required participants to press the

button within a specific 1s-interval in order to successfully avoid the forthcoming tone. In contrast, the GIVE-UP button could be used by participants at any time within the cue phase to signal that they were “giving-up”, leading to the presentation of a 2s-tone. It is important to note that participants were informed that the AVOID button required a correctly-timed press in order to be effective whereas the GIVE-UP did not have a specific-timing requisite. In other words, the AVOID button required participants to exert cognitive effort to learn its correct response.

Each type of cue presented in the various phases of the experiment was associated its individual correct response. Participants could only make one button press for each cue presentation and any missed response during the 4s-window was registered as a lapse trial that carried a $1 monetary penalty on the experimental compensation. Each cue phase end with a jittered 1 to 5-seconds inter-stimulus interval (ISI) before the onset of the tone phase.

3.2.2.1.2 Tone phase

In the tone phase, participants were presented with one of three possible outcomes depending on what button (i.e., AVOID or GIVE-UP) they pressed during the cue phase: 1. If they pressed the AVOID button within the correct 1s-interval for a particular cue, they would hear no associated tone (i.e., 0-s tone). 2. If they failed to press the AVOID button within the correct 1s-interval for that cue, they would hear the associated tone for 4s. 3. If they pressed the GIVE-UP button, they would hear the associated tone for 2s. This design allowed us to manipulate the controllability of each cue-tone context in order to probe the influence of controllability on behavior. For instance, in an uncontrollable context,

participants would never be able to successfully avoid the tone, allowing them to learn that their actions had no bearings on the outcomes.

Each tone phase was followed by a jittered 1 to 5-seconds inter-trial interval (ITI) to conclude the trial. To ensure that all trials lasted the same amount of time, we added 2 seconds to the inter-trial interval (ITI) whenever the participant made a GIVE-UP button press. This was done to disincentivize participants from pressing the GIVE-UP button for the sole purpose of shortening the experimental duration. We also note that any lapse trial registered during the cue phase always featured a 4s-tone.

3.2.2.2 Run structure

The experiment was divided into four runs each lasting 202-seconds: two *exposure* runs, one *uncontrollable* run and one *controllable* run.

3.2.2.2.1 Exposure phase

The *exposure* runs each featured one block of 8 aversive-tone trials (i.e., 4000Hz) and one block of 8 neutral-tone trials (i.e., 500Hz). The block presentation order was counterbalanced across participants (Figure 3.1). Despite how participants were briefed on the AVOID presses (see section 3.2.2.1.1), all trials in the *exposure* runs were uncontrollable where participants, in actuality, never received correct no-tone feedback for any AVOID presses they made in the cue phase. Participants learned through negative feedback (i.e., 4s of tone) that they had no effective behavioral control over the tone presentation. All participants underwent two consecutive *exposure* runs (i.e., early and late) that repeated the same sets of aversive and neutral cues.

3.2.2.2.2 Uncontrollable and controllable runs

The *uncontrollable* and *controllable* runs, each comprised 16 aversive-tone trials, followed the *exposure* runs in the aforementioned order. Both the *uncontrollable* and *controllable* runs respectively introduced one new cue that was different from those that the participants experienced in the *exposure* runs. These new cues were paired with the same aversive tones (i.e., 4000Hz) that participants had experienced previously.

Like the *exposure* runs, the *uncontrollable* run featured uncontrollable (i.e., no correct 0s-tone feedback) trials which participants could not successfully avoid the tones. In contrast, to examine the effects of controllability on participants' avoidance behavior, the *controllable* run allowed participants to successfully avoid the aversive tones. In other words, during the *controllable* run, whenever participants made the AVOID press, unlike the previous *exposure* and *uncontrollable* runs, they were able to successfully avoid the aversive tone. The reinforcement schedule during this run was deterministic where the first AVOID button press always yielded an incorrect feedback and the feedback for each subsequent AVOID button press was on an interleaved 50% correct/50% incorrect schedule. We set the outcome of the first AVOID press as incorrect to flush out participants who made an AVOID press by accident. In addition, we chose this schedule to ensure that all participants received the same order of feedback regardless of during which trial number they made an initial AVOID button press.

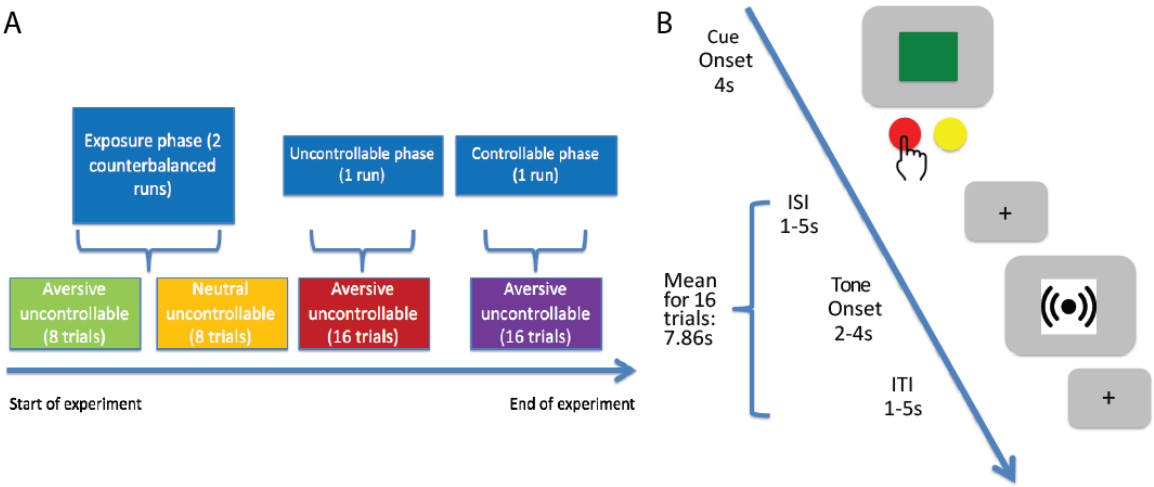


Figure 3.1 Experimental timeline of *Control in Aversive Domain* (CAD) task. **(A).** The CAD task consisted of four runs. The first two runs were the *exposure* runs where participants responded to either an uncontrollable aversive (4000 Hz) or uncontrollable neutral tone (500 Hz). The third run was the *uncontrollable* phase where participants experienced a series of uncontrollable aversive tones (4000 Hz) represented by a different cue compared to the *exposure* phase. The last run was the *controllable* phase where participants were given a series of controllable aversive tones (4000 Hz) paired with yet another novel cue. In all four runs, participants were provided the same task instructions for the AVOID and GIVE-UP button.

(B). *Example trial.* In each trial, regardless of the run, participants were presented a cue displayed for exactly four seconds. During the cue phase, participants had the option to either press the AVOID or GIVE-UP button. By choosing to press the AVOID button, participants could try to control and avoid the associated tone. A successful AVOID press yielded no tone presentation whereas a failed AVOID press yielded four seconds of tone during the tone

phase. By choosing the GIVE-UP button, participants would receive two seconds of the associated tone. The cue and tone phases respectively ended with a jittered interstimulus and intertrial interval signaled by a crosshair.

3.2.3 Neuroimaging data acquisition

Images were collected using a 3T Siemens MAGNETOM Trio scanner with the 12-channel head at the Rutgers University Brain Imaging Center (RUBIC). High-resolution structural images encompassing the whole brain were acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR): 1900 ms; echo time (TE): 2.52 ms; matrix 256 x 256; field of view (FOV): 256 mm; voxel size 1.0 x 1.0 x 1.0 mm; 176 slices; flip angle: 9°). The blood-oxygenation-level-dependent (BOLD) functional images were obtained using a single-shot T_2*-weighted echo-planar imaging (EPI) sequence (TR: 2000 ms; TE: 25 ms; matrix 64 x 64; FOV: 192 mm; voxel size 3.0 x 3.0 x 3.0 mm; 35 slices (0% gap); flip angle: 90°). In addition, B_0 field maps (TR: 400 ms; TE_1: 5.19 ms; TE_2: 7.65 ms; matrix 64 x 64; FOV: 192 mm; voxel size 3.0 x 3.0 x 3.0 mm; 35 slices (0% gap); flip angle: 60°) were collected prior to the functional images to correct for geometric distortion in the functional images.

3.2.4 FMRI preprocessing

The neuroimaging data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12; Ashburner 2012). First, we defined the origin of each image to align with the anterior and posterior commissure plane (Ardekani & Bachman 2009). After we motion-corrected each time series to its first volume, we then performed spatial unwarping to minimize geometric distortions due to susceptibility artifacts (Andersson et al 2001, Hutton

et al 2002). Next, we coregistered the mean functional image to the anatomical scan and normalized the anatomical using the unified segmentation model (Ashburner & Friston 2005). The normalized anatomical was subsequently used to reslice the functional data to standard stereotaxic space defined by the Montreal Neurological Institute (MNI). We applied a spatial smoothing at full-width half-maximize of 6mm to the normalized functional data.

To minimize the impact of head motion on the neuroimaging data, we applied additional preprocessing steps using tools from FSL (FMRIB Software Library version 5.0.4; http://www.fmrib.ox.ac.uk/fsl; Smith et al 2004). We detected motion spikes using the FSL tools *fsl_motion_outliers*. The motion spikes were evaluated with two metrics: 1) root-mean-square (RMS) intensity difference of each volume relative to the reference volume obtained from the first time point; and 2) frame-wise displacements calculated as the mean RMS change in rotation/translation parameters relative to the same reference volume. We subjected the metric values within a run to a boxplot threshold (75^{th} percentile plus 1.5 times the interquartile range) and labeled volumes as spikes, which were subsequently removed via regression (Power et al 2015, Satterthwaite et al 2013). Across all participants, this method removed 6.2% of volumes (range: 0.99 to 13.6%). After the removal of motion spikes, no participants exhibited extreme average volume-to-volume head motion (M = 0.058mm; range: 0.027 to 0.10mm) or maximum volume-to-volume head motion (M = 0.13mm; range: 0.060 to 0.26mm). Following the removal of motion spikes, we extracted brain material from the functional images (Smith 2002) and

normalized the entire 4D dataset using a single scaling factor (grand-mean intensity scaling). We also passed the images through the SUSAN (Smallest Univalue Segment Assimilating Nucleus) noise reduction filter, part of the FSL software package, using a 2mm kernel (Smith & Brady 1997). This step allowed us to achieve greater signal-to-noise ratio while preserving the image structure. Lastly, we applied a high-pass temporal filter with a 100-second cutoff (Gaussian-weighted least-squares straight line fitting, with sigma = 50s) to remove low frequency drift in the MR signal. Applying the temporal filter after the removal of motion spikes helps to minimize ringing artifacts (Carp 2013, Satterthwaite et al 2013, Weissenbacher et al 2009).

3.2.5 Data analysis

3.2.5.1 Behavioral analysis of choices in the CAD task

We were primarily interested in participants' avoidance behavior towards the aversive tone across the different experimental conditions (i.e., *exposure, uncontrollable and controllable*). These conditions together allowed us to ultimately examine the protective effects of controllability on avoidance behavior across aversive contexts. First, in the two *exposure* runs, we tested for differences in both total avoidance attempts and changes in avoidance behavior over time associated with the aversive and neutral tones. Second, using a novel cue in the *uncontrollable* phase, we studied the development of behavioral passivity in participants exposed to aversive contexts. And finally, by presenting participants with a controllable but aversive context in the last *controllable* phase, we investigated the protective effects of controllability on avoidance behavior.

3.2.5.1.1 Exposure runs

We first established, using paired *t*-tests, any potential differences in participants subjective tone ratings and their AVOID presses between the aversive and neutral conditions. We then conducted a repeated-measure two-way ANOVA examining the effect of run order (i.e., early vs late run) and cue type (i.e., aversive vs neutral) on the number of AVOID presses. Overall, we hypothesized that participants would rate the 4000Hz tone to be more aversive and show more avoidance behavior in the aversive compared to the neutral condition, particularly in the early aversive run.

3.2.5.1.2 Uncontrollable and controllable runs

We first compared the aversive trials in the *exposure* and *uncontrollable* runs utilizing a paired *t*-test to examine changes in avoidance behavior. We hypothesized that participants would show more avoidance behavior in the *exposure* compared to the *uncontrollable* run. Furthermore, we modeled participants' proportion of AVOID presses in both *exposure* runs into a probit regression to investigate whether the aversive or neutral *exposure* avoidance behavior predicted participants' avoidance behavior in the *uncontrollable* run. We hypothesized that the aversive *exposure* compared to the neutral runs would better predict participants' avoidance behavior in the *uncontrollable* run.

For the *controllable* run, we implemented a paired *t*-test to probe any differences in the proportion of AVOID presses made in the *uncontrollable* compared to *controllable* run. We predicted that participants would demonstrate more avoidance behavior in the *controllable* run compared to the *uncontrollable* run. Finally, to examine the avoidance behavior across all four aversive runs, we

analyzed the proportion of AVOID presses using condition as the factor (i.e., early *exposure,* late *exposure*, *uncontrollable, controllable*) in a repeated-measure one-way ANOVA model to test for behavioral differences.

3.2.5.2 Neuroimaging analysis

Neuroimaging analyses were carried out with FSL FEAT (FMRI Expert Analysis Tool) Version 6.0 (Smith et al 2004). All of the general linear models (GLM) described below included a reaction time (RT) regressor of no-interest for the cue phase with the duration set to the RT of a button press in each cue phase and an intensity of one. We regressed out the RTs for each cue phase in order to remove RT-related confounds that were unrelated to participants' choices between AVOID and GIVE-UP presses. All GLMs described below also included regressors of no-interest for any lapse trials for the cue phase with the duration set to four seconds and an intensity of one. For the first-level analysis, the regressors in all the general linear models (GLM) were convolved with the canonical hemodynamic response function and incorporated temporal derivatives and temporal filtering.

For the second-level analysis, unless otherwise stated, the data were combined across the two runs for each participant in the second-level analysis utilizing a fixed-effects model. At the group-level analysis, we performed a mixed-effects one-sample *t*-tests using FEAT's FLAME 1 + 2, which first fits the model using Bayesian modelling for mixed-effects variance estimation before processing all voxels that were close to threshold using the Metropolis-Hastings Markov Chain Monte Carlo sampling to obtain a more precise estimation of the mixed-effect variance (Woolrich et al 2004). Unless stated otherwise, for all z-

statistics images discussed, we thresholded and corrected for multiple comparisons across the whole brain using a false-discovery rate-corrected voxel-extent threshold of $p < 0.05$ (Lieberman & Cunningham 2009, Worsley 2001). We used MRIcroN and MRIcroGL to create the statistical overlay images (https://www.mccauslandcenter.sc.edu/crnl/tools; Rorden et al 2007).

3.2.5.2.1 Exposure runs

For the *exposure* runs, we were interested in differences in neural responses towards aversive and neutral cues in the early and late runs. To investigate this question, we performed a 2 (aversive vs neutral) X 2 (early vs late) ANOVA. This ANOVA would allow us to probe whether the context (i.e., aversive or neutral) influenced participants to exhibit different cue responses to the initial and latter stages of learning to avoid uncontrollable tones. Building on our behavioral predictions, we hypothesized that participants would react to the aversive cue more unfavorably, particularly in the late run when they have learned that the cue was unavoidable, due to the twofold setbacks of aversive context coupled with uncontrollability. Based on previous studies implicating the amygdala and ventral striatum in aversive learning (Kienast et al 2008, Schoenbaum & Setlow 2003), we hypothesized that participants would show greater activation in these regions when we examine the contrast of aversive – neutral x late – early interaction.

For the first-level GLM analysis, we modeled participant-specific design matrices for each run with the following regressors: (1) a linear regressor encoding the aversive cue phase with duration corresponding to four seconds and intensity set to one; (2) a linear regressor encoding the neutral cue phase with duration corresponding to four seconds and intensity set to one; (3) a linear

regressor encoding the aversive tone phase with duration corresponding to four seconds and intensity set to one; (4) a linear regressor encoding the neutral tone phase with duration corresponding to four seconds and intensity set to one. This model also included RT regressors of no-interest with duration set to the RT for the button press during the cue phase and intensity of one. In addition, we also added nuisance regressors for any lapse trials occurring in the cue and tone phases with the duration set to four seconds and an intensity of one. For the first-level model, we created the following contrasts: (1) aversive – neutral cue phase; (2) aversive – neutral tone phase; (3) aversive + neutral cue phase; (4) aversive + neutral tone phase. Accordingly, the first-level contrasts allowed us to model the aversive and neutral runs separately.

In the second-level analysis, we used a fixed-effects model to either combine the data across the two runs or contrasted the early and late runs. This setup resulted in three second-level contrasts: (1) early + late; (2) early – late; (3) late – early. In effect, the second level contrasts permitted us to model the temporal element of the task.

In the group-level analysis, we added a participant-specific covariate corresponding to their subjective rating difference between the aversive and neutral tones. This covariate was included to account for the subjective differences in tone perception. We performed a mixed-effects ANOVA to test the main effects of run order (late - early) and cue type (aversive – neutral) as well as the interaction between these two factors.

3.2.5.2.2 Uncontrollable and controllable runs

For the *uncontrollable* and *controllable* runs, we wanted to examine differential neural responses towards uncontrollable and controllable cues in the *uncontrollable* and *controllable* runs respectively. We hypothesized that in the *uncontrollable* – *controllable* contrast, participants would show stronger activation in the striatum, amygdala and insula. This hypothesis was grounded on previous work suggesting that the loss or lack of perceived control in an aversive context (e.g., receiving painful stimuli) is associated with increased activity in regions related to negative emotion arousal and the anticipation of aversive events (Alvarez et al 2015, Bräscher et al 2016, Mohr et al 2008, Salomons et al 2004, Tanaka et al 2006). In addition, based on our prediction that participants would develop behavioral passivity in the *uncontrollable* run, previous animal research suggested that regions such as the dorsal striatum and amygdala might be involved in the neural mechanism subserving behavioral passivity (Clark et al 2014, Maier et al 1993, Strong et al 2011, Thierry et al 1976). On the other hand, in the *controllable* – *uncontrollable* contrast, we anticipated that participants would have greater activity in the ventral striatum (i.e., nucleus accumbens) and vmPFC. This prediction was based on our previous finding (Wang & Delgado 2019) and others (e.g., Leotti & Delgado 2011, Maier & Watkins 2010) showing that the nucleus accumbens and vmPFC served as key nodes in the neural circuitry for perceived control. To test these hypotheses, we performed a GLM contrasting the *uncontrollable* and *controllable* runs.

For the first-level analysis, we modeled participant-specific design matrices with the following regressors: (1) a linear regressor encoding the cue

phase with duration corresponding to four seconds and intensity set to one; (2) a linear regressor encoding the tone phase with duration corresponding to four seconds and intensity set to one. This model also included RT regressors of no-interest with duration set to the RT for the button press in the cue phase and intensity of one as well as nuisance regressors for any lapse trials occurring in the cue and tone phases with the duration set to four seconds and an intensity of one.

In the second-level analysis, using a fixed-effects model, we compared the two runs by creating two contrasts: (1) *uncontrollable – controllable*; (2) *controllable – uncontrollable*. Finally, in the group-level analysis, we added a participant-specific covariate accounting for their subjective tone rating for the aversive tone. We carried out mixed-effects *t*-tests to examine differences in neural activation in cue and tone phase between the two runs.

3.3 Results

3.3.1 Behavioral results

Prior to the experiment, participants rated the aversiveness of each tone on a Likert scale of 1 to 7. Participants on average rated the aversive tone (M = 5.55, SD = 1.41) significantly higher than the neutral tone (M = 2.09, SD = 1.02); ($t(21) = 9.80$, $p < 0.0001$; Figure 3.2).

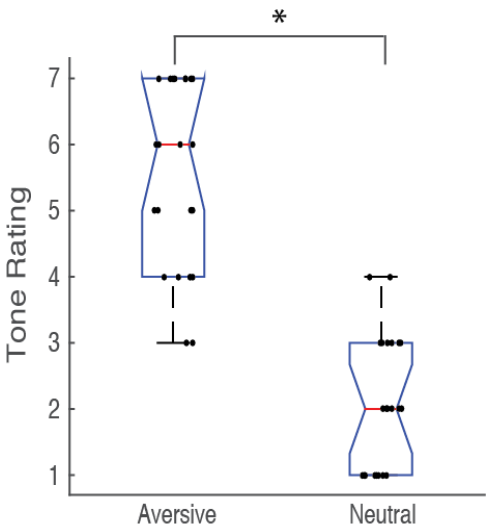


Figure 3.2 Subjective tone rating. Participants subjectively rated the aversive tone (4000Hz) as significantly more aversive (i.e., higher tone rating) compared to the neutral tone (500Hz).

3.3.1.1 Aversive vs neutral exposure runs

In the *exposure* runs, participants made more AVOID than GIVE-UP presses during both the aversive (AVOID: M = 12.09, SD = 2.94; GIVE-UP: M = 3.64, SD = 3.05) and neutral (AVOID: M = 12.09, SD = 2.79; GIVE-UP: M = 3.64, SD = 2.84) conditions, without any difference in AVOID presses between the two conditions ($t(21) = 0.00$, $p = 1.00$). We ran a 2 x 2 ANOVA to examine the effects of condition (aversive vs neutral) and time (early vs late) on the proportion of AVOID presses. We did not find a significant interaction between condition and run order ($F(1,66) = 0.19$, $p = 0.67$). However, there was a significant main effect of time ($F(1,66) = 6.31$, $p = 0.015$; Figure 3.3) and *post hoc* pairwise comparisons of mean revealed a significant difference between the early and late aversive runs ($p = 0.041$) but not the neutral runs ($p = 0.15$).

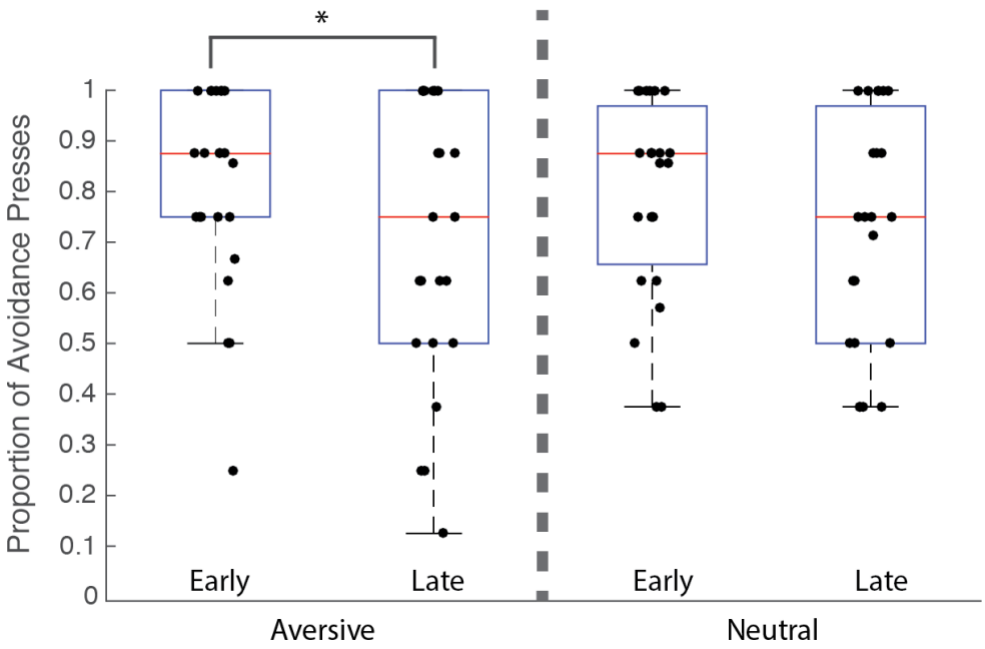


Figure 3.3 Behavioral findings in the *exposure* runs. Participants' avoidance behavior revealed a significant main effect of run order ($F(1,66) = 6.31$, $p = 0.015$). Pairwise comparisons showed that this significant effect was driven by the marked decrease in AVOID presses unilaterally present in the aversive ($p = 0.041$) but not neutral condition ($p = 0.15$).

3.3.1.2 Aversive exposure vs uncontrollable runs

In the *uncontrollable* run, participants made more AVOID (M = 9.14, SD = 4.75) than GIVE-UP presses (M = 6.59, SD = 4.84) in a novel aversive context. Using a nonparametric Mann-Whitney test to contrast participants' behavior in the aversive *exposure* and *uncontrollable* runs, we found that participants made significantly fewer proportion of AVOID presses in the *uncontrollable* compared to the *exposure* run (Fig. 3.4a; $z = -1.99$, $p = 0.047$), suggesting that participants showed less avoidance and more giving-up behavior in response to uncontrollable aversive cues over time.

Interestingly, we also found that the total proportion of AVOID presses in the aversive *exposure* runs (β = 2.43; z = 3.96; $p < 0.0001$) but not the neutral *exposure* runs (β = 0.79; z = 1.22; p = 0.22 predicted participants' proportion of AVOID presses in the *uncontrollable* run. To investigate further, we examined changes in avoidance behavior in aversive *exposure* and *uncontrollable* runs. Strikingly, we found that participants' change in avoidance attempts from the early to late aversive *exposure* runs, but not changes in the neutral runs (r = 0.33, p = 0.14), showed a strongly positive relationship with their change in avoidance attempts from the *exposure* to *uncontrollable* runs (Fig. 3.4b; r = 0.54, p = 0.01), suggesting that those with greater decrease in avoidance behavior between the early and late *exposure* also showed greater decrease in avoidance behavior in the *uncontrollable* compared to *exposure.*

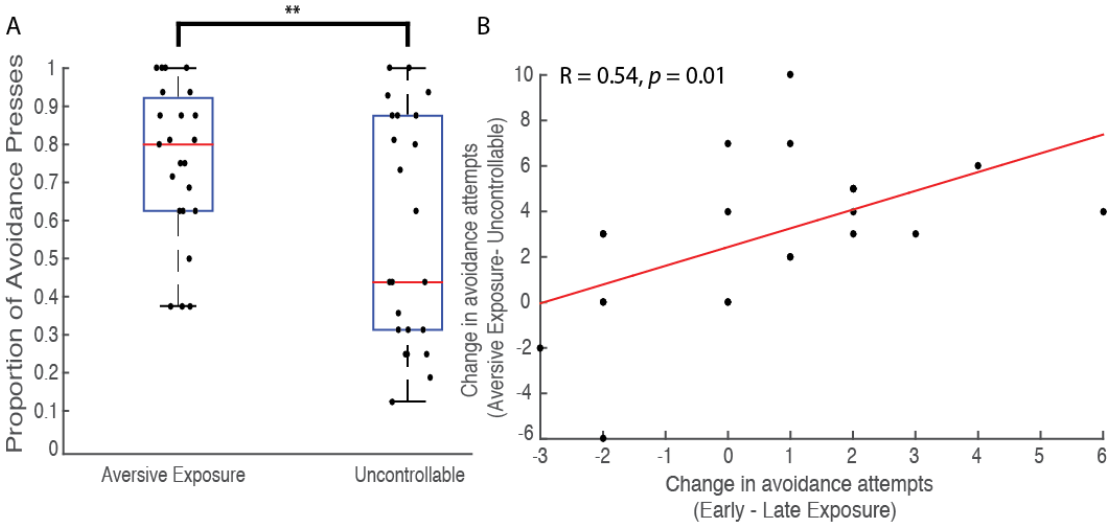


Figure 3.4 Behavioral findings in the *exposure* and *uncontrollable* runs. (A). Participants significantly decreased their avoidance behavior in the *uncontrollable* run when compared to the aversive *exposure* runs (z = -1.99, p = 0.047). **(B).** We compared participants' changes in avoidance behavior between

the early and late aversive *exposure* runs as well as the *exposure* (combined) and *uncontrollable* runs. We found that participants who showed greater decrease in their avoidance behavior from the early to late *exposure* runs (i.e., larger x-axis) also showed greater decrease in their avoidance behavior from the *exposure* to *uncontrollable* runs (i.e., larger y-axis).

3.3.1.3 Uncontrollable vs controllable runs

In the *controllable* run, the participants similarly made more AVOID (M = 14.64, SD = 3.26) than GIVE-UP presses (M = 1.27, SD = 3.28). Using a nonparametric Mann-Whitney test, we found that participants made significantly more proportion of AVOID presses in the *controllable* compared to the *uncontrollable* run (Figure 3.5; $z = 4.17$, $p < 0.0001$), alluding to increases in avoidance behavior that was driven by the presence of controllability in an otherwise aversive but novel context.

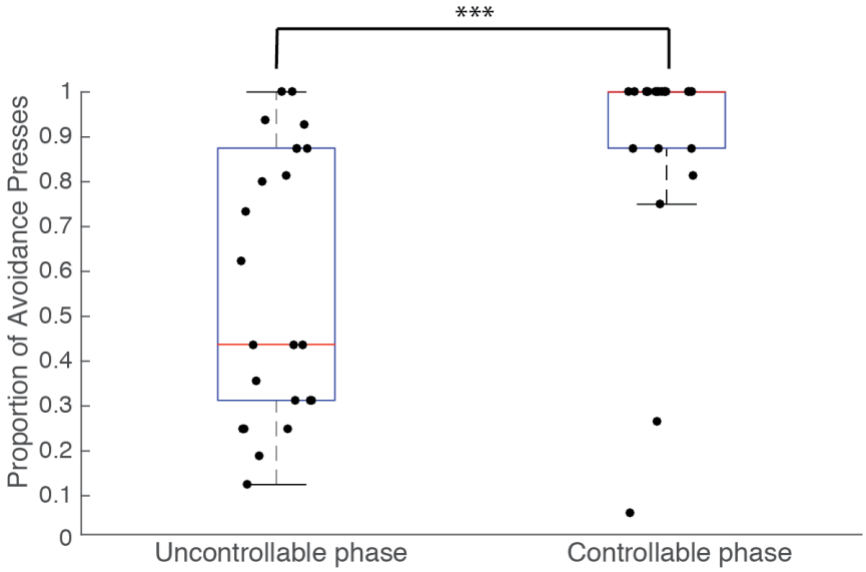


Figure 3.5 Behavioral findings in the *uncontrollable* and *controllable* runs. Participants significantly increased their avoidance behavior in the *controllable* run when compared to the *uncontrollable* run (z = -4.17, p < 0.0001).

Looking at the avoidance behavior across the four aversive runs (i.e., early and late *exposure, uncontrollable, controllable*), we used a Kruskal-Wallis rank test and found a significant effect of condition (Figure 3.6; $\chi^2(3)$= 21.2, p = 0.0001). We conducted *post hoc* pairwise comparisons using Dunn's test (Dunn 1964) and found a significant difference between early *exposure* and *uncontrollable* (z = 2.38, p = 0.0086) as well as late *exposure* and *controllable* (z = -2.96, p = 0.0016). We also observed significant difference between early *exposure* and *controllable* (z = -2.13, p = 0.017) and a marginal significant difference between late *exposure* and *uncontrollable* (z = 1.55, p = 0.06).

These results collectively depicted a behavioral pattern where participants showed a significance decrease in avoidance behavior from the early *exposure* to *uncontrollable* phase, all of which were uncontrollable but novel aversive contexts, before rebounding in their avoidance behavior in the *controllable* run. Put differently, across the first three aversive runs (i.e., early and late *exposure* and *uncontrollable*), participants showed marked decline in their avoidance behavior, with the lowest avoidance behavior captured in the *uncontrollable* run where participants were subjected to prolonged uncontrollable but novel aversive context. However, participants increased their avoidance behavior in the *controllable* run when controllability was present in a novel aversive context and their avoidance behavior was on par with what they showed in the early *exposure*

run, suggesting that controllability served protective effects to rescue participants' avoidance behavior.

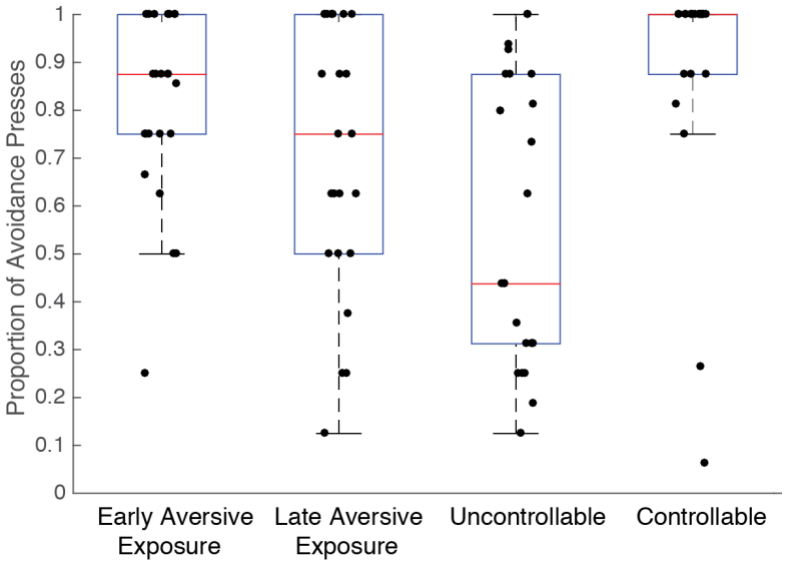


Figure 3.6 Behavioral findings in all aversive runs. We found a significant effect of condition on participants' avoidance behavior across all the aversive runs.

3.3.2 Neuroimaging results

3.3.2.1 Exposure runs

In the *exposure* runs, we were interested in the neural activation due to a sustained aversive context. In our 2 (aversive vs neutral) X 2 (early vs late) ANOVA, parallel to our behavioral findings, we did not find any regions that survived multiple comparisons for the interaction of condition and run order. In addition, we also did not find regions after correcting for multiple comparisons for both the main effects of condition and run order.

3.3.2.2 Uncontrollable and controllable runs

In our behavioral findings, we showed that participants made significantly more avoidance behaviors in the *controllable* compared to the *uncontrollable* run,

suggesting that participants recognized the difference in controllability between the two contexts. We performed a GLM to examine whether there exist differences in neural activation towards the *controllable* and *uncontrollable cues*. In the contrast of *uncontrollable – controllable,* we found neural activation in the amygdala (Figure 3.7; peak *z*-stats = 3.4 at $MNI_{x, y, z}$ = 19, -4, -20, $p_{FDR\ voxel\text{-}corrected}$ < 0.05), insula (Figure 3.7; peak *z*-stats = 4.0 at $MNI_{x, y, z}$ = 42, 0, 7, $p_{FDR\ voxel\text{-}corrected}$ < 0.05) and caudate nucleus (Figure 3.7; peak *z*-stats = 5.0 at $MNI_{x, y, z}$ = -10, 11, 7, $p_{FDR\ voxel\text{-}corrected}$ < 0.05). On the other hand, in the contrast of *controllable – uncontrollable,* we did not find any region that survived correction for multiple comparisons. In addition, region-of-interest analysis using a combined functional mask (3mm) of the two hypothesized regions (i.e., ventral striatum and vmPFC) created from the peak coordinates as detailed in Aim 1 also did not yield significant findings after correcting for multiple comparisons.

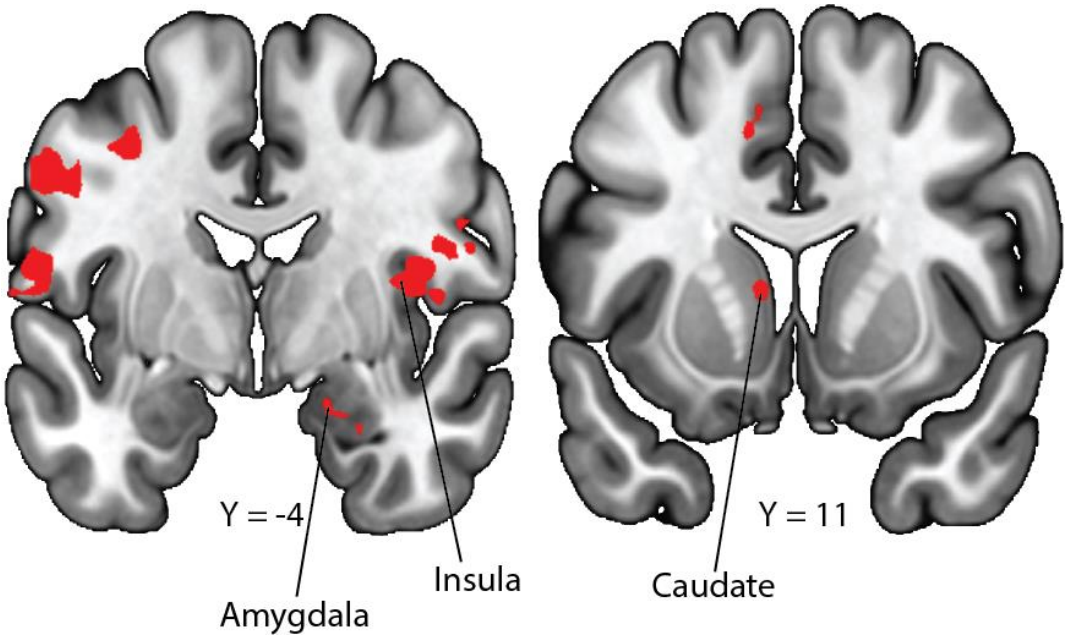


Figure 3.7 Neural correlates for uncontrollable cues. To examine differences in neural activation between the *uncontrollable* and *controllable* conditions, we conducted a GLM contrasting the uncontrollable – controllable conditions. We found significant activity in the amygdala (peak *z*-stats = 3.4, $p_{FDR\ voxel\text{-}corrected} < 0.05$), insula (peak *z*-stats = 4.0, $p_{FDR\ voxel\text{-}corrected} < 0.05$), and caudate nucleus (peak *z*-stats = 5.0, $p_{FDR\ voxel\text{-}corrected} < 0.05$) after correcting for multiple comparisons.

In our previous study (Wang & Delgado 2019), we reported that the subjective value of control was tracked in the vmPFC. Given that our current experiment investigated how controllability influenced avoidance behavior, we were interested to examine whether vmPFC activity in the controllable context showed any relationship with participants' avoidance behavior. Specifically, in the contrast between *controllable* – *uncontrollable* runs, we used the peak vmPFC coordinate reported by Wang and Delgado (2019; $MNI_{x, y, z}$ = -6, 32, -14) and created a 3mm region-of-interest functional mask. With this vmPFC mask, we extracted the peak activation (M = 47.07, bootstrap bias-corrected and accelerated 95% confidence interval = [36.80, 61.46]) and correlated this activation with participants' change in avoidance behavior between the *controllable* – *uncontrollable* runs using a spearman's correlation (Rousselet & Pernet 2012). We found that participants who had higher vmPFC peak activation in the *controllable* run also had greater increase in avoidance behavior in the *controllable* compared to *uncontrollable* run (Figure 3.8; ρ= 0.43, p = 0.04). To investigate whether vmPFC activity in the *controllable* condition can predict

participants' behavior change, we also performed a robust regression, which can minimize the effects of outliers (Verardi & Croux 2009), to reveal that vmPFC activity can significantly predict participants' corresponding behavioral changes (t = 4.45, p < 0.0001). These findings suggest that participants with stronger vmPFC activation in the controllable context had a correspondingly larger increase in avoidance behavior when presented with a controllable compared to an uncontrollable context.

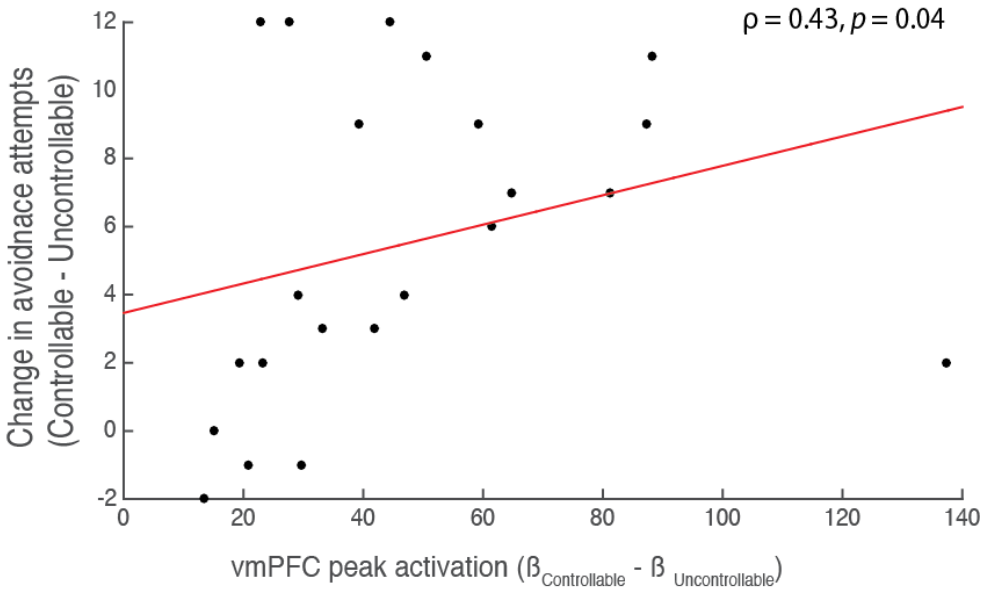


Figure 3.8 Correlation of avoidance behavior and neural activity. We examined the relationship between vmPFC activity in the *controllable – uncontrollable* contrast and participants' changes in avoidance behavior between the two conditions. Using a functional mask created from the peak coordinate (peak $MNI_{x, y, z}$ = -6, 32, -14) reported in Wang and Delgado (2019), we extracted the peak activation and correlated them with participants' change in avoidance attempts from the *controllable* to *uncontrollable* run. We found that participants

with a larger vmPFC peak activation also had a bigger increase in avoidance behavior in the *controllable* condition.

3.4 Discussion

We investigated the influence of perceived control on reversing behavioral passivity and probed the neural basis underlying the consequential behavioral change. We found that after exposure to prolonged uncontrollability, participants developed behavioral passivity as demonstrated by their decreased avoidance attempts towards a novel aversive cue. However, the introduction of control in a new aversive context was able to rescue participants' avoidance behavior and reverse the learned helpless state. Neurally, the *uncontrollable* condition elicited activation in regions such as the insula, amygdala and caudate nucleus as predicted. Interestingly, in the *controllable* condition, we found that participants who had stronger vmPFC activity also showed greater behavioral increase due to the presence of control.

In the *exposure* runs, we specifically tested for behavioral and neural differences in response to cues associated with aversive and neutral tones respectively. While participants rated the aversive tone as significantly more aversive compared to the neutral tone, we did not find correspondingly different behavioral and neural activity when we performed a 2 x 2 ANOVA to test for the interaction effects between cue aversiveness and run order. However, we did find a main effect of run order that was driven by reduced avoidance behavior in the late compared to early aversive *exposure* run. We reason that because participants learned over time that both contexts, regardless of aversive or neutral, were uncontrollable, this uncontrollability by itself can be perceived as

aversive. Indeed, previous research have reported that uncontrollability by itself is perceived as both aversive and undesirable (Grillon et al 2008, Kim et al 2017, Rodin 1986) and can serve as a stressor to trigger cortisol release (Peters et al 1998, Weiner 1992). As such, in the current design, participants might regard both types of cues as equally aversive due to their uncontrollability. A potential way to start probing this presumption would have been to ask participants to subjectively rate the aversiveness of the two cues at the conclusion of each *exposure* run. Their subjective ratings would have offered some insights into participants' subjective perception of the two cues.

Although we did not find a significant interaction in the aforementioned ANOVA, we reported a significant decrease in avoidance behavior that was unilaterally present in the aversive but not the neutral *exposure* runs. Coupled with this finding was the observation that participants made significantly fewer avoidance attempts in the *uncontrollable* compared to the *exposure* aversive trials. Taken together, these results suggest that participants' avoidance behavior reduced over time as they endured persistent uncontrollability across several aversive contexts. This reduction in avoidance behavior was observed even after participants were shown novel cues, suggesting that they were in some learned helplessness state (Maier & Seligman 2016), which is in line with previous studies examining learned helplessness in both rodents (Anisman & Merali 2001, Seligman et al 1975), dogs (Seligman et al 1979) and humans (Hiroto 1974, Hiroto & Seligman 1975).

Our current experimental design allowed us to take this finding one step further to demonstrate that participants' behavioral change from the early to late aversive *exposure* runs positively correlated with their behavioral changes from *exposure* to *uncontrollable* runs. Importantly, only the behavioral change in aversive *exposure* phase but not the neutral *exposure* phase predicated participants' ensuring behavioral change in the *uncontrollable* phase. In other words, participants with a larger decrease in avoidance attempts in the aversive *exposure* phase also showed a larger decrease in avoidance attempts in the *uncontrollable* phase, hence were more prone to developing behavioral passivity. This finding suggests that cue aversiveness and uncontrollability could possibly interact to better predict behavior towards future aversive cues rather than uncontrollability alone. Participants' behavioral responses towards aversive cues in the late stages of experiencing uncontrollability mimicked their behavior in the early stages where those who gave up quicker also gave up more over time. Future studies should replicate and extend our current findings to investigate possible explanations for this observation. We hypothesize that this finding could be partially reconciled if participants who gave up quicker were also less persistent in general, hence alluding to a potential interaction of susceptibility to behavioral passivity and the behavioral trait of persistence (Cloninger et al 1998). Persistence is a personality trait characterized by a person persevering through setbacks and fatigue (Lucas et al 2015) and can be measured via the grit score (Duckworth et al 2007). It remains to be studied whether persistence personality

trait can predict participants' susceptibility to the learned helplessness effect, and in theory, depression (Seligman 1974).

In addition to the aforementioned behavioral findings, we also observed that the *uncontrollable* run elicited activation in neural regions such as the insula, amygdala and caudate nucleus. There are two potential interpretations for this finding. First, uncontrollability and behavioral passivity in a learned helplessness state have previously been described as undesirable and are associated with negative emotions (Chorpita & Barlow 1998, Pryce et al 2012, Robbins 2005, Sanjuán & Magallares 2009). In addition, it has been also shown that uncontrollability can be a stressor in and of itself (Hayes et al 2014). As such, we hypothesized that participants perceived uncontrollability as aversive and undesirable and our finding of the insula (Caria et al 2010, Lutz et al 2013), amygdala (Bornhövd et al 2002, Büchel et al 1998, Shabel & Janak 2009) and caudate nucleus (Cowdrey et al 2011, Jensen et al 2003, Phillips et al 1997) supports the conclusion that these regions are involved in the processing of aversive stimuli. In addition, the amygdala and caudate nucleus observations are consistent with prior animal studies reporting that these regions contribute to the neural circuitry underlying the behavioral consequences of uncontrollable stressor (i.e., learned helplessness state), particularly the role of serotonergic activity within these regions in mediating the learning deficits induced by uncontrollability (Amat et al 1998, Strong et al 2011).

Second, because participants made more GIVE-UP than AVOID presses in the *uncontrollable* run, we postulate that their choices represented an indirect

form of avoidance learning because a GIVE-UP press resulted in a 2s tone period rather than the 4s from an AVOID press. Note that to prevent potential motor confounds, we had to balance the motor responses between choosing to avoid and choosing to give up. At the same time, we had to differentiate the outcomes for the two button presses and hence purposefully paired the GIVE-UP button with a shorter tone presentation. From this design, participants were learning to choose the lesser of the two evils after realizing that the tones were uncontrollable. We argue that instead learning to avoid the tones, they were learning to lessen the aversiveness of the stimuli (i.e., by choosing to endure a shortened aversive tone). Therefore, our finding of activation in the insula, amygdala and caudate nucleus concurs with previous research that these regions serve important roles in avoidance learning (Atlas et al 2016, Choi et al 2010, Delgado et al 2009, Palminteri et al 2012). Future studies should examine neural differences when participants made the choice to AVOID or GIVE-UP. This would make an interesting inquiry into whether in the early run, AVOID presses were more related to regions implicated in avoidance learning (e.g., striatum and amygdala; for review see Krypotos et al 2015) whereas GIVE-UP presses were more strongly associated with regions underlying negative emotional arousal such as disgust (e.g., insula; for review see Singer et al 2009) and if in the late run, there is a role reversal where AVOID presses engages more negative emotions and GIVE-UP presses engages more avoidance learning.

After exposure to prolonged uncontrollable aversive stimuli in the *exposure* and *uncontrollable* phases, we presented participants with a series of novel cues associated with controllable aversive stimuli. We found that the controllable stimuli rescued participants' avoidance behavior and returned it on par to the early *exposure* run at the beginning of the experiment. Across the course of the experiment, participants showed progressively fewer avoidance behaviors, reaching the lowest proportion of avoidance behavior in the *uncontrollable* run before significantly rebounding in the *controllable* run. This suggested that presence of control was potent enough to reverse behavioral passivity even after exposure to prolonged uncontrollability in an aversive domain. However, we note that that we observed two participants whose behavior did not rebound when control was present in the controllable *test* run. Instead, these two participants demonstrated persistent behavioral passivity even when control was introduced, suggesting that control was not able to reverse behavioral passivity in them and they exhibited the classic learned helplessness behavior. Although these two participants were behavioral outliers, their behavior points to the individual differences that exist where presence of control does not exert the same protective effects for everyone across the board. It would be worthwhile for future research to investigate personality traits and behavioral tendencies that could make an individual more resistant to the protective effects of control.

From our behavioral findings, we inferred that participants who rebounded the most in terms of avoidance behavior, or in other words, benefitted the most

from the protective effects of controllability, was expected to subjectively value control the most. Because they inherently had a higher subjective value and desire for control, they would accordingly respond more strongly to detecting control in the environment perhaps driven by a stronger coping and resilient tendency (Maier & Watkins 2010). However, we did not, as hypothesized, observe significant activation in the ventral striatum and vmPFC when in the contrast of *controllable* – *uncontrollable*. We reason that this could be due to the unbalanced ratio in participants' AVOID vs GIVE-UP presses between the two runs. Even though both runs had equal number of trials, participants made significantly more AVOID presses in the *controllable* compared to *uncontrollable* runs. A way that could overcome this complication was to only compare participants' AVOID presses between the two conditions. However, in our current design, removing the GIVE-UP trials from analysis would result in the loss of statistical power and an unbalanced number of AVOID-press trials between the two conditions.

Another way that could possibly overcome this limitation was to consider participants' behavioral changes between the *uncontrollable* and *controllable* conditions in the neural analysis. Specifically, we were intrigued by whether the vmPFC, which was shown in our previous work to encode participants' subjective value of control (Wang & Delgado 2019), was related to participants' avoidance behavioral change between the two conditions. We indeed found that vmPFC activity in the contrast of *controllable* – *uncontrollable* positively correlated with participants' avoidance behavioral change in the *controllable* run from the

uncontrollable run. This finding supports the hypothesis that a neural region (i.e., vmPFC) associated with encoding perceived control could predict participants' changes in avoidance behavior under controllable conditions. Inferring from this finding, we further reason that how much an individual subjectively values control could help to predict their susceptibility to behavioral passivity, which has significant implications on an individual's vulnerability towards developing depression (Bargai et al 2007, Li et al 2011, Shumake & Gonzalez-Lima 2003, Vollmayr & Gass 2013). However, further research using a larger sample size is warranted to lend support to this correlational finding. In addition, future studies should directly probe whether individuals with a stronger subjective value of control, either quantified via subjective scales such as the locus of control scale (Rotter 2011) or experimentally-derived measures (Wang & Delgado 2019), are also more likely to exert more avoidance and escape behavior towards aversive stimuli. This would have important implications in the effort to use personal traits to predict individual susceptibility to depression (Boyce et al 1991, Chioqueta & Stiles 2005, Kendler et al 2006).

In short, we set out to examine whether controllability can confer protective effects against prolonged exposure to uncontrollability in an aversive domain. We found that even after participants showed signs (i.e., reduced avoidance behavior) of behavioral passivity, the detection of control in a novel aversive environment was able to rescue their avoidance behavior. Neurally, we found that uncontrollability elicited activation in the insula, amygdala and caudate

nucleus. Controllability and its protective effects, on the other hand, was associated with activity in the vmPFC.

Chapter IV: Aim 3. The effects of acute stress on the subjective value and behavioral impacts of perceived control

4.1 Introduction

Uncontrollable aversive stimuli can induce an organism to succumb to a learned helplessness state (Maier & Seligman 1976), which is characterized by a reduction in the organism's motivational and affective drive to try and avoid or escape from aversive stimuli (Abramson et al 1978). Accompanying this notion is the observation that the lack of control over an aversive environment is associated with decreased mood (Scarpa & Luscher 2002), increased stress responses (Bandura 1982, Bollini et al 2004, Hadad-Ophir et al 2017), and heightened passivity and anxiety (Havranek et al 2016, Wallston et al 1987), all contributing to the development and exacerbation of behavioral passivity. As such, experiencing uncontrollability can lead to maladaptive behaviors, particularly when coupled with already-aversive stimuli. It is thus proposed that the lack of control or uncontrollability can also act as a stressor, able to intensify the stressfulness associated with an aversive context and can lead to cortisol release (Peters et al 1998, Weiner 1992), which is a hallmark response of increased physiological stress (Hellhammer et al 2009).

On the other hand, the detection of controllability in an aversive stimulus can serve as a buffer against the negative effects elicited by an otherwise aversive environment. Previous research has consistently found that compared to an uncontrollable aversive stimulus, the same aversive stimulus that is perceived as controllable by the organism can reduce behavioral passivity (Amat

et al 2005, Bhanji et al 2016, Keinan 1987, Maier & Watkins 2005, Wortman & Brehm 1975) and even protect against behavioral passivity induced by prolonged exposure to uncontrollability (Aim 2). Taken together, these prior findings hint at a potential interaction between stress and controllability. If the lack of controllability can induce a stress response, could exposure to acute stress prior to experiencing uncontrollability further exacerbate behavioral passivity towards aversive stimuli? And does acute stress alter participants' subjective value of control and lead to the dampening of the protective effects conferred by controllability?

Previous research has shown that exposure to acute stress can lead to maladaptive behaviors (Arnsten 2015, Maren & Holmes 2016, Porcelli & Delgado 2009) as well as increased anxiety and reduced reward responsiveness (Bogdan & Pizzagalli 2006, Grillon et al 2007, Maier & Watkins 2005). Acute stress has also been implicated to alter value-based decision making (Berghorst et al 2013, Kinner et al 2016, Shafiei et al 2012), particularly its effects on the evaluation of risk (Porcelli & Delgado 2009) and delayed rewards (Kimura et al 2013). If controllability can be perceived as a reward that carries inherent subjective value (Leotti & Delgado 2011, Wang & Delgado 2019), we proposed that under acute stress, the organism would attribute a lower subjective value towards perceiving and exercising control, thereby weakening the protective effects of controllability against behavioral passivity towards an aversive stimulus. To test this hypothesis, we designed an experiment to examine the effects of acute stress on

participants' subjective valuation of control and their behavioral responses towards uncontrollable and controllable aversive stimuli.

We used a between-subject design to randomly subject participants to either the socially-evaluated cold-pressor manipulation or its non-stress equivalent (Schwabe et al 2008). We collected four time-locked salivary samples to track changes in participants' cortisol levels, which served as a dependable biomarker of the hypothalamus-pituitary-adrenal axis response to stress (Hellhammer et al 2009). Using our previously established *Value of Control* (VoC) task (Wang & Delgado 2019), we obtained each participants' pre- and post- stress exposure subjective value of control measure as well as a measure during the stress-induced peak-cortisol period. In addition, participants underwent an adapted version of our *Control in Aversive Domain* (CAD) task (Aim 2) during the peak cortisol levels to examine differences in behavioral responses towards uncontrollable and controllable aversive stimuli, thereby allowing us to assess changes in the protective effects of controllability due to acute stress. We predict that participants subjected to acute stress would show a decrease in their valuation of control compared to participants in the non-stress group. In addition, exposure to acute stress would weaken the protective effects of control, evident in participants' reduced behavioral changes in the *controllable* compared to *uncontrollable* condition.

4.2 Methods

4.2.1 Participants

95 right-handed individuals (40 Males and 55 Females) between the ages of 18 and 40 (Mean (M) = 19.67, Standard Deviation (SD) = 3.49) were recruited from

the Rutgers University Department of Psychology R-Points System. A power analysis for two-sample *t*-test (stress vs non-stress cortisol change) was conducted according to the guidelines established by Cohen (1992) using G*Power (version 3.1; Faul et al 2007). To achieve an alpha of 0.05, a power of 0.9 and a large effect size of 0.8, the desired sample size was 68, with 34 per group for a between-subject design. Participants were given research credits for class work as well as a chance to earn a monetary bonus (up to $5) based on task performance. All participants provided written informed consent in accordance with the experimental protocol approved by the Rutgers University Institutional Review Board. Nine participants were removed due to failure to complete stress induction procedure (i.e., place hand in water <30s in cold pressor task or insufficient quantity of saliva for cortisol measurement). Four participants were removed due to experimental complications (i.e., failure of equipment or time delay for salivary sample collection). Four additional participants were removed due to failure to understand CAD task instruction. Final participant count for all analyses, except where noted, was 78 with 38 assigned to the stress group (18 Males and 20 Females) and 40 assigned to the non-stress group (20 Males and 20 Females). Only for the behavioral analyses associated with the VoC task, four more participants from the stress group and six more participants from the non-stress group were removed due to failure to understand task instructions, resulting in a final participant count of 34 in the stress group (17 Males and 17 Females) and 34 in the non-stress group (18 Males and 16 Females).

4.2.2 Experimental task and design

Participants were randomly assigned to either the stress or non-stress group. For those in the stress group, the experimenter donned a white lab coat as part of the stress induction procedure for the duration of the entire experiment. In contrast, those assigned to the non-stress group interacted with an experimenter not dressed in a white lab coat. Upon arrival at the lab, all participants were first briefed on the tasks that they were to perform during the experiment. They were also given instructions on the VoC task and subsequently underwent a 4-trial training version of the VoC task (see Chapter 2.2.2.1 for details).

Following the experimental briefing, we attached electrodes to participants' non-dominant index and middle finger to collect their skin conductance responses throughout the experiment (see Chapter 4.2.2.3 for more details). Their skin conductance responses were constantly being recorded from the first trial of the first VoC session until the last trial of the third VoC session which occurred at the end of the entire experiment. Upon setting up the skin conductance measurement, all participants underwent the first session of the VoC task (see Chapter 2.2.2.1 for detailed task description). This first session of the VoC task allowed us to obtain a pre-stress baseline for participants' subjective value of control. Upon finishing the first VoC task, participants were asked to provide the first salivary sample for cortisol measurement (Cort 1). The first salivary sample was collected at around 10 minutes after the participants' arrival at the lab and this collection time served as the reference timepoint for the remainder of the experiment (timepoint 0 of timeline in Figure 4.1).

At the conclusion of the first salivary collection, depending on their group assignment, participants subsequently underwent either the stress or non-stress induction procedure (see *Acute Stress Manipulation* section for more details). Immediately after the stress procedure, participants were given three paper questionnaires to complete in this specific order: 1. Internal-External Locus of Control (Rotter 2011) 2. Mini mood and anxiety symptom questionnaire (Clark & Watson 1995) 3. Need for Cognition (Cacioppo & Petty 1982). Participants then provided a second salivary sample (Cort 2), after which they performed the second session of the VoC task. Cort 2 was anticipated to match onto the rise-to-peak phase of the stress-induced cortisol change and as a result, the second VoC task was expected to take place during the initial cortisol increase due to the acute stress manipulation, thereby allowing us to measure the potential effects of acute stress on participants' subjective value of control. Upon finishing the second VoC task, participants were first asked to subjectively rate the aversiveness of the tone that they would hear in the CAD task before undergoing the CAD task (see *Chapter* 4.2.2.4 for more details). Note that the tone was set at an uncomfortable but not painful 4000Hz. The CAD task was predicted to occur during the anticipated peak of the cortisol response. Another salivary sample collection took place immediately after participants completed the CAD task and this Cort 3 was expected to track the return-to-baseline fall of the cortisol levels.

After the third salivary sample collection, participants were given another three questionnaires in the specific order: 1. Adult Measure of Behavioral

Inhibition (AMBI) and Retrospective Measure of Behavioral Inhibition (RMBI; Gladstone & Parker 2005) 2. Behavioral inhibition system/ behavioral activation system (BIS/BAS) scale (Carver & White 1994) 3. Desirability of Control Scale (Burger & Cooper 1979). Subsequent to finishing the questionnaires, participants were asked to perform the third and final session of the VoC task. This third VoC task was expected to have occurred when the cortisol has returned to near baseline levels and thus was considered the post-stress baseline measure of participants' subjective value of control. Finally, participants were asked to provide a fourth and final salivary sample (Cort 4) and were then debriefed to conclude the experiment.

In short, we collected salivary samples at four different timepoints during the experiment to capture cortisol changes due to the acute stress manipulation. We also implemented the VoC task at three different timepoints in an attempt to track the changes in subjective value of control due to acute stress. Furthermore, participants performed the CAD task during the anticipated peak of the cortisol change so as to allow us to probe differences in behavior between the stress and non-stress groups. Finally,

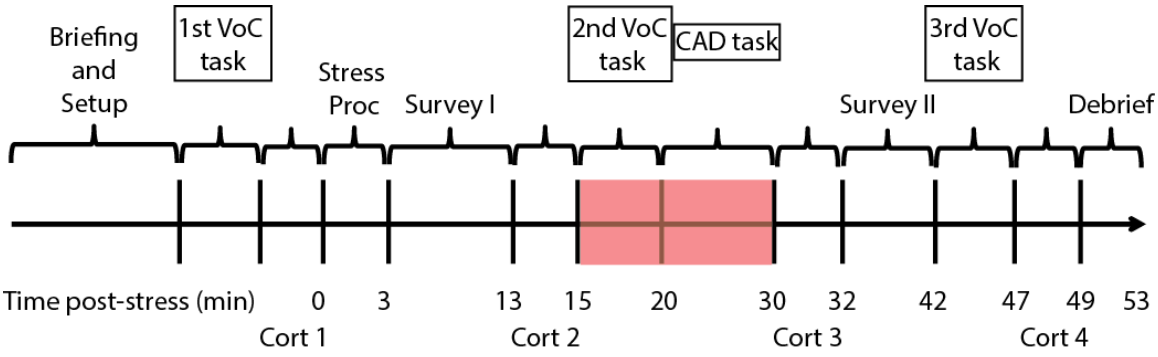


Figure 4.1 Experimental timeline. The entire experiment lasted approximately 60 minutes. During the 60 minutes, we collected a total of four cortisol samples at various time intervals during the experiment. Interleaved between the cortisol sample collections were three separate sessions of the VoC task and one session of the CAD task. Participants were randomly assigned to either the stress or non-stress group where they underwent either the stress or non-stress manipulation respectively. This timeline was strictly followed to ensure time-locked collection of salivary samples to account for the time-sensitive nature of cortisol changes. Shaded red region indicates the anticipated period of peak cortisol response for the stress group.

4.2.2.1 Acute stress manipulation

Participants who were assigned to the stress group underwent the socially evaluated cold-pressor test (Schwabe et al 2008). During this procedure, they were asked to submerge their right hand into 2-3°C ice water for two minutes while being videotaped by an experimenter donning a white lab coat. The experiment was terminated if the participant was unable to keep his or her hand in the water for at least 30 consecutive seconds. In contrast, participants assigned to the non-stress control group were instructed to submerge their right hand into lukewarm water for two minutes without being videotaped by an experimenter wearing a white lab coat. Immediately following the hand-submergence manipulation, participants rated the subjective stressfulness of the procedure on a 100-point scale (in intervals of 10-points), which was used to subjectively measure the aversiveness of the procedure.

4.2.2.2 Salivary cortisol measurements

A total of four salivary samples were collected throughout the experiment. The first salivary sample was taken at around 10 minutes after participants' arrival, serving as both the reference timepoint for the entire experiment as well as the baseline cortical level for each participant. The three remaining samples were collected to track the changes in cortisol levels due to the stress manipulation. All participants completed the experiment between the hours of 1pm and 4pm and participants were instructed to refrain from eating and drinking (except water) within two hours of experimental start time. We collected the salivary samples by asking participants to place a Salimetrics oral swab underneath their tongue for one minute. Upon removal from their mouth, the swab was immediately placed into an individual centrifuge tube and kept frozen in cold storage below -10°C. We subsequently packaged the samples on dry ice and sent to Salimetrics Laboratory (State College, PA) for duplicate biochemical assay analysis.

To quantify cortisol levels (µG/dL), we first converted the data into nmol/L. Subsequently, the area under the curve with respect to increase (AUCI) was computed for each cortisol data collection timepoint and compared to the baseline (first) sample to depict increases and decreases of cortisol over time (Pruessner et al 2003). This AUCI analysis method factors out the baseline cortisol level for each participant and is better suited for our purpose than the area under the curve with respect to ground (AUCG) approach because we were primarily interested in capturing the relative changes in cortisol rather than the absolute cortisol levels. To evaluate participants' cortisol response to the stress manipulation, we also classified participants into either cortisol responders or

non-responders by computing the percent increase from baseline (first sample) to peak (maximum cortisol level). We set the minimum threshold for cortisol responders at 15.47% (Miller et al 2013).

4.2.2.3 Skin conductance measurement

Skin conductance data were collected throughout the experiment, which enabled the tracking of participants' sympathetic arousal states during different parts of the paradigm. Four participants' skin conductance data were not collected due to experimental complications and therefore were removed from skin conductance response (SCR) analyses. We were particularly interested in the arousal states during the acute stress manipulation and during the CAD task. We used the BIOPAC conductance module and AcqKnowledge software to acquire the data. For the acute stress manipulation, we averaged the skin conductance (microsiemens, μS) levels (SCL) during the two minutes that the participants' hands were in the water. For the CAD task, we used the continuous decomposition analysis (Benedek & Kaernbach 2010) with the Ledalab software toolkit (Karenbach 2005) to compute the SCR during the 5-second tone period in the *uncontrollable* and *controllable* phase. Any response that was less than the minimum threshold of 0.01 μS in amplitude was replaced with zero. In addition, we removed the SCR data from analysis for any participant who failed to show supra-threshold SCRs on at least one third of the *uncontrollable* and *controllable* trials and those participants' SCL data were also excluded from the acute stressor analysis (N = 3). We obtained the mean SCLs during the acute stress manipulation and the decomposed SCRs for the CAD task for each participant and log-transform them to correct for positive skew.

4.2.2.4 CAD task (behavioral version)

We adapted this behavioral version of the CAD Task (Figure 4.2) from the fMRI version (described in Chapter 3.2.2) by making the following changes. First, instead of four runs, the behavioral version only had an *uncontrollable* and *controllable* phase, lasting 200-second and 270-second respectively. Given that we were not interested in examining behavioral differences between aversive and neutral cues, we chose to omit the *exposure* phase that was present in the fMRI version of the task (Aim 2). Second, the *uncontrollable* and *controllable* phases were modified to be more in line with classic learned helplessness paradigms using physical effort instead of cognitive effort (e.g., Hiroto 1974).

4.2.2.4.1 Uncontrollable phase

For the *uncontrollable* phase, unlike the fMRI version, this version did not have the cue period but rather only the tone period. The *uncontrollable* phase featured 20 unsignaled 5-second trials of aversive (4000Hz) tone, with a 5-second ITI showing a crosshair at the center of the screen. Participants was given the following instruction prior to the *uncontrollable* phase

> From time to time, you will hear some loud tones. When the tones come on, you might be able to do something about them. It is up to you to figure out how to use the SPACEBAR to get control over the tones. Please do not take off the headphones at any moment during the experiment.

We tracked the total number of spacebar presses during the ITI and tone period, which represented participants' effort to gain control over the aversive stimuli. Similar to the fMRI *uncontrollable* phase, in reality, the participants had no control over the presentation of the tone.

4.2.2.4.2 Controllable phase

Prior to beginning the *controllable* phase, we presented participants with the following instruction

> You are about to hear a new series of loud tones presented at different intervals. This time the tones have visual cues. Yellow light means the tone is about to come on. Red light means the tone is on. There is something you can do to stop the tone with the SPACEBAR. Please do not take off the headphones at any moment during the experiment.

Distinct from the *uncontrollable* period, there was a correct response that participants could learn in order to successfully stop the tones: participants had to make at least 30 successive spacebar presses during the 5-second window. They were given two windows of opportunity to try and gain control over the tones: either as an avoidance attempt during the cue period or as an escape attempt during the tone period.

The *controllable* phase consisted of 18 signaled 10-second trials each succeeded by a 5-second ITI displaying a fixation crosshair. By changing from unsignaled trials in the *uncontrollable* phase to signaled trials in the *controllable* phase, we adapted from previous learned helplessness paradigms (Hiroto 1974) to include salient features in the task that simulated novel contexts between the two phases (similar to the introduction of novel cues in the fMRI CAD task of aim 2). Each 10-second trial was broken down into a 5-second presentation of a cue (a yellow circle) followed by the onset of a 5-second auditory tone. During the cue period, a yellow circle was displayed, whereas during the tone period, a red circle was shown on screen along with the presentation of the tone. Participants could respond with spacebar presses during both the cue and tone periods. If

they made the correct response during the cue period, they would see the yellow circle change into a green circle to indicate that they had successfully avoided the tone and no tone was presented during the tone phase. It is important to note that at least 30 presses would have to be made before the 5s cue period expired. If they were successful, the green circle would stay on until the conclusion of the trial, which was always 10s in length excluding the ITI period. We registered any successful 30 spacebar presses during the cue period as a successful avoidance attempt.

Should participants fail to make the correct response within the allocated 5-second cue window, their button press count was zeroed and they entered the tone period with the presentation of the red circle along with the aversive tone. During the tone period, participants could try for the correct responses again during this 5-second window. If they successfully achieved at least 30 button presses during the tone phase, they would see the red circle change into a green circle along with the instantaneous cessation of the tone. We registered any successful 30 spacebar presses during the tone period as a successful escape attempt.

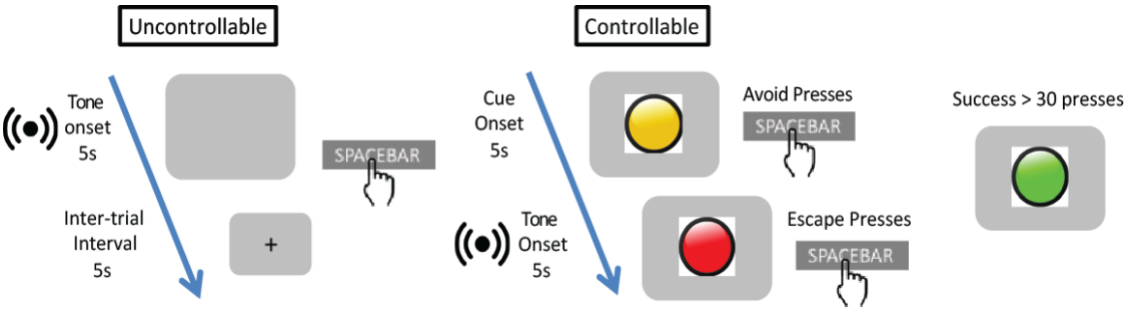


Figure 4.3 Control in Aversive Domain (CAD) task. The CAD task consisted of two separate runs. The *uncontrollable* run featured 18 unsignaled trials that was

divided into a tone phase lasting 5s and an inter-trial interval lasting 5s. During the tone phase, an uncomfortable but not painful tone (4000Hz) was presented and participants were instructed to try to terminate the tone using the spacebar. However, the spacebar had no effective control over the tone. In contrast, the *controllable* run featured 18 signaled trials that was split into a cue and tone phase. The cue phase lasting 5s included a yellow circle presentation where participants could turn green by making at least 30 spacebar presses (coded as avoidance press) to successfully avoid the ensuing tone. If unsuccessful, participants would be presented with a red circle along with the tone to signal the tone phase. During the tone phase, participants could again make at least 30 spacebar presses to terminate the tone and turn the red circle green.

4.2.3 Data analysis

4.2.3.1 Effect of acute stress on subjective value of control

To assess the effect of acute stress on participants' subjective value of control, we conducted a 3 (POE 1 vs POE 2 vs POE 3) x 2 (stress vs non-stress) ANOVA to test for interaction and main effects. Specifically, participants' subjective value of control was derived from the point of equivalence (POE) measure (see Chapter 2.2.5.1.1 for mathematical derivation). We hypothesized that the stress participants would show a larger change in their subjective value of control (i.e., larger decrease in POE) compared to the non-stress group.

4.2.3.2 Effect of acute stress on behavior in the CAD task

We were interested in the influence of acute stress on participants' behavior in response to controllable and uncontrollable aversive contexts. We implemented a 2 (stress vs non-stress) x 2 (controllable vs uncontrollable tone) ANOVA for the

total number of button presses across all trials. In addition, we also calculated the change in participants' button presses across the *uncontrollable* and *controllable* runs and used a two-sample *t*-test to investigate behavioral changes. We predicted that acute stress would impair participants' behavior in the *controllable* context and weaken the protective effects of controllability.

4.3 Results

4.3.1 Acute stress induction via increases in physiological and subjective measures

The socially evaluated cold-pressor task successfully elicited an elevation in salivary cortisol levels associated with a stress response. By computing the area under the curve with respect to increase (AUCI), we were able to quantify the rise and fall of cortisol over time with respect to the baseline cortisol measure at the first timepoint. A two-tailed *t*-test revealed that the stress group had significantly elevated cortisol AUCI compared to the non-stress group (Figure 4.3, $t(76) = 3.02$, $p = 0.0034$). Accompanying the cortisol data were two other measures of the effectiveness of the acute stress manipulation. First, we found that the stress group (M = 0.56 $\log_{10}\mu S$, SD: 0.25) had significantly elevated average SCR during the two-minute cold-pressor test when compared to the non-stress group (M = 0.40 $\log_{10}\mu S$, SD: 0.30; $t(72) = 2.43$, $p = 0.018$). Second, participants' subjective stress ratings immediately post-stress manipulation revealed that the stress group (M = 44.47, SD = 28.54) had significantly higher ratings compared to the non-stress (M = 9.00, SD = 17.51) group ($t(76) = 6.65$, $p < 0.0001$).

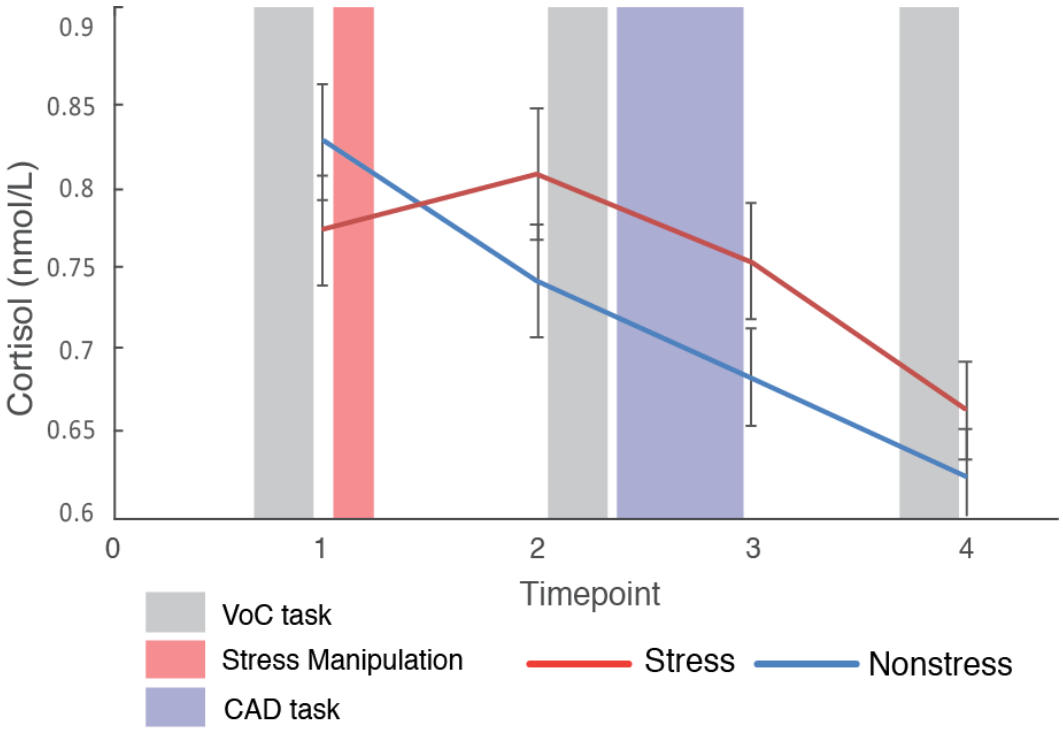


Figure 4.3 Salivary cortisol levels. Participants under acute stress had significantly greater increase in cortisol levels compared to participants in the non-stress group. Participants completed the second VoC and CAD tasks between saliva sample collection timepoints 2 and 3, during which the stress participants had significantly higher mean cortisol levels than the non-stress participants.

4.3.2 Acute stress did not significantly change the subjective value of control

We conducted a 3 (POEs) x 2 (groups) repeated-measure (RM) ANOVA to examine the effects of acute stress on the subjective value of control. From the ANOVA, we did not find a significant effect of POE by group interaction (Figure 4.4; $F(2,132) = 0.73$, $p = 0.48$) or main effects of POE ($F(2,132) = 1.87$, $p = 0.16$) and group ($F(1,132) = 0.54$, $p = 0.46$). As we expected POE 1 and 3 to have been collected when participants' cortisol levels were at or returning to baseline,

we did not anticipate they would be significantly different. As such, we had predicted that any differences in participants' subjective value of control would be driven by changes at POE 2. Therefore, we performed an exploratory 2 (POE 1 and 2) x 2 (groups) ANOVA to probe whether there were any group differences between the pre- and post-stress POE measures. We did not find a significant interaction effect (($F(1,66) = 0.53$, $p = 0.76$) or main effects of POE ($F(1,66) = 2.62$, $p = 0.11$) and group ($F(1,66) = 0.45$, $p = 0.51$).

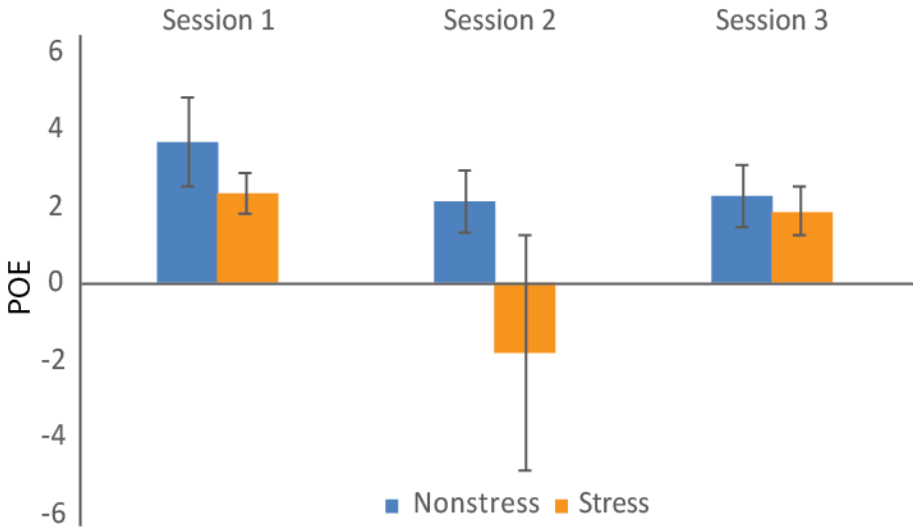


Figure 4.4 Changes in subjective value of control. Participants underwent three separate sessions of the VoC task (i.e., session) to allow us to obtain POEs measures for each task (i.e., POE 1, POE, POE 3) where the POE 2 occurred near the peak cortisol increase due to stress manipulation.

One potential factor that could help to explain the non-significant effect of acute stress on subjective value of control could be participants' varying physiological responses to the socially-evaluated cold-pressor test. To investigate this possibility, we divided the participants into responder (N = 13) and non-responders (N = 55) based on the Miller et al (2013) criteria of 15.47%

cortisol increase from baseline to peak. Note that this classification was made without regards to whether participants were in the stress or non-stress group. We performed a 2 (POE 1 vs POE 2) x 2 (responder vs non-responder) RM ANOVA and found no significant interaction between POE and group ($F(1, 76) = 0.26$, $p = 0.61$) and no main effects of POE ($F(1, 76) = 0.09$ $p = 0.76$) or group ($F(1, 76) = 0.77$, $p = 0.38$). While this exploratory analysis did not yield significant results, we argue that we did not have enough responders to accurately perform this analysis.

4.3.3 Acute stress increased behavioral responses to uncontrollable aversive stimuli

First and foremost, participants in the stress (M = 4.46, SD = 1.41) and non-stress (M = 4.33, SD: 1.87) groups did not show significantly different subjective ratings for the auditory tone ($t(75) = 0.35$, $p = 0.72$). To test the effects of acute stress on participants' behavior towards the aversive tone, we conducted a 2 (stress vs non-stress) x 2 (uncontrollable vs controllable) ANOVA. We found a significant interaction of stress by context (Figure 4.5a; $F(1, 75) = 4.03$, $p = 0.048$) as well as a significant simple main effect of context $F(1, 75) = 19.61$, $p < 0.0001$) but not a significant simple main effect of stress ($F(1, 75) = 0.76$, $p = 0.38$). In particular, we found that acute stress induced participants to make significantly more button presses in response to the aversive tones in the *uncontrollable* context (Figure 4.5a; stress: M = 236.76, SD: 156.42; non-stress: M = 155.75, SD: 87.76; $t(76) = 2.94$, $p = 0.0058$) but not in the *controllable* context (stress: M = 270.68, SD: 182.55; non-stress: M = 248.33, SD: 167.02; $t(76) = 0.59$, $p = 0.55$). To further investigate this significant interaction, we

computed the difference in behavioral responses between the *uncontrollable* and *controllable* runs and found that the stress participants (M = 33.92, SD = 105.5), compared to the non-stress participants (M = 92.68, SD = 134.98), showed a significantly smaller increase in button presses from *uncontrollable* to *controllable* runs (Figure 4.5b; $t(76) = -2.13$, $p = 0.036$).

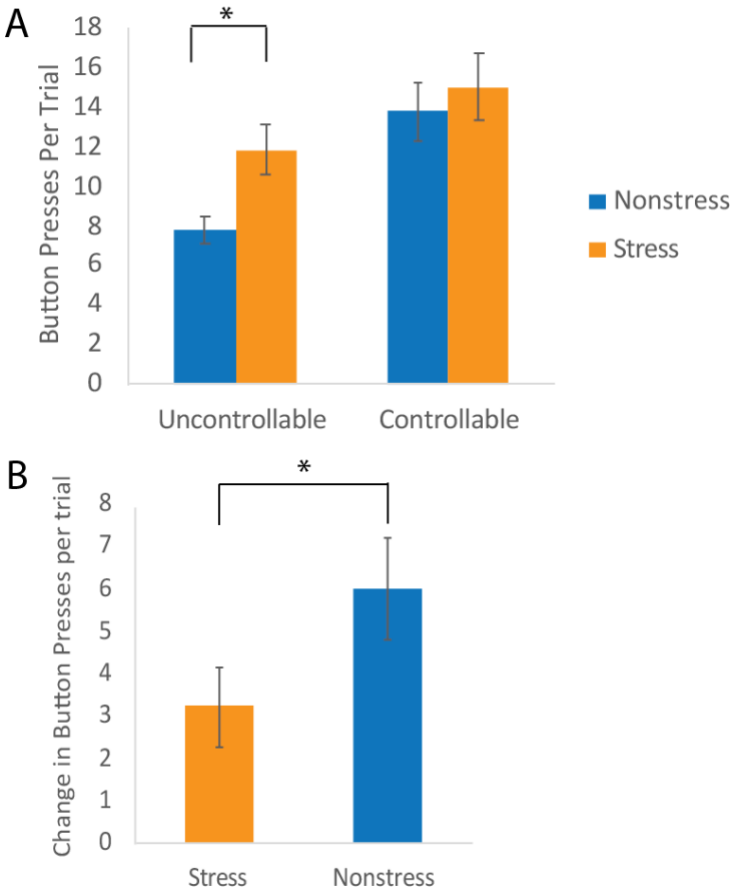


Figure 4.5 Effect of acute stress on behavioral responses to uncontrollable and controllable conditions. A. We found a significant interaction of stress X condition ($F(1, 75) = 4.03$, $p = 0.048$). In particular, the stress participants made significantly fewer button presses per trial in the *uncontrollable* condition compared to the non-stress participants. **B.** We computed the changes in button presses per trial between the *controllable* and *uncontrollable* runs and found that

the stress participants had a significantly lower increase in button presses in the *controllable* condition compared to the non-stress participants $t(76) = -2.13$, $p = 0.036$.

To further investigate the effect of acute stress on participants' behavior in the *controllable* condition, we subdivided participants' button presses into either avoidance or escape presses (see Chapter 4.2.2.4.2 for details). We conducted a 2 (stress vs non-stress) x 2 (avoidance vs escape) ANOVA and found no significant interaction between the two factors $F(1, 76) = 0.04$, $p = 0.84$) but a main effect of avoidance vs escape presses ($F(1, 76) = 30.25$, $p < 0.0001$). In addition, we also defined the mean response latencies in the *controllable* run to look for differences between the stress and non-stress groups. Specifically, each avoidance response had a response latency of 5-seconds or less compared to an escape response that had a response latency between 5- and 10-seconds post trial onset. If participants failed to avoid and escape the tone, that particular trial was logged with a 5-seconds and 10-seconds response latency for avoidance and escape presses respectively. A two-sample *t*-test revealed no significant difference in response latency between the two groups (stress vs non-stress) in avoidance ($t(76) = 0.86$, $p = 0.39$) and escape ($t(76) = 0.90$, $p = 0.37$) presses.

4.3.4 Acute stress did not significantly affect participants' SCRs in the uncontrollable condition

In addition to participants' behavior in the CAD task, we also assessed their physiological responses via SCRs towards controllability under acute stress (i.e., *uncontrollable* condition vs *controllable* condition). The SCRs were computed

using continuous decomposition analysis (Benedek & Kaernbach 2010) on the 5-second tone period for all trials in the *uncontrollable* and *controllable* runs respectively. We performed a 2 (stress vs non-stress) x 2 (*uncontrollable* vs *controllable*) ANOVA to test the effects of acute stress and controllability on participants' SCRs and found a significant interaction between stress and context (Figure 4.6; $F(1,69) = 5.41$, $p = 0.023$) but no simple main effects of stress ($F(1,69) = 1.42$, $p = 0.24$) and controllability ($F(1,69) = 0.01$, $p = 0.94$). In particular, *post hoc* pairwise comparisons revealed marginal difference between stress and non-stress groups (stress: M = 0.14, SD = 0.13; non-stress: M = 0.19, SD = 0.16) in the *uncontrollable* condition ($p = 0.073$) but not between groups (stress: M = 0.18, SD = 0.17; non-stress: M = 0.22, SD = 0.22) in the *controllable* condition ($p = 0.29$). Collectively, these findings showed that the stress participants showed lower SCRs compared to the non-stress group across the CAD task but there was no significant difference between the two groups within each task condition.

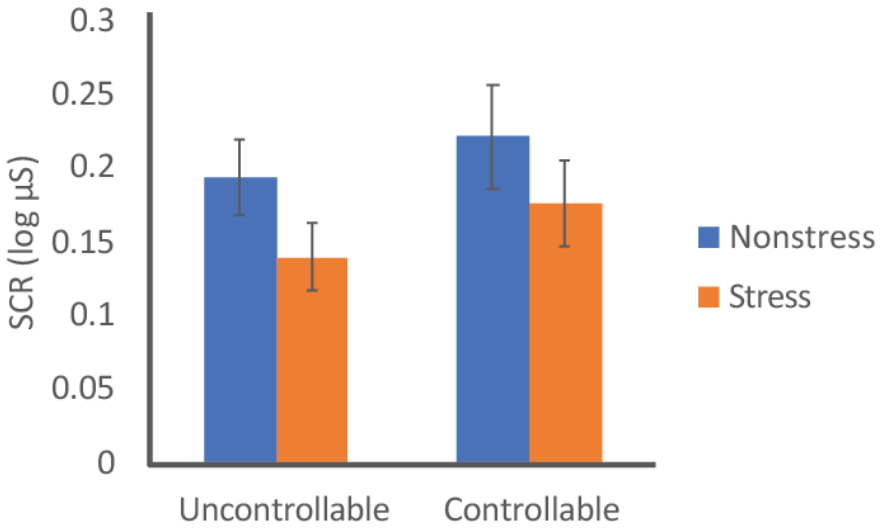


Figure 4.6 Effect of acute stress on SCRs in response to uncontrollable and controllable conditions. We found a significant interaction of stress X condition ($F(1,69) = 5.41$, $p = 0.023$). Specifically, there was a marginal significant difference between stress and non-stress groups under the *uncontrollable* condition ($p = 0.073$).

To further probe SCRs differences between groups, we conducted an exploratory analysis to examine any potential relationship between participants' SCRs and escape behavior during the 5-second tone period. For the *uncontrollable* phase, we did not find either the non-stress ($r = 0.21$, $p = 0.22$) or stress ($r = -0.054$, $p = 0.76$) group demonstrated any significance relationship between SCR and behavior. However, for the *controllable* phase, we found that the non-stress ($r = 0.37$, $p = 0.024$) but not the stress ($r = 0.12$, $p = 0.49$) participants showed a significant positive relationship between number of escape presses and SCR.

4.3.5 Participants' subjective value of control did not correlate with participants' behavior in the CAD task

To examine whether there was any relationship between participants' subjective value of control (i.e., POE measure) and their behavior in the CAD task, we conducted an exploratory analysis by correlating participants' POE under stress manipulation (i.e., POE 2) and their button presses in the *uncontrollable* and *controllable* runs of the CAD task. We did not find significant correlations between participants' behavior in the *uncontrollable* context and their POE measure for both the stress (r = 0.011, p = 1.000) and non-stress (r = -0.19, p = 0.88) groups. Likewise, the POE measure of the stress (r = 0.27, p = 0.35) and non-stress (r = -0.011, p = 1.000) groups did not correlate significantly with their behavior in the controllable context.

4.3.6 Questionnaire results

We conducted exploratory analyses to investigate the relationship between the questionnaires and participants' behavior in the CAD task. Specifically, we focused on the Internal-External Locus of Control (LOC) and the BIS/BAS scales based on past studies (Aim 1). Using Bonferroni-adjusted significance levels, we did not find significant correlations between participants' behavior in the *uncontrollable* condition and the questionnaires for the stress (LOC: r = -0.093, p = 1.00; BAS-reward responsiveness: r = 0.34, p = 0.71; BAS- drive: r = 0.054, p = 1.00; BAS-fun seeking: r = 0.32, p = 0.56) and the non-stress (LOC: r = -0.10, p = 1.00; BAS-reward responsiveness: r = -0.079, p = 1.00; BAS- drive: r = -0.28, p = 1.00; BAS-fun seeking: r = -0.10, p = 1.00) groups. Likewise, we did not find significant correlations between participants' behavior in the *controllable*

condition and the questionnaires for the stress (LOC: r = -0.035, *p* = 1.00; BAS-reward responsiveness: r = 0.20, *p* = 1.00; BAS- drive: r =0.01, *p* = 1.00; BAS-fun seeking: r = 0.19, *p* = 1.00) and the non-stress (LOC: r = 0.22, *p* = 1.00; BAS-reward responsiveness: r = 0.20, *p* = 1.00; BAS- drive: r = -0.15, *p* = 1.00; BAS-fun seeking: r = -0.10, *p* = 1.00) groups. We also did not find significant correlations between participants' change in behavior from the *uncontrollable* to *test* condition and the questionnaires for the stress (LOC: r = 0.073, *p* = 1.00; BAS-reward responsiveness: r = -0.14, *p* = 1.00; BAS- drive: r =-0.066, *p* = 1.00; BAS-fun seeking: r = -0.14, *p* = 1.00) and the non-stress (LOC: r = 0.33, *p* = 0.77; BAS-reward responsiveness: r = 0.29, *p* = 1.00; BAS- drive: r =-0.008, *p* = 1.00; BAS-fun seeking: r = -0.059, *p* = 1.00) groups.

For completeness, we reported all the questionnaire results (Table 1a) and their first-order correlation (stress- Table 1b; nonstress- Table 1c) after correcting for multiple comparisons using Bonferroni-adjusted significance levels.

A	**NoCog**	**DoC**	**MASQ**	**AMBI**	**RMBI**
Stress	62.07 +/- 11.11	102.17 +/- 17.65	20.89 +/- 6.77	15.90 +/- 4.84	23.93 +/- 6.43
Nonstress	55.24 +/- 11.13	96.28 +/- 14.04	23.21 +/- 5.57	17.72 +/- 3.93	26.07 +/- 7.16

B

	LOC	BAS-RR	BAS-D	BAS-FS	NOCOG	DOC	MASQ	AMBI
BAS-RR	-0.35 p = 1.00							
BAS-D	**-0.60** **p = 0.03**	0.52 p = 0.19						
BAS-FS	-0.48 p = 0.46	**0.69** **p = 0.0016**	0.57 p = 0.074					
NoCog	-0.01 p = 1.00	0.069 p = 1.00	0.28 p = 1.00	0.12 p = 1.00				
DOC	**-0.61** **p = 0.02**	0.25 p = 1.00	**0.78** **p < 0.0001**	0.32 p = 1.00	0.47 p = 0.52			
MASQ	0.24 p = 1.00	-**0.66** **p = 0.006**	-0.53 p = 0.18	-0.33 p = 1.00	-0.32 p = 1.00	-0.35 p = 1.00		
AMBI	0.40 p = 1.00	-0.45 p = 0.77	**-0.59** **p = 0.041**	**-0.67** **p = 0.0044**	-0.31 p = 1.00	-0.52 p = 0.23	0.42 p = 1.00	
RMBI	0.30 p = 1.00	-0.10 p = 1.00	-0.30 p = 1.00	-0.22 p = 1.00	-0.0014 p = 1.00	-0.27 p = 1.00	0.34 p = 1.00	0.34 p = 1.00
Controllable	-0.09 p = 1.00	0.34 p = 1.00	0.054 p = 1.00	0.32 p = 1.00	-0.060 p = 1.00	-0.0076 p = 1.00	-0.13 p = 1.00	-0.13 p = 1.00
Uncontrollable	-0.04 p = 1.00	0.20 p = 1.00	0.0059 p = 1.00	0.19 p = 1.00	0.038 p = 1.00	-0.013 p = 1.00	-0.16 p = 1.00	-0.090 p = 1.00

RMBI	Controllable
0.086 p = 1.00	
0.046 p = 1.00	**0.81** **P < 0.0001**

C

	LOC	BAS-RR	BAS-D	BAS-FS	NOCOG
BAS-RR	0.10 p = 1.00				
BAS-D	-0.041 p = 1.00	-0.016 p = 1.00			
BAS-FS	-0.23 p = 1.00	0.28 p = 1.00	0.068 p = 1.00		
NoCog	-0.11 p = 1.00	-0.17 p = 1.00	0.27 p = 1.00	0.10 p = 1.00	
DOC	-0.33 p = 1.00	0.089 p = 1.00	0.11 p = 1.00	0.46 p = 0.67	0.29 p = 1.00
MASQ	0.24 p = 1.00	-.25 p = 1.00	0.13 p = 1.00	-0.13 p = 1.00	-0.076 p = 1.00
AMBI	0.029 p = 1.00	0.77 p = 1.00	-0.040 p = 1.00	-0.20 p = 1.00	-0.15 p = 1.00
RMBI	0.24 p = 1.00	-0.15 p = 1.00	-0.24 p =1 .00	-0.27 p = 1.00	-0.44 p = 0.92
Controllable	-0.12 p = 1.00	-0.068 p = 1.00	-0.030 p = 1.00	-0.052 p = 1.00	0.29 p = 1.00
Uncontrollable	0.21 p = 1.00	0.21 p = 1.00	-0.16 p = 1.00	-0.069 p = 1.00	-0.011 p = 1.00

DOC						-0.48 p = 0.45	-0.20 p = 1.00	-0.36 p = 1.00	0.026 p = 1.00	-0.11 p = 1.00
MASQ							-0.14 p = 1.00	0.19 p = 1.00	0.023 p = 1.00	0.040 p = 1.00
AMBI								0.48 p = 0.49	0.066 p = 1.00	0.11 p = 1.00
RMBI									-0.052 p = 1.00	-0.045 p = 1.00
Controllable										0.55 p = 0.11

Table 4.1. Questionnaire results. A. Average questionnaire scores for stress and nonstress groups. **B.** First-order correlation table between questionnaire scores and participants' behavior in the uncontrollable and controllable conditions for the stress group. **C.** First-order correlation table between questionnaire scores and participants' behavior in the uncontrollable and controllable conditions for the nonstress group. Significant correlations are highlighted in bold.

4.4 Discussion

We set out to examine the influence of acute stress on the subjective value and protective effects of perceived control. We found participants' subjective value of control did not significantly change under acute stress. In addition, we also found that participants showed different behavioral responses towards aversive stimuli under acute stress and this was driven by the stress participants showing more

behavioral responses under the *uncontrollable* condition than their non-stress counterparts.

Given that previous findings have concluded that perceived control can have a taming effect on the aversiveness of acute stress (e.g., Grote et al 2007), we set out to investigate the reverse relationship of whether acute stress can impact the perception of control. Our finding suggested that exposure to acute stress did not significantly influence participants' subjective value of control in appetitive decision making. This is surprising considering we had hypothesized that the induction of acute stress would dampen participants' subjective value of control. We formulated this hypothesis based on the notion that perceived control is a form of reward in and of itself (Leotti et al 2010, Ly et al 2019) and that prior work have shown acute stress to reduce reward-related neural responses and decrease behavioral responsiveness towards both primary (Born et al 2010, Bryce & Floresco 2016, Maier et al 2015, Wemm & Wulfert 2017) and secondary (Bogdan & Pizzagalli 2006, Porcelli et al 2012, Potts et al 2019) rewards.

We can reconcile this surprising finding in two ways. First, it is likely that the stress group already showed a dampened POE 1 because they were exposed to a potential stressor in the form of the white coat for the duration of the experiment rather than just during the two-minute cold-pressor task. This could mean that the stress group's POE 1 was not an accurate measure of their true baseline POE compared to the non-stress group. This speculation is plausible given the observation that the stress group showed a lower POE 1 average compared to the non-stress group. An important adaptation for future studies will

be to have the experimenter don the white coat for the stress group only after the collection of any baseline measures.

Second, it is known that participants show varying responses towards the cold-pressor task could be captured in their cortisol responses (Skoluda et al 2015). To account for this factor, previous studies have divided participants into cortisol responders vs non-responders based on the criteria set by Miller et al., (2013) to investigate potential differences driven by cortisol responses (e.g, Bhanji et al 2016, Lewis et al 2014). Therefore, we took this approach and divided our participants into cortisol responders and non-responders, and in doing so, noted the low proportion of responders that made the final analysis pool. Across several studies, the responder rate for the socially-evaluated cold-pressor test was found to range from 48% to 84% with an average of 60% (Schwabe & Schächinger 2018). After accounting for participant removal due to reasons other than the acute stress manipulation, the stress responder in our final participant count was approximately 40%, which was below the general rate observed in other studies. As such, our attempt to investigate differences between responders and non-responders was hindered by the low responder ratio. If our dependent measure of the induction of acute stress was salivary cortisol increase and we wanted to draw a strong conclusion on the effects of acute stress, we needed to ensure that we had a sufficiently-powered and matched-group of cortisol responders, cortisol non-responders and non-stress non-responders. Future studies improving on our current design should take note of the cortisol responder rate from past studies to plan the recruitment of more

stress than non-stress participants in order to obtain the desired balanced sample of responder and non-responder within the stress group.

In light of the two aforementioned caveats, we attempt to make some inferences on our current finding to offer future studies some insights into the relationship between acute stress and subjective value of control. Although we did not find a significant effect of stress on POE changes, we note the dampened POE 2 for the stress group. In conjunction with the first caveat mentioned above, this could potentially suggest that there was some marginal decrease in their subjective value of control due to acute stress. Another observation worth mentioning is the large variability (as shown by the large error bar) in the stress participants' POE 2 that was not observed in other POE measures throughout the experiment for either group. Prior work have suggested that the effects of acute stress is largely dependent on individual variability both in terms of physiological responses and behavioral responses (for review see Sapolsky 2015), which could suggest that participants' subjective value of control fluctuates more under a stressed state. Therefore, it is of interest to emphasize individual differences in participants' changes in POE under stress. In other words, rather than viewing stress as a construct that can uniformly impact control-related decision making and its relevant behavior in a well-defined way, we should be mindful of individual differences when trying to decipher the effects of stress on control-related behavior. This was hinted in previous studies showing, for example, that participants' trait bias can govern the varying effect of stress on the same decision-making process (Berghorst et al 2013, Goette et al

2015, Lempert et al 2012). Thus, it could be fruitful to explore this individual difference angle such as using participants' cortisol change as a covariate in the analysis (Foley & Kirschbaum 2010, Skoluda et al 2015). Taken together, it is possible that under acute stress, participants' subjective value of control is lowered on average but there is more noise in participants' choices between the COMP- and SELF-options in the VoC task that might be explained by looking at their physiological responses. Future studies should consider these when attempting to improve on our current design to probe the effect of acute stress on subjective value of control.

In addition to the subjective value of control, we also investigated the effect of acute stress on behavioral responses in *uncontrollable* and *controllable* aversive contexts. We found that the stress participants showed a smaller decrease in their behavioral change from the *uncontrollable* to *controllable* conditions that was due to a significantly higher response rate towards the uncontrollable stimuli. Acute stress seems to confer some protection against uncontrollability in the form of heightened behavioral responses. This observation reconciles with the theory on stress depicted in the eustress vs distress (Le Fevre et al 2003, O'Sullivan 2011, Parker & Ragsdale 2015, Selye 1975) and challenge vs threat (Blascovich & Tomaka 1996, Frankenhaeuser 1986, Jerusalem & Schwarzer 1992, Seery 2011, Tomaka et al 1997) literature. According to the eustress vs distress model, eustress or "good stress" is the right amount of stress to motivate performance while distress or "bad stress" is too little or too much stress to hinder performance (Selye 1975, Selye 1976). Along

the same vein, the concept of challenge vs threat stipulates that “good stress” is perceived as a challenge that can elevate an individual’s behavioral responses toward a given task whereas “bad stress” is appraised as a threat that exacerbate an individual’s failure (Drach-Zahavy & Erez 2002).

In light of these theories, we postulate that participants subjected to acute stress were biased towards cognitively appraising the task at hand as a challenge to overcome rather than a threat. In other words, in the *uncontrollable* run, participants had not yet learnt that the context was uncontrollable and the amount of stress induced was at the optimal level to stimulate participants to perform more behavioral responses to try and avoid or escape from the aversive stimuli. However, at the conclusion of the *uncontrollable* run when participants learned that the context was uncontrollable, since uncontrollability is a stressor in and of itself (Cabib & Puglisi-Allegra 1994, Maier et al 1986), the combination of the existing acute stress and the realization that the aversive stimuli were uncontrollable together grew into too much of a stress load. This ensuing tipping of the scale towards too much stress consequently led to a distressful state in the *controllable* run where participants did not show significant increase in their behavioral responses even though the environment was controllable. However, this interpretation needs to be viewed with caution considering that the stress participants made more behavioral responses in the preceding *uncontrollable* condition and thus, there is less room for them to further increase their responses (e.g., ceiling effect) in the ensuing *controllable* condition. One way to decipher this could be to counterbalance the presentation order of the two runs, which

would disentangle whether run order or stimuli controllability was driving stress participants' behavioral differences.

Although we did not find a significant relationship between participants' subjective value of control and their behavior in the CAD task, we reason that this could be driven by the fact that the subjective value of control was extracted from a different context than the CAD task and we did not measure participants' subjective value of control in the CAD task directly. Nevertheless, it is plausible that how much an individual subjectively values control would have an impact on the protective effects of controllability on avoidance and escape behaviors. According to the theory of planned behavior (Ajzen 1991, Ajzen & Madden 1986), a person's attitudes and beliefs in a given context directly contribute to the person's behavior in said context. As such, should the person's subjective valuation of the context changes, such as when acute stress effectively diminishes how much the individual values control in the context, then it is quite possible that the change in the perception of control could lead to the weakened protective effects of controllability. Future studies should refine and improve on our experimental design to directly probe, within a single task framework, the relationship between subjective value and protective effects of control. If this relationship can be established, it could point to an identifiable trait that could predict how perceived control begets behavior. This would have implications in considering personality-based susceptibility to disorders such as depression and addiction where patients are afflicted with the hallmark symptom of loss of control (Belin et al 2013, Robbins 2005).

In conclusion, we set out to examine the effects of acute stress on participants' subjective value of control and behavioral responses towards controllability. We found that acute stress did not significantly change participants' subjective value of control. But under acute stress, participants showed heightened behavioral responses towards uncontrollable aversive stimuli.

Chapter V: General Discussion

We set out to examine both the rewarding properties and protective effects of perceived control on behavior. We carried out a series of experiments to probe into both the behavioral consequences and neural basis of perceived control in appetitive and aversive decision making. First, in aim 1, we found that perceived control carried a positive subjective value that biased participants' behavior towards retaining and exerting control in a reward-seeking context. The mere presence of the opportunity for control in the task elicited activation in the ventral striatum (i.e., NAcc) but more importantly, participants' subjective bias towards control (i.e., the subjective value of control) was encoded and tracked in the vmPFC.

Next, in aim 2, we subjected participants to prolonged uncontrollability in an aversive context and induced participants to develop behavioral passivity with the reduction in their avoidance behavior over time. We observed activation in neural regions such as the insula, amygdala and striatum towards the uncontrollable but aversive cues. In the last phase of the experiment, we instated behavioral control into a novel aversive environment and found that the presence of control rescued participants' avoidance behavior to the levels that they exhibited at the very beginning of the experiment. Strikingly, participants with stronger vmPFC activation in the *controllable* trials predicted greater behavioral reversal (i.e., greater increase in the avoidance behavior in controllable vs uncontrollable conditions).

Finally, in aim 3, we investigated the influence of a physiological factor such as acute stress on the subjective value and behavioral responses towards

controllability. We found that the induction of acute stress did not significantly alter participants' subjective value of control in an appetitive decision-making context. However, acute stress was able to induce participants to significantly increase their behavioral responses towards aversive but uncontrollable stimuli. Taken together, these studies collectively support two conclusions about perceived control, that it carries subjective value to bias behavior in an appetitive context and that it confers protective effects against behavioral passivity in an aversive environment.

5.1 Perceived Control can Bias Behavior

To interpret our findings, we have to first appreciate the inherent behavioral bias that we display towards any control-conferring option. To do so, let us briefly return to the airline example in the Introduction. When we pay to choose our own seat, we feel a sense of control over the outcome, even under the knowledge that the airline computer has the same repertoire of seats to choose from. An aisle economy seat is, after all, just an aisle economy seat regardless of who chose it for us. But the fact that we are willing to pay to choose the aisle economy seat yields two assumptions: one, we have preference for choosing rather than deferring our choices to others, irrespective of outcome; and two, the resulting outcome associated with our self-choice is artificially inflated by our act of choosing. Thus, we can argue that our sense of control over the outcome alone carries decisional value and this value is powerful enough to bias our behavior. Put this into perspective with our findings in aim 1 where we computed a 30% value inflation for the SELF-option, we can conclude that perceiving control over an outcome can augment how much the outcome is subjectively

valued relative to its actual objective value. So perceived control has a subjective value and can generate approach behavior to bias our actions. But what is subserving this subjective value of control?

Based on a survey of literature, we reason that perceived control is both behaviorally motivating and emotionally rewarding. Motivation is defined as the propensity to exert effort towards a given goal (Weiner 2012). As such, perceiving control in a given context can act as a drive to motivate control-seeking behaviors. This has been demonstrated empirically when an organism, be it a rodent or human, is willing to expend energy to work towards a goal when control is present but becomes behaviorally passive when control is absent in the same context (Bhanji et al 2016, Bongard 1995). In aims 2 and 3, we similarly found that when controllability was introduced into a previously uncontrollable aversive environment, participants' increase in avoidance and escape behavior hinted at their increase motivation to do something about the stimuli rather than give up. Moreover, it has also been reported that both animals and humans alike show the preference to choose just for the sake of choosing, without any tangible benefit such as a larger objective reward (Bown et al 2003, Catania & Sagvolden 1980, Suzuki 1997, Suzuki 1999). We bolstered this observation by showing in aim 1 that participants overwhelmingly chose the SELF-option in order to exert control over the ensuing computer game, even when doing so conferred no objective advantage to maximize their monetary reward.

We can perhaps attribute this strong desire for control to two potential driving forces. One, by choosing rather than letting someone else choose, we

effectively lower the uncertainty associated with the outcome (Behrens et al 2007). For example, in the *Value of Control* task in aim 1, by taking control over the card-guessing game (with a SELF-choice), they could subjectively interpret that they have more information on winning the game and this value placed on having information, even if useless (Eliaz & Schotter 2010), is preferred because it lowers uncertainty (Bordia et al 2004, Tricomi & Fiez 2012). Two, having agency over an outcome fulfills our need for self-efficacy, which is described by Bandura (1997) as the belief that we as individuals are capable of performing actions to achieve our goals. The idea of having agency and control over an outcome is contingent upon the premise that we have the competence and power to dictate the outcome. In other words, by choosing to choose, we ascribe a greater subjective value to our own capabilities over that of an external agent to accomplish the goal and successfully obtain the desired outcome. It should be noted however, that this desire for control is not always true in all circumstances. There are plenty of instances where we voluntarily relinquish control, whether it is to a more-knowledgeable party such as deferring control over our treatment plan to a physician or when too many choices become a burden (Chernev et al 2015).

In addition to being behaviorally motivating, perceiving control is also emotionally rewarding, which explains why it is a basic need that helps to maintain our physical and psychological wellbeing (Skinner 1995). Indeed, early psychological studies examining the effects of control on participants' emotional states have repeatedly found that endowing individuals with control, whether it is via giving them control over the caring of a potted plant (Langer & Rodin 1976) or

over their academic progress (Patrick et al 1993), can reliably elicit strong positive emotions such as being content, satisfied and happy as well as heighten subjective wellbeing. These findings are further bolstered by the observation that participants who were subjected to controllable compared to uncontrollable pain showed greater tolerance and rated the painful stimuli as less aversive (Carlsson et al 2006, Müller 2012, Thompson 1981). We corroborated the notion that perceived control has rewarding and affective properties by showing in aim 1, that the striatum (particularly the ventral striatum), a crucial neural node for reward processing (Schultz 2015, Wang et al 2016), was recruited for the *controllable* baseline condition. In other words, the mere presence of the opportunity for control in the environment, with no bearings on behavior, triggered striatal activation. And importantly, this affective signal in the striatum was significantly correlated with the individual's locus of control (Rotter 2011) where those with a more internal locus of control (i.e., greater sense of control) showed stronger striatal activity.

If perceived control can elicit positive emotions and generate affect, then it ought to carry weight in value-based decision making. This was indeed the case when in aim 1, we asked participants to make choices along both the dimension of reward expected value and perceived controllability. By scrutinizing their choice pattern, we were able to determine that on average, participants were as likely to choose a 10-point control-conferring option as they were to choose a 13-point control-relinquishing option, while governed by the important assumption that both options were equally likely to be successful. This value inflation was not

observed when control was rendered a nonfactor in the decision by presenting participants with either a pair of control-conferring or control-relinquishing options. This implied that when participants had to consider their preference for control in a reward-seeking decision, they ascribed a 3-point reward value to the option conferring control. Collectively, these findings hint at a positively-reinforcing cycle where a controllable environment triggers positive affect in an organism and the subsequent detection of control motivates the organism to perform more control-seeking behaviors.

5.2 Perceived Control has Protective Effects

In an aversive setting, the ability to avoid or escape the aversive stimuli is paramount to preventing the organism from succumbing to behavioral passivity. Previous studies using paradigms such as learned helplessness and forced swim tests have reported that controllable stressors protected animals from the negative effects associated with an otherwise aversive environment (Lucas et al 2014, Seligman et al 1979, Seligman et al 1975). We similarly found in aim 3 that the non-stress group showed a significant increase in their behavioral responses to controllable aversive stimuli. Put differently, participants were willing to exert greater physical effort to gain control over the aversive stimuli when they sensed that the environment was controllable. This observation supports prior work showing that organisms worked harder both physically and cognitively when the environment was perceived as controllable compared to uncontrollable (Bandura & Wood 1989, Hiroto & Seligman 1975, Mineka & Hendersen 1985).

On the other hand, when the organism perceives the surrounding environment as uncontrollable, such as the presence of an inescapable shock,

the organism is susceptible to becoming behaviorally passive with little interest and motivation in trying to perform actions to avoid or escape from the stimulus (Havranek et al 2016, Kim et al 2017, Mineka & Kihlstrom 1978, Pryce et al 2012). This was indeed what we saw in aim 2 where participants who were subjected to persistent uncontrollability in an aversive context showed progressively fewer avoidance behaviors, even when novel cues were introduced. Specifically, after prolonged exposure to uncontrollable aversive stimuli, participants were no longer inclined to exert cognitive effort to try and learn to avoid the aversive stimuli but rather biased towards the less cognitively-demanding GIVE-UP button to voluntarily receive the aversive stimuli. Because this behavioral change occurred even after the aversive stimuli were paired with a novel cue, we interpreted this to indicate that participants were behaviorally passive and entering a learned helpless state. However, when controllability was introduced into the aversive environment with a novel cue, participants showed a dramatic behavioral reversal and the reinstatement of avoidance behavior. Participants regained the vigor to exert cognitive effort to learn to avoid the aversive stimuli when they detected control in the environment. Their avoidance behavior under the controllable context returned to a level on par with what they exhibited at the beginning of the experiment.

Combining the findings in aims 2 and 3, we can make two inferences. First, participants were inherently biased towards seeking and exerting control in the environment and this appears to be true even after exposure to persistent uncontrollability. In other words, the default behavior, at least in healthy

individuals, is to perceive the environment as controllable and make an effort to exercise control. In the case of aims 2 and 3, the effort was associated with the energy expenditure when participants exerted cognitive and behavioral efforts to try and control the stimuli. We also similarly observed in aim 1 that participants biased towards the control-conferring option even at a cost in terms of monetary reward.

Second, perceiving control in the environment lowers participants' motivational threshold, or alternatively increases their motivational drive, associated with exerting effort to control the environment. In aim 2, when participants were subjected to prolonged uncontrollability, we can argue that what changed was not their subjective value of control in the context, but rather the motivation to exert effort or the amount of cost they were willing to incur to try and influence the environment in their favor. The more times they failed at trying to gain control over the environment, or otherwise received negative feedback, the higher the threshold or cost for their next behavioral attempt to exercise control. When participants sensed control in the environment, the perceived controllability effectively reduced the threshold associated with participants' motivation to perform actions and so the cost for behavioral responses was lowered. Indeed, in both aims 2 and 3, participants showed that when they sensed control in the environment, they were willing to consistently exert more effort to exercise control. The reinforcing nature of control lowers the cost associated with the effort to maintain control and strengthens the motivational drive to perform control-seeking behaviors (Ly et al 2019).

Both of these inferences relate to what White (1959) called “effectance motivation” and what Bandura (1977) termed “self-efficacy”. Both concepts are rooted in the observation that organisms inherently have a need to influence our environment to our advantage via our own behaviors. And so perceiving control feeds into the idea that we inherently believe that our own actions have a cause-and-effect relationship with external outcomes. The perception of control becomes reinforcing where the more we sense control in the environment, the more motivated we are to exercise that control, which becomes a positive feedback loop where perceiving control begets more control-seeking actions. And the opposite is also true where the lack of control (i.e., uncontrollability) begets fewer control-seeking actions. The lower the sense of control we feel in the environment, the lower the motivation we have and the fewer actions we perform to do something about the environment.

5.3 The Role of the Striatum and vmPFC in Mediating Perceived Control

Previous research has implicated both the striatum and the vmPFC as key regions in the neural circuitry subserving perceived control. For example, the striatum was found to be involved in mediating the positive affect generated by cues associated with choice compared to no-choice (Fujiwara et al 2013, Leotti & Delgado 2011). Likewise, in aim 1, we found that in the baseline condition, the *controllable* condition compared to the *uncontrollable* condition generated striatal activity. The essential difference between the two contexts was that the controllable context always gave participants agency over the game whereas the uncontrollable context never did. Although there were no behavioral differences

between the two contexts, we argue that participants still found the controllable context to be more enjoyable because perceiving control is a reward in and of itself. This assumption was supported by the observation that the striatum was recruited for the controllable context. This is in line with previous animal work showing that dopamine transmission from ventral tegmental area into the NAcc (i.e., ventral striatum) is increased when rodents are placed in a controllable compared to uncontrollable environment (Cabib & Puglisi-Allegra 2012). Just placing the participants in a controllable environment can be rewarding irrespective of whether there are any other tangible differences between the two environments. Notably, this affective signal in the striatum was related to participants' inherent general perception of control (i.e., their locus of control). In short, control has affective properties that induce people to prefer and be attracted to an environment that confers the perception of control.

It is important to highlight that control carries affective properties as long as it is subjectively perceived, regardless of whether there is objective control (i.e., behavioral contingency between action and outcome). The perception of control alone is sufficient to generate positive affect without the need for objective control to actually exist. Perhaps more revealing, even if there is objective control, if the organism does not perceive so, the protective effects and positive affect associated with control will not manifest. This is perhaps most recognizable in patients suffering from post-traumatic stress disorder where because the trauma that the patient suffered through was deemed uncontrollable, this facilitates an generalized assessment that all future negative events are

uncontrollable with no regards to their actual controllability (Frazier et al 2001). On the flip side, the perception of control, rather than objective control, is so powerful to the extent that people are able to perceive control when objectively none exist. This phenomenon is termed the “illusion of control” and can help to explain why people often attribute purely chance events to their own undertakings (Langer 1975, Langer & Roth 1975). The most telling example is when gamblers believe that their success at the slot machine is a result of how they pulled the lever when in actuality, it is a complete pull of luck.

If control carries affective properties, it ought to be able to generate approach behavior and bias an organism towards performing control-seeking actions. We recapitulate our point in the previous section, control is behaviorally motivating and an organism will put in the effort, or take on a cost, to be able to perceive and exert control. This is indeed what we found in the mixed condition in aim 1 where we showed that participants showed a significant behavioral bias towards the control-conferring option at the expense of sometimes taking on a cost (i.e., choosing the option with the lower reward expected value) to have control. In other words, control carries a subjective value that has decisional consequences. This subjective value is dependent on both the organism making the decision and the context that the organism is placed in. An organism might ascribe a greater subjective value to having control in one context vs another while two organisms might attribute different subjective values to having control within the same context. This suggests both how malleable our perception of

control is as well as the individual differences associated with the behavioral effects of perceived control.

We tapped into this individual difference in the mixed condition of aim 1 where we derived the POE measure as a correlate for participants' subjective value of control. We argue that this POE measure represented how much weight perceived control contributed to participants' reward-seeking decisions. If control was very important to individuals, they would yield a higher POE, which translated into being willing to take on a higher cost (in terms of reward expected value) to retain and exercise control. On the other hand, if control mattered little to individuals or was even shunned, then they would generate a near zero or even negative POE and thus be unwilling to incur a cost to have control. As such, the POE measure allowed us to compute the subjective value that perceived control carried in terms of the expected value of the reward. The POE measure operated on two premises: one, participants have to be able to dissociate the two choices as one that conferred control and the other that relinquished control; two, participants' choice patterns revealed their choice preference between the pair of options. In other words, the neural regions underlying the POE measure has to both be involved in the detection of control as well as subserve the affective properties of control (to bias participants' choices). Our finding that the vmPFC tracked the POE measure fits this bill because a) vmPFC is activated when an organism perceived controllability in the environment (Amat et al 2005, Christianson et al 2009, Maier et al 2006); b) vmPFC is implicated in value-based

decision making where it is a cortical hub involved in encoding affective value for many types of rewarding stimuli (Chib et al 2009).

In addition to linking the vmPFC to the subjective value of control, we also found that this same region was involved in mediating participants' behavioral changes due to the presence of control in the environment. Behaviorally, participants were shown to substantially increased their behavior responses when they detected that the environment is controllable. This increase in behavior correlated with activity in the vmPFC, suggesting that vmPFC was not only important in encoding the affective value of control but also in facilitating the behavioral changes brought on by the presence of control. Prior work in animals provided a plausible mechanistic explanation for our vmPFC finding where under controllable conditions, the vmPFC sends downstream projections to the DRN to suppress serotonin release and quench behavioral passivity and anxiety (Amat et al 2005, Maier & Watkins 2005).

5.4 Proposed candidates for the neural circuit of perceived control

Taken altogether, we can conclude that perceived control has affective and rewarding underpinnings that recruit the striatum and vmPFC and more importantly, the subjective valuation of control and its consequential behavioral effects are encoded in the vmPFC. Although we show that the corticostriatal circuitry mediates perceived control, there remain gaps in our understanding of the neural mechanism subserving perceived control. Within the neural circuit for perceived control, the striatum and vmPFC ought to exhibit functional connectivity based on previous and our current findings. If so, how are they connected? We conjecture that their functional connectivity is an indirect one that

is mediated by other neural regions. Several main candidates come to mind. First, the DRN is one possible player because it has been implicated as a key recipient of efferent projections from the vmPFC during the detection of control (Maier & Watkins 2005, Maswood et al 1998). Prior work has reported that the stimulation of DRN 5-HT can inhibit dopaminergic transmission in the striatum (De Deurwaerdère & Spampinato 1999, Gervais & Rouillard 2000, Tao & Auerbach 1995, Trent & Tepper 1991). Therefore, it is conceivable that vmPFC projects to the DRN to inhibit 5-HT transmission, which in turn prevents a potential suppression on dopaminergic activity in the striatum, thereby allowing the striatum to play its part in mediating the affective properties of perceived control.

Second, the amygdala is another probable player because of its role in both appetitive and aversive reinforcement (for review see Cunningham & Brosch 2012, Morrison & Salzman 2010, Moscarello & LeDoux 2013). In particular, 5-HT activity in the amygdala, presumably driven by the DRN, is increased only after exposure to uncontrollability but not controllability (Christianson et al 2010, Maswood et al 1998). We corroborated this by observing, in aim 2, that the amygdala is only activated during the uncontrollable but not the controllable context. In relation to uncontrollability, it has been shown that the vmPFC sends projections to the amygdala to suppress conditioned fear responses such as anxiety and behavioral passivity (Milad et al 2004, Quirk et al 2003, Rosenkranz et al 2003). Furthermore, the basolateral amygdala is reported to potentiate dopaminergic activity in the NAcc during reward-seeking behaviors (Ambroggi et

al 2008, Brog et al 1993, Cardinal et al 2002, Stuber et al 2011, Wright et al 1996). Considering all of these findings, it is hypothesized that the vmPFC and striatum could be connected indirectly via the amygdala. While in a controllable environment, the vmPFC could be inhibiting the amygdala while the basolateral amygdala is potentiating the NAcc and together, these regions form a neural circuit to mediate the emotional and behavioral effects of perceived control.

Third, the anterior cingulate cortex (ACC) could be yet another player in the neural circuitry mediating control. According to the expected value of control theory (Shenhav et al 2013), the ACC is important in integrating both the reward and cost associated with control, both are which are governed by regions such as the ventral PFC and striatum (Shenhav et al 2016a, Shenhav et al 2016b). In view of our finding that the ACC was activated, alongside the striatum, in the controllable baseline condition, it is plausible that the ACC integrates the reward signal from the striatum and the subjective value (i.e., cost) signal from the vmPFC into a higher-level signal to govern action selection and behavioral responses.

5.5 Experimental Limitations

The series of experiments presented here collectively bear out a few key limitations that could constrain our general interpretations. First, one's perception of control is a highly malleable trait that both subjective and context-dependent. As such, our interrogation of perceived control was similarly conducted in a very specific context (e.g., within framework of a monetary-based task in aim 1 and within an aversive setting generated by presentation of high-pitch tones in aim 2) on a selected group of individuals. Therefore, to fully appreciate our findings, we

needed to pay close attention to the individual differences so as to detect nuances that could help further our understanding of both the behavioral and neural basis of perceived control. For example, we attempted to do so in both aims 1 and 2 in terms of behavioral measures such as POE and avoidance changes and relating them to neural activity. Nonetheless, our experimental measures are quite restricted to the task framework and its widespread applicability remains to be investigated and explored in more studies and varying populations.

Second, in relation to the aforementioned limitation, both our aims 1 and 2 (despite attaining the sample size of typical neuroimaging experiments and sufficient statistical power) suffer from a relatively small sample size for generalizable interpretations on individual differences (Gignac & Szodorai 2016, Marszalek et al 2011). One way to partially overcome this was to, for instance, pool together participants from all three aims who underwent the VoC task and make more generalized conclusions on participants POE measures. Although this would satisfy our immediate desire for answers, this type of analysis would inherently be flawed because of the subtle contextual differences in how each VoC task was implemented and we do not yet know how these factors influence the POE measure. Therefore, the replication of our work in a larger population is necessary to not only lend support to our current finding but also to probe deeper into potential driving forces for the POE measure.

Third, with regards to the neuroimaging data, our current analysis method only allowed us to make inferences on the neural basis of perceived control

based on the comparison of neural activation between experimental contrasts. This method has its inherent limitations where we can only map brain regions to task states without the ability to infer functional relationships between these regions. With some important experimental-redesigning such as randomizing all trial types within the same run and considering using ascending or descending slice acquisition order (Kiebel et al 2007, Stephan et al 2010), it is possible to leverage analytical tools such as dynamic causal modeling (Friston et al 2003) to help probe more deeply into the connectivity between brain regions. It would be interesting, for example, to examine whether the ACC serves as a functional hub mediating the relationship between vmPFC and NAcc. This type of analysis would shed light on not only the neural correlates for perceived control, but also the effective connectivity between these neural hubs during different task states.

5.6 Remaining questions and future directions

In addition to the uncertainties surrounding the neural circuitry for control, there remain several questions regarding the behavioral implications of control to be explored in future experiments. We share a couple of them here. First, we showed that participants ascribed a subjective value to perceiving control. Under what contextual factors could this subjective value be altered? Because the value of perceived control is subjective, it ought to be adaptable to both internal and external factors. One such external factor that comes to mind is the framing of the context in which control is presented. The framing effect is a well-recognized cognitive bias that powerfully influences people's decisions and choices (Tversky & Kahneman 1981) and within the realm of value-based decision making, our subjective value is remarkably susceptible to changes depending on contextual

framing (Kahneman & Frederick 2007, Kühberger 1998). Therefore, it would be of interest to examine whether participants' choice behavior in the *Value of Control* task is lowered when the game is presented as a potential loss compared to a potential gain.

Second, again with regards to the subjective value of control, it would be worthwhile to probe the subjective value of control in patient populations in addition to healthy individuals. The loss or lack of control is reported as a core symptom across a diverse spectrum of psychopathologies from addiction (Belin et al 2013) to depression (Ang & Pizzagalli 2019) to post-traumatic stress disorder (Larsen & Fitzgerald 2011) to Parkinson's disease (Walihagen et al 1997). As such, it is likely that patient populations would reveal a lower POE measure and a correspondingly dampened vmPFC. This would not only contribute to the development of promising behavioral assessment tools but also advance our understanding of the neural underpinnings for a common disease link. Besides patient populations, another equally important population to study is older adults. It is likely that our subjective value of control is adaptive as we age due to growing life experiences and shifting priorities (Aldwin 1991, Lachman 1986). Given that health decline and lower living independence could be potential byproducts of aging, it is possible that older participants would attribute a greater subjective value to perceived control as other aspects of their lives change.

In summary, we presented a series of experiments examining both the behavioral effects and neural underpinning of perceived control. First, we found that perceived control carries a subjective value that induces a preference for

having control. This subjective value of control is vulnerable to the organism's pre-existing stress state where exposure to acute stress can reduce its subjective value. Neurally, the desire for control triggers affective signals in the striatum that relate to the individual's inherent locus of control. The desire for control translated into a subjective value that is encoded in the vmPFC. Next, we observed that being in an uncontrollable and aversive environment makes an individual susceptible to behavioral passivity, which was associated with activation in brain regions such as the insula, caudate and amygdala. Importantly, the introduction of control into the aversive environment rescued participants' avoidance behavior, highlighting the protective effects conferred by perceived control. This increase in behavioral responses when control was detected in the aversive environment was driven by vmPFC activity. In short, perceived control confers both affective value and protective effects that recruit the corticostriatal circuitry.

References

Abrams JK, Johnson PL, Hollis JH, Lowry CA. 2004. Anatomic and functional topography of the dorsal raphe nucleus. *Annals of the New York Academy of Sciences* 1018: 46-57

Abramson LY, Seligman ME, Teasdale JD. 1978. Learned helplessness in humans: Critique and reformulation. *Journal of abnormal psychology* 87: 49

Ajzen I. 1991. The theory of planned behavior. *Organizational behavior and human decision processes* 50: 179-211

Ajzen I, Madden TJ. 1986. Prediction of goal-directed behavior: Attitudes, intentions, and perceived behavioral control. *Journal of experimental social psychology* 22: 453-74

Akkal D, Bioulac B, Audin J, Burbaud P. 2002. Comparison of neuronal activity in the rostral supplementary and cingulate motor areas during a task with cognitive and motor demands. *European Journal of Neuroscience* 15: 887-904

Aldwin CM. 1991. Does age affect the stress and coping process? Implications of age differences in perceived control. *Journal of gerontology* 46: P174-P80

Alvarez R, Kirlic N, Misaki M, Bodurka J, Rhudy J, et al. 2015. Increased anterior insula activity in anxious individuals is linked to diminished perceived control. *Translational psychiatry* 5: e591

Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature neuroscience* 8: 365-71

Amat J, Christianson JP, Aleksejev RM, Kim J, Richeson KR, et al. 2014. Control over a stressor involves the posterior dorsal striatum and the act/outcome circuit. *European Journal of Neuroscience* 40: 2352-58

Amat J, Matus-Amat P, Watkins LR, Maier SF. 1998. Escapable and inescapable stress differentially alter extracellular levels of 5-HT in the basolateral amygdala of the rat. *Brain research* 812: 113-20

Ambroggi F, Ishikawa A, Fields HL, Nicola SM. 2008. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. *Neuron* 59: 648-61

Andersson JL, Hutton C, Ashburner J, Turner R, Friston K. 2001. Modeling geometric deformations in EPI time series. *NeuroImage* 13: 903-19

Ang Y-S, Pizzagalli DA. 2019. Understanding Personal Control and the Brain Reward System for Psychopathology Is Challenging but Important. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 4: 105-07

Anisman H, Merali Z. 2001. Rodent models of depression: learned helplessness induced in mice. *Current protocols in neuroscience* 14: 8.10 C. 1-8.10 C. 15

Apicella P, Ljungberg T, Scarnati E, Schultz W. 1991. Responses to reward in monkey dorsal and ventral striatum. *Experimental brain research* 85: 491-500

Ardekani BA, Bachman AH. 2009. Model-based automatic detection of the anterior and posterior commissures on MRI scans. *NeuroImage* 46: 677-82

Arnsten AF. 2015. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature neuroscience* 18: 1376-85

Ashburner J. 2012. SPM: a history. *NeuroImage* 62: 791-800

Ashburner J, Friston KJ. 2005. Unified segmentation. *NeuroImage* 26: 839-51

Atlas LY, Doll BB, Li J, Daw ND, Phelps EA. 2016. Instructed knowledge shapes feedback-driven aversive learning in striatum and orbitofrontal cortex, but not the amygdala. *Elife* 5: e15192

Bandura A. 1977. Self-efficacy: toward a unifying theory of behavioral change. *Psychological review* 84: 191

Bandura A. 1982. Self-efficacy mechanism in human agency. *American psychologist* 37: 122

Bandura A. 1997. *Self-efficacy: The exercise of control*. Macmillan.

Bandura A, Wood R. 1989. Effect of perceived controllability and performance standards on self-regulation of complex decision making. *Journal of personality and social psychology* 56: 805

Bargai N, Ben-Shakhar G, Shalev AY. 2007. Posttraumatic stress disorder and depression in battered women: The mediating role of learned helplessness. *Journal of Family Violence* 22: 267-75

Barkley-Levenson E, Galván A. 2014. Neural representation of expected value in the adolescent brain. *Proceedings of the National Academy of Sciences* 111: 1646-51

Bartra O, McGuire JT, Kable JW. 2013. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *NeuroImage* 76: 412-27

Bechara A. 2005. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature neuroscience* 8: 1458-63

Behrens TE, Woolrich MW, Walton ME, Rushworth MF. 2007. Learning the value of information in an uncertain world. *Nature neuroscience* 10: 1214-21

Belin D, Belin-Rauscent A, Murray JE, Everitt BJ. 2013. Addiction: failure of control over maladaptive incentive habits. *Current opinion in neurobiology* 23: 564-72

Benedek M, Kaernbach C. 2010. A continuous measure of phasic electrodermal activity. *Journal of neuroscience methods* 190: 80-91

Berghorst LH, Bogdan R, Frank MJ, Pizzagalli DA. 2013. Acute stress selectively reduces reward sensitivity. *Frontiers in human neuroscience* 7: 133

Berkson J. 1944. Application of the Logistic Function to Bio-Assay. *Journal of the American Statistical Association* 39: 357-65

Berridge KC. 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191: 391-431

Berridge KC. 2012. From prediction error to incentive salience: mesolimbic computation of reward motivation. *European Journal of Neuroscience* 35: 1124-43

Berridge KC, Aldridge JW. 2008. Special review: Decision utility, the brain, and pursuit of hedonic goals. *Social cognition* 26: 621-46

Berridge KC, Robinson TE. 2003. Parsing reward. *Trends in neurosciences* 26: 507-13

Berridge KC, Robinson TE, Aldridge JW. 2009. Dissecting components of reward:'liking','wanting', and learning. *Current opinion in pharmacology* 9: 65-73

Bhanji JP, Kim ES, Delgado MR. 2016. Perceived control alters the effect of acute stress on persistence. *Journal of Experimental Psychology: General* 145: 356

Blascovich J, Tomaka J. 1996. The biopsychosocial model of arousal regulation In *Advances in experimental social psychology*, pp. 1-51: Elsevier

Bobadilla-Suarez S, Sunstein CR, 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: 187-202

Bogdan R, Pizzagalli DA. 2006. Acute stress reduces reward responsiveness: implications for depression. *Biological psychiatry* 60: 1147-54

Bollini AM, Walker EF, 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: 245-60

Bongard S. 1995. Mental effort during active and passive coping: A dual-task analysis. *Psychophysiology* 32: 242-48

Bordia P, Hunt E, Paulsen N, Tourish D, DiFonzo N. 2004. Uncertainty during organizational change: Is it all about control? *European journal of work and organizational psychology* 13: 345-65

Born JM, Lemmens SG, Rutters F, Nieuwenhuizen AG, Formisano E, et al. 2010. Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. *International journal of obesity* 34: 172

Bornhövd K, Quante M, Glauche V, Bromm B, Weiller C, Büchel C. 2002. Painful stimuli evoke different stimulus–response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain* 125: 1326-36

Bown NJ, Read D, Summers B. 2003. The lure of choice. *Journal of Behavioral Decision Making* 16: 297

Boyce P, Parker G, Barnett B, Cooney M, Smith F. 1991. Personality as a vulnerability factor to depression. *The British Journal of Psychiatry* 159: 106-14

Brainard DH. 1997. The Psychophysics Toolbox. *Spat Vis* 10: 433-6

Bräscher A-K, Becker S, Hoeppli M-E, Schweinhardt P. 2016. Different brain circuitries mediating controllable and uncontrollable pain. *Journal of Neuroscience* 36: 5013-25

Brog JS, Salyapongse A, Deutch AY, Zahm DS. 1993. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *Journal of comparative neurology* 338: 255-78

Bryce CA, Floresco SB. 2016. Perturbations in effort-related decision-making driven by acute stress and corticotropin-releasing factor. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 41: 2147

Büchel C, Morris J, Dolan RJ, Friston KJ. 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 20: 947-57

Burger JM, Cooper HM. 1979. The desirability of control. *Motivation and emotion* 3: 381-93

Cabib S, Puglisi-Allegra S. 1994. Opposite responses of mesolimbic dopamine system to controllable and uncontrollable aversive experiences. *Journal of Neuroscience* 14: 3333-40

Cabib S, Puglisi-Allegra S. 2012. The mesoaccumbens dopamine in coping with stress. *Neuroscience & Biobehavioral Reviews* 36: 79-89

Cacioppo JT, Petty RE. 1982. The need for cognition. *Journal of personality and social psychology* 42: 116

Cardinal RN, Parkinson JA, Hall J, Everitt BJ. 2002. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience & Biobehavioral Reviews* 26: 321-52

Caria A, Sitaram R, Veit R, Begliomini C, Birbaumer N. 2010. Volitional control of anterior insula activity modulates the response to aversive stimuli. A real-

time functional magnetic resonance imaging study. *Biological psychiatry* 68: 425-32

Carlsson K, Andersson J, Petrovic P, Petersson KM, Öhman A, Ingvar M. 2006. Predictability modulates the affective and sensory-discriminative neural processing of pain. *NeuroImage* 32: 1804-14

Carp J. 2013. Optimizing the order of operations for movement scrubbing: Comment on Power et al. *NeuroImage* 76: 436-38

Carver CS, White TL. 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *Journal of Personality and Social Psychology* 67: 319-33

Catania AC. 1980. Freedom of choice: A behavioral analysis. *Psychology of Learning and Motivation* 14: 97-145

Catania AC, Sagvolden T. 1980. Preference for free choice over forced choice in pigeons. *Journal of the experimental analysis of behavior* 34: 77-86

Celada P, Puig MV, Casanovas JM, Guillazo G, Artigas F. 2001. Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: involvement of serotonin-1A, GABAA, and glutamate receptors. *Journal of Neuroscience* 21: 9917-29

Chen H, Cohen P, Chen SJCiSS, Computation®. 2010. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. 39: 860-64

Chernev A. 2003. When more is less and less is more: The role of ideal point availability and assortment in consumer choice. *Journal of consumer Research* 30: 170-83

Chernev A. 2006. Decision focus and consumer choice among assortments. *Journal of Consumer Research* 33: 50-59

Chernev A, Böckenholt U, Goodman J. 2015. Choice overload: A conceptual review and meta-analysis. *Journal of Consumer Psychology* 25: 333-58

Chib VS, Rangel A, Shimojo S, O'Doherty JP. 2009. Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. *Journal of Neuroscience* 29: 12315-20

Chioqueta AP, Stiles TC. 2005. Personality traits and the development of depression, hopelessness, and suicide ideation. *Personality and individual differences* 38: 1283-91

Choi J-S, Cain CK, LeDoux JE. 2010. The role of amygdala nuclei in the expression of auditory signaled two-way active avoidance in rats. *Learning & memory* 17: 139-47

Chorpita BF, Barlow DH. 1998. The development of anxiety: the role of control in the early environment. *Psychological bulletin* 124: 3

Christianson JP, Ragole T, Amat J, Greenwood BN, Strong PV, et al. 2010. 5-hydroxytryptamine 2C receptors in the basolateral amygdala are involved in the expression of anxiety after uncontrollable traumatic stress. *Biological psychiatry* 67: 339-45

Christianson JP, Thompson BM, Watkins LR, Maier SF. 2009. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. *Stress* 12: 445-50

Clark L, Watson D. 1995. The mini mood and anxiety symptom questionnaire (Mini-MASQ). *Unpublished manuscript, University of Iowa*

Clark PJ, Ghasem PR, Mika A, Day HE, Herrera JJ, et al. 2014. Wheel running alters patterns of uncontrollable stress-induced cfos mRNA expression in rat dorsal striatum direct and indirect pathways: A possible role for plasticity in adenosine receptors. *Behavioural brain research* 272: 252-63

Cloninger C, Svrakic D, Przybeck T. 1998. A psychobiological model of temperament and character. *The development of psychiatry and its complexity*: 1-16

Cockburn J, Collins AG, Frank MJ. 2014. A reinforcement learning mechanism responsible for the valuation of free choice. *Neuron* 83: 551-57

Cohen J. 1992. A power primer. *Psychological bulletin* 112: 155

Costello CG. 1978. A critical review of Seligman's laboratory experiments on learned helplessness and depression in humans.

Cowdrey FA, Park RJ, Harmer CJ, McCabe C. 2011. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. *Biological psychiatry* 70: 736-43

Cunningham WA, Brosch T. 2012. Motivational salience: Amygdala tuning from traits, needs, values, and goals. *Current Directions in Psychological Science* 21: 54-59

Davidson R, MacKinnon JG. 2004. *Econometric theory and methods*. Oxford University Press New York.

De Deurwaerdère P, Spampinato U. 1999. Role of serotonin2A and serotonin2B/2C receptor subtypes in the control of accumbal and striatal dopamine release elicited in vivo by dorsal raphe nucleus electrical stimulation. *Journal of neurochemistry* 73: 1033-42

Deci EL, Ryan RM. 1987. The support of autonomy and the control of behavior. *Journal of personality and social psychology* 53: 1024

Delgado M, Beer J, Fellows L, Huettel S, Platt M, et al. 2016. Viewpoints: Dialogues on the functional role of the ventromedial prefrontal cortex. *Nature neuroscience* 19: 1545-52

Delgado MR. 2007. Reward-Related Responses in the Human Striatum. *Annals of the New York Academy of Sciences* 1104: 70-88

Delgado MR, Jou RL, LeDoux JE, Phelps EA. 2009. Avoiding negative outcomes: tracking the mechanisms of avoidance learning in humans during fear conditioning. *Frontiers in Behavioral Neuroscience* 3

Delgado MR, Nearing KI, LeDoux JE, Phelps EA. 2008. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron* 59: 829-38

Delgado MR, Nystrom LE, Fissell C, Noll D, Fiez JA. 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of neurophysiology* 84: 3072-77

Dembroski TM, MacDougall JM, Musante L. 1984. Desirability of control versus locus of control: Relationship to paralinguistics in the Type A interview. *Health Psychology* 3: 15

Diekhof EK, Kaps L, Falkai P, Gruber O. 2012. The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude – An activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. *Neuropsychologia* 50: 1252-66

Drach-Zahavy A, Erez M. 2002. Challenge versus threat effects on the goal–performance relationship. *Organizational Behavior and Human Decision Processes* 88: 667-82

Duckworth AL, Peterson C, Matthews MD, Kelly DR. 2007. Grit: perseverance and passion for long-term goals. *Journal of personality and social psychology* 92: 1087

Dunn OJ. 1964. Multiple comparisons using rank sums. *Technometrics* 6: 241-52

Duvarci S, Pare D. 2014. Amygdala microcircuits controlling learned fear. *Neuron* 82: 966-80

Eliaz K, Schotter A. 2010. Paying for confidence: An experimental study of the demand for non-instrumental information. *Games and Economic Behavior* 70: 304-24

Etkin A, Wager TD. 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* 164: 1476-88

Everitt BJ, Robbins TW. 2016. Drug addiction: updating actions to habits to compulsions ten years on. *Annual review of psychology* 67: 23-50

Faul F, Erdfelder E, Lang A-G, Buchner A. 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods* 39: 175-91

Feather N, Volkmer R. 1988. Preference for situations involving effort, time pressure, and feedback in relation to Type A behavior, locus of control, and test anxiety. *Journal of Personality and Social Psychology* 55: 266

Foley P, Kirschbaum C. 2010. Human hypothalamus–pituitary–adrenal axis responses to acute psychosocial stress in laboratory settings. *Neuroscience & Biobehavioral Reviews* 35: 91-96

Fosco E, Geer JH. 1971. Effects of gaining control over aversive stimuli after differing amounts of no control. *Psychological Reports* 29: 1153-54

Frankenhaeuser M. 1986. A psychobiological framework for research on human stress and coping In *Dynamics of stress*, pp. 101-16: Springer

Frazier P, Berman M, Steward J. 2001. Perceived control and posttraumatic stress: A temporal model. *Applied and Preventive Psychology* 10: 207-23

Frazier P, Steward J, Mortensen H. 2004. Perceived control and adjustment to trauma: A comparison across events. *Journal of Social and Clinical Psychology* 23: 303

Friston KJ, Harrison L, Penny W. 2003. Dynamic causal modelling. *NeuroImage* 19: 1273-302

Fujiwara J, Usui N, Park SQ, Williams T, Iijima T, et al. 2013. Value of freedom to choose encoded by the human brain. *Journal of neurophysiology* 110: 1915-29

Gabbott PL, Warner TA, Jays PR, Salway P, Busby SJ. 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *Journal of Comparative Neurology* 492: 145-77

Gallagher MW, Bentley KH, Barlow DH. 2014. Perceived control and vulnerability to anxiety disorders: A meta-analytic review. *Cognitive Therapy and Research* 38: 571-84

Gatchel RJ, Proctor JD. 1976. Physiological correlates of learned helplessness in man. *Journal of Abnormal Psychology* 85: 27

Gervais J, Rouillard C. 2000. Dorsal raphe stimulation differentially modulates dopaminergic neurons in the ventral tegmental area and substantia nigra. *Synapse* 35: 281-91

Gignac GE, Szodorai ET. 2016. Effect size guidelines for individual differences researchers. *Personality and individual differences* 102: 74-78

Gladstone G, Parker G. 2005. Measuring a behaviorally inhibited temperament style: development and initial validation of new self-report measures. *Psychiatry Research* 135: 133-43

Glass D, McKnight J. 1996. Perceived control, depressive symptomatology, and professional burnout: A review of the evidence. *Psychology and health* 11: 23-48

Glass DC, Singer JE. 1972. Urban stress: Experiments on noise and social stressors.

Goette L, Bendahan S, Thoresen J, Hollis F, Sandi C. 2015. Stress pulls us apart: Anxiety leads to differences in competitive confidence under stress. *Psychoneuroendocrinology* 54: 115-23

Gorgolewski KJ, Varoquaux G, Rivera G, Schwarz Y, Ghosh SS, et al. 2015. NeuroVault. org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. *Frontiers in neuroinformatics* 9: 8

Grabenhorst F, Rolls ET. 2011. Value, pleasure and choice in the ventral prefrontal cortex. *Trends in cognitive sciences* 15: 56-67

Grahn RE, Will MJ, Hammack SE, Maswood S, McQueen MB, et al. 1999. Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. *Brain research* 826: 35-43

Greenwood BN, Foley TE, Day HE, Campisi J, Hammack SH, et al. 2003. Freewheel running prevents learned helplessness/behavioral depression: role of dorsal raphe serotonergic neurons. *Journal of Neuroscience* 23: 2889-98

Grillon C, Duncko R, Covington MF, Kopperman L, Kling MA. 2007. Acute stress potentiates anxiety in humans. *Biological psychiatry* 62: 1183-86

Grillon C, Lissek S, Rabin S, McDowell D, Dvir S, Pine DS. 2008. Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder. *American Journal of Psychiatry* 165: 898-904

Grote NK, Bledsoe SE, Larkin J, Lemay Jr EP, Brown C. 2007. Stress exposure and depression in disadvantaged women: The protective effects of optimism and perceived control. *Social Work Research* 31: 19-33

Haber SN. 2016. Corticostriatal circuitry. *Dialogues Clin Neurosci* 18: 7-21

Haber SN, Knutson B. 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 35: 4-26

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: 271-80

Hajós M, Richards C, Székely AD, Sharp T. 1998. An electrophysiological and neuroanatomical study of the medial prefrontal cortical projection to the midbrain raphe nuclei in the rat. *Neuroscience* 87: 95-108

Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, et al. 2015. Mesolimbic dopamine signals the value of work. *Nature neuroscience* 19: 117

Hammen C. 2005. Stress and depression. *Annu. Rev. Clin. Psychol.* 1: 293-319

Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A. 2008. Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. *The Journal of Neuroscience* 28: 5623-30

Hartley CA, Gorun A, Reddan MC, Ramirez F, Phelps EA. 2014. Stressor controllability modulates fear extinction in humans. *Neurobiology of learning and memory* 113: 149-56

Hashimoto H, Fukuhara S. 2004. The influence of locus of control on preferences for information and decision making. *Patient education and counseling* 55: 236-40

Havranek MM, Bolliger B, Roos S, Pryce CR, Quednow BB, Seifritz E. 2016. Uncontrollable and unpredictable stress interacts with subclinical depression and anxiety scores in determining anxiety response. *Stress* 19: 53-62

Hayes DJ, Duncan NW, Xu J, Northoff G. 2014. A comparison of neural responses to appetitive and aversive stimuli in humans and other mammals. *Neuroscience & Biobehavioral Reviews* 45: 350-68

Hayes SC, Kapust J, Leonard SR, Rosenfarb I. 1981. Escape from freedom: Choosing not to choose in pigeons. *Journal of the Experimental Analysis of Behavior* 36: 1-7

Hellhammer DH, Wüst S, Kudielka BM. 2009. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology* 34: 163-71

Hiroto DS. 1974. Locus of control and learned helplessness. *Journal of experimental psychology* 102: 187

Hiroto DS, Seligman ME. 1975. Generality of learned helplessness in man. *Journal of personality and social psychology* 31: 311

Hoffstaedter F, Grefkes C, Zilles K, Eickhoff SB. 2012. The “what” and “when” of self-initiated movements. *Cerebral cortex* 23: 520-30

Holmes DS, Jackson TH. 1975. Influence of locus of control on interpersonal attraction and affective reactions in situations involving reward and punishment. *Journal of personality and social psychology* 31: 132

Hutton C, Bork A, Josephs O, Deichmann R, Ashburner J, Turner R. 2002. Image distortion correction in fMRI: a quantitative evaluation. *NeuroImage* 16: 217-40

Hyman JM, Holroyd CB, Seamans JK. 2017. A novel neural prediction error found in anterior cingulate cortex ensembles. *Neuron* 95: 447-56. e3

Ikemoto S, Yang C, Tan A. 2015. Basal ganglia circuit loops, dopamine and motivation: A review and enquiry. *Behav Brain Res* 290: 17-31

Iyengar SS, Lepper MR. 2000. When choice is demotivating: Can one desire too much of a good thing? *Journal of Personality and Social Psychology* 79: 995-1006

Jankowski MP, Sesack SR. 2004. Prefrontal cortical projections to the rat dorsal raphe nucleus: Ultrastructural features and associations with serotonin and γ-aminobutyric acid neurons. *Journal of Comparative Neurology* 468: 518-29

Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S. 2003. Direct activation of the ventral striatum in anticipation of aversive stimuli. *Neuron* 40: 1251-57

Jerusalem M, Schwarzer R. 1992. Self-efficacy as a resource factor in stress appraisal processes. *Self-efficacy: Thought control of action* 195213

Jocham G, Klein TA, Ullsperger M. 2011. Dopamine-mediated reinforcement learning signals in the striatum and ventromedial prefrontal cortex underlie value-based choices. *Journal of Neuroscience* 31: 1606-13

Joe VC. 1971. Review of the internal-external control construct as a personality variable. *Psychological reports* 28: 619-40

Kahneman D, Frederick S. 2007. Frames and brains: Elicitation and control of response tendencies. *Trends in cognitive sciences* 11: 45-46

Karenbach C. 2005. Ledalab-a software package for the analysis of phasic electrodermal activity. *Internal report, Allgemeine Psychologie, Institut für Psychologie, Institut ftir Psychologie, Tech. Rep.*

Keinan G. 1987. Decision making under stress: Scanning of alternatives under controllable and uncontrollable threats. *Journal of personality and social psychology* 52: 639

Kendler KS, Gatz M, Gardner CO, Pedersen NL. 2006. Personality and major depression: a Swedish longitudinal, population-based twin study. *Archives of general psychiatry* 63: 1113-20

Kennerley SW, Behrens TE, Wallis JD. 2011. Double dissociation of value computations in orbitofrontal and anterior cingulate neurons. *Nature neuroscience* 14: 1581

Kiebel SJ, Klöppel S, Weiskopf N, Friston KJ. 2007. Dynamic causal modeling: a generative model of slice timing in fMRI. *NeuroImage* 34: 1487-96

Kienast T, Hariri AR, Schlagenhauf F, Wrase J, Sterzer P, et al. 2008. Dopamine in amygdala gates limbic processing of aversive stimuli in humans. *Nature neuroscience* 11: 1381

Kim JY, Yang SH, Kwon J, Lee HW, Kim H. 2017. Mice subjected to uncontrollable electric shocks show depression-like behaviors irrespective of their state of helplessness. *Behavioural brain research* 322: 138-44

Kimura K, Izawa S, Sugaya N, Ogawa N, Yamada KC, et al. 2013. The biological effects of acute psychosocial stress on delay discounting. *Psychoneuroendocrinology* 38: 2300-08

Kinner VL, Wolf OT, Merz CJ. 2016. Cortisol alters reward processing in the human brain. *Hormones and behavior* 84: 75-83

Knutson B, Taylor J, Kaufman M, Peterson R, Glover G. 2005. Distributed neural representation of expected value. *The Journal of Neuroscience* 25: 4806-12

Kolling N, Wittmann MK, Behrens TE, Boorman ED, Mars RB, Rushworth MF. 2016. Value, search, persistence and model updating in anterior cingulate cortex. *Nature neuroscience* 19: 1280

Koob GF, Volkow ND. 2016. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry* 3: 760-73

Krypotos A-M, Effting M, Kindt M, Beckers T. 2015. Avoidance learning: a review of theoretical models and recent developments. *Frontiers in Behavioral Neuroscience* 9: 189

Kühberger A. 1998. The influence of framing on risky decisions: A meta-analysis. *Organizational behavior and human decision processes* 75: 23-55

Lachman ME. 1986. Locus of control in aging research: A case for multidimensional and domain-specific assessment. *Psychology and aging* 1: 34

Langer EJ. 1975. The illusion of control. *Journal of personality and social psychology* 32: 311

Langer EJ, Rodin J. 1976. The effects of choice and enhanced personal responsibility for the aged: a field experiment in an institutional setting. *Journal of personality and social psychology* 34: 191

Langer EJ, Roth J. 1975. Heads I win, tails it's chance: The illusion of control as a function of the sequence of outcomes in a purely chance task. *Journal of personality and social psychology* 32: 951

Larsen SE, Fitzgerald LF. 2011. PTSD symptoms and sexual harassment: The role of attributions and perceived control. *Journal of Interpersonal Violence* 26: 2555-67

Le Fevre M, Matheny J, Kolt GS. 2003. Eustress, distress, and interpretation in occupational stress. *Journal of managerial psychology* 18: 726-44

Lefcourt HM. 2014. *Locus of control: Current trends in theory & research*. Psychology Press.

Lempert KM, Porcelli AJ, Delgado MR, Tricomi E. 2012. Individual differences in delay discounting under acute stress: the role of trait perceived stress. *Frontiers in psychology* 3: 251

Leotti LA, Delgado MR. 2011. The inherent reward of choice. *Psychological science* 22: 1310-18

Leotti LA, Delgado MR. 2014. The value of exercising control over monetary gains and losses. *Psychological science* 25: 596-604

Leotti LA, Iyengar SS, Ochsner KN. 2010. Born to choose: The origins and value of the need for control. *Trends in cognitive sciences* 14: 457-63

Levy DJ, Glimcher PW. 2012. The root of all value: a neural common currency for choice. *Current opinion in neurobiology* 22: 1027-38

Lewis AH, Porcelli AJ, Delgado MR. 2014. The effects of acute stress exposure on striatal activity during Pavlovian conditioning with monetary gains and losses. *Frontiers in behavioral neuroscience* 8: 179

Li B, Piriz J, Mirrione M, Chung C, Proulx CD, et al. 2011. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. *Nature* 470: 535

Lieberman MD, Cunningham WA. 2009. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Social cognitive and affective neuroscience* 4: 423-28

Lieberman MD, Ochsner KN, Gilbert DT, Schacter DL. 2001. Do amnesics exhibit cognitive dissonance reduction? The role of explicit memory and attention in attitude change. *Psychological science* 12: 135-40

Lipsey MW. 1990. *Design sensitivity: Statistical power for experimental research*. Sage.

Lubow RE, Rosenblatt R, Weiner I. 1981. Confounding of controllability in the triadic design for demonstrating learned helplessness. *Journal of Personality and Social Psychology* 41: 458

Lucas GM, Gratch J, Cheng L, Marsella S. 2015. When the going gets tough: Grit predicts costly perseverance. *Journal of Research in Personality* 59: 15-22

Lucas M, Ilin Y, Anunu R, Kehat O, Xu L, et al. 2014. Long-term effects of controllability or the lack of it on coping abilities and stress resilience in the rat. *Stress* 17: 423-30

Lutz A, McFarlin DR, Perlman DM, Salomons TV, Davidson RJ. 2013. Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage* 64: 538-46

Ly V, Wang KS, Bhanji J, Delgado MR. 2019. A Reward-Based Framework of Perceived Control. *Frontiers in neuroscience* 13: 65-65

Mackey S, Petrides M. 2014. Architecture and morphology of the human ventromedial prefrontal cortex. *European Journal of Neuroscience* 40: 2777-96

Maier SF, Amal J, Baratta MV, Paul E, Watkins LR. 2006. Behavioral control, the medial prefrontal cortex, and resilience. *Dialogues in clinical neuroscience* 8: 397

Maier SF, Grahn RE, Kalman BA, Sutton LC, Wiertelak EP, Watkins LR. 1993. The role of the amygdala and dorsal raphe nucleus in mediating the behavioral consequences of inescapable shock. *Behavioral neuroscience* 107: 377

Maier SF, Grahn RE, Watkins LR. 1995. 8-OH-DPAT microinjected in the region of the dorsal raphe nucleus blocks and reverses the enhancement of fear conditioning and interference with escape produced by exposure to inescapable shock. *Behavioral neuroscience* 109: 404

Maier SF, Ryan SM, Barksdale CM, Kalin NH. 1986. Stressor controllability and the pituitary-adrenal system. *Behavioral neuroscience* 100: 669

Maier SF, Seligman ME. 1976. Learned helplessness: Theory and evidence. *Journal of experimental psychology: general* 105: 3

Maier SF, Seligman ME. 2016. Learned helplessness at fifty: Insights from neuroscience. *Psychological Review* 123: 349

Maier SF, Seligman ME, Solomon RL. 1969. Pavlovian fear conditioning and learned helplessness. *Punishment and aversive behavior. New York: Appleton-Century-Crofts*: 299-342

Maier SF, Watkins LR. 2005. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neuroscience & Biobehavioral Reviews* 29: 829-41

Maier SF, Watkins LR. 2010. Role of the medial prefrontal cortex in coping and resilience. *Brain research* 1355: 52-60

Maier SU, Makwana AB, Hare TA. 2015. Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits. *Neuron* 87: 621-31

Maren S, Holmes A. 2016. Stress and fear extinction. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 41: 58-79

Marszalek JM, Barber C, Kohlhart J, Cooper BH. 2011. Sample size in psychological research over the past 30 years. *Perceptual and motor skills* 112: 331-48

Maswood S, Barter JE, Watkins LR, Maier SF. 1998. Exposure to inescapable but not escapable shock increases extracellular levels of 5-HT in the dorsal raphe nucleus of the rat. *Brain research* 783: 115-20

McClure SM, Laibson DI, Loewenstein G, Cohen JD. 2004. Separate neural systems value immediate and delayed monetary rewards. *Science* 306: 503-07

McDonald A, Mascagni F, Guo L. 1996. Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. *Neuroscience* 71: 55-75

Milad M, Vidal-Gonzalez I, Quirk G. 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behavioral neuroscience* 118: 389

Miller R, Plessow F, Kirschbaum C, Stalder T. 2013. Classification criteria for distinguishing cortisol responders from nonresponders to psychosocial stress: evaluation of salivary cortisol pulse detection in panel designs. *Psychosomatic Medicine* 75: 832-40

Mineka S, Hendersen RW. 1985. Controllability and predictability in acquired motivation. *Annual review of psychology* 36: 495-529

Mineka S, Kihlstrom JF. 1978. Unpredictable and uncontrollable events: a new perspective on experimental neurosis. *Journal of abnormal psychology* 87: 256

Mohr C, Leyendecker S, Helmchen C. 2008. Dissociable neural activity to self-vs. externally administered thermal hyperalgesia: a parametric fMRI study. *European Journal of Neuroscience* 27: 739-49

Morrison SE, Salzman CD. 2010. Re-valuing the amygdala. *Current opinion in neurobiology* 20: 221-30

Moscarello JM, LeDoux JE. 2013. The contribution of the amygdala to aversive and appetitive Pavlovian processes. *Emotion Review* 5: 248-53

Müller MJ. 2012. Will it hurt less if I believe I can control it? Influence of actual and perceived control on perceived pain intensity in healthy male individuals: A randomized controlled study. *Journal of behavioral medicine* 35: 529-37

O'Sullivan G. 2011. The relationship between hope, eustress, self-efficacy, and life satisfaction among undergraduates. *Social indicators research* 101: 155-72

Öngür D, Price J. 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral cortex* 10: 206-19

Owens D, Grossman Z, Fackler R. 2014. The control premium: A preference for payoff autonomy. *American Economic Journal: Microeconomics* 6: 138-61

Padoa-Schioppa C, Assad JA. 2006. Neurons in the orbitofrontal cortex encode economic value. *Nature* 441: 223

Palminteri S, Justo D, Jauffret C, Pavlicek B, Dauta A, et al. 2012. Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. *Neuron* 76: 998-1009

Parker KN, Ragsdale JM. 2015. Effects of distress and eustress on changes in fatigue from waking to working. *Applied Psychology: Health and Well-Being* 7: 293-315

Patrick BC, Skinner EA, Connell JP. 1993. What motivates children's behavior and emotion? Joint effects of perceived control and autonomy in the academic domain. *Journal of Personality and social Psychology* 65: 781

Peters ML, Godaert GL, Ballieux RE, van Vliet M, Willemsen JJ, et al. 1998. Cardiovascular and endocrine responses to experimental stress: effects of mental effort and controllability. *Psychoneuroendocrinology* 23: 1-17

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: 443-68

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, et al. 1997. A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389: 495

Pittenger C, Duman RS. 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 33: 88-109

Porcelli AJ, Delgado MR. 2009. Acute stress modulates risk taking in financial decision making. *Psychological Science* 20: 278-83

Porcelli AJ, Lewis AH, Delgado MR. 2012. Acute stress influences neural circuits of reward processing. *Frontiers in neuroscience* 6: 157

Potts SR, McCuddy WT, Jayan D, Porcelli AJ. 2019. To trust, or not to trust? Individual differences in physiological reactivity predict trust under acute stress. *Psychoneuroendocrinology* 100: 75-84

Power JD, Schlaggar BL, Petersen SE. 2015. Recent progress and outstanding issues in motion correction in resting state fMRI. *NeuroImage* 105: 536-51

Press SJ, Wilson S. 1978. Choosing between Logistic Regression and Discriminant Analysis. *Journal of the American Statistical Association* 73: 699-705

Price CJ, Friston KJ. 1997. Cognitive conjunction: a new approach to brain activation experiments. *NeuroImage* 5: 261-70

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. 2003. Two formulas for computation of the area under the curve represent measures

of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 28: 916-31

Pryce CR, Azzinnari D, Sigrist H, Gschwind T, Lesch K-P, Seifritz E. 2012. Establishing a learned-helplessness effect paradigm in C57BL/6 mice: behavioural evidence for emotional, motivational and cognitive effects of aversive uncontrollability per se. *Neuropharmacology* 62: 358-72

Quaglieri PL. 1980. Locus of control and perceived utility of feedback. *Psychological Reports* 46: 859-62

Quirk GJ, Beer JS. 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Current opinion in neurobiology* 16: 723-27

Quirk GJ, Likhtik E, Pelletier JG, Paré D. 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *Journal of Neuroscience* 23: 8800-07

Ramsey AT, Etcheverry PE. 2013. Aligning task control with desire for control: Implications for performance. *Basic and applied social psychology* 35: 467-76

Rangel A, Camerer C, Montague PR. 2008. A framework for studying the neurobiology of value-based decision making. *Nature reviews. Neuroscience* 9: 545-56

Rangel A, Hare T. 2010. Neural computations associated with goal-directed choice. *Current opinion in neurobiology* 20: 262-70

Ratner RK, Kahn BE. 2002. The impact of private versus public consumption on variety-seeking behavior. *Journal of Consumer Research* 29: 246-57

Rauch SL, Shin LM, Phelps EA. 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biological psychiatry* 60: 376-82

Reed DD, Reed FDD, Chok J, Brozyna GA. 2011. The" tyranny of choice": Choice overload as a possible instance of effort discounting. *The Psychological Record* 61: 547

Reed LJ, Berkson J. 1929. The application of the logistic function to experimental data. *The Journal of Physical Chemistry* 33: 760-79

Robbins TW. 2005. Controlling stress: how the brain protects itself from depression. *Nature neuroscience* 8: 261

Rodin J. 1986. Aging and health: Effects of the sense of control. *Science* 233: 1271-76

Rodin J, Langer EJ. 1977. Long-term effects of a control-relevant intervention with the institutionalized aged. *Journal of personality and social psychology* 35: 897

Rorden C, Karnath H-O, Bonilha L. 2007. Improving lesion-symptom mapping. *Journal of cognitive neuroscience* 19: 1081-88

Rosenkranz JA, Moore H, Grace AA. 2003. The prefrontal cortex regulates lateral amygdala neuronal plasticity and responses to previously conditioned stimuli. *Journal of Neuroscience* 23: 11054-64

Rotter J. 2011. Rotter Internal-External Locus of Control Scale. *28 MEASURES OF LOCUS OF CONTROL* 10

Rotter JB. 1966. Generalized expectancies for internal versus external control of reinforcement. *Psychological monographs: General and applied* 80: 1

Rousselet GA, Pernet CR. 2012. Improving standards in brain-behavior correlation analyses. *Frontiers in human neuroscience* 6: 119

Roy M, Shohamy D, Wager TD. 2012. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends in cognitive sciences* 16: 147-56

Ruff CC, Fehr E. 2014. The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience* 15: 549-62

Rushworth MF, Kolling N, Sallet J, Mars RB. 2012. Valuation and decision-making in frontal cortex: one or many serial or parallel systems? *Current opinion in neurobiology* 22: 946-55

Ryan RM, Deci EL. 2000. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *American psychologist* 55: 68

Saez RA, Saez A, Paton JJ, Lau B, Salzman CD. 2017. Distinct roles for the amygdala and orbitofrontal cortex in representing the relative amount of expected reward. *Neuron* 95: 70-77. e3

Salomons TV, Johnstone T, Backonja M-M, Davidson RJ. 2004. Perceived controllability modulates the neural response to pain. *Journal of Neuroscience* 24: 7199-203

Sanjuán P, Magallares A. 2009. A longitudinal study of the negative explanatory style and attributions of uncontrollability as predictors of depressive symptoms. *Personality and Individual Differences* 46: 714-18

Sapolsky RM. 2015. Stress and the brain: individual variability and the inverted-U. *Nature neuroscience* 18: 1344

Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J, et al. 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *NeuroImage* 64: 240-56

Scarpa A, Luscher KA. 2002. Self-esteem, cortisol reactivity, and depressed mood mediated by perceptions of control. *Biological psychology* 59: 93-103

Scheibehenne B, Greifeneder R, Todd PM. 2009. What moderates the too-much-choice effect? *Psychology & Marketing* 26: 229-53

Scheibehenne B, Greifeneder R, Todd PM. 2010. Can there ever be too many options? A meta-analytic review of choice overload. *Journal of consumer research* 37: 409-25

Schoenbaum G, Setlow B. 2003. Lesions of nucleus accumbens disrupt learning about aversive outcomes. *Journal of Neuroscience* 23: 9833-41

Schoenbaum G, Takahashi Y, Liu TL, McDannald MA. 2011. Does the orbitofrontal cortex signal value? *Annals of the New York Academy of Sciences* 1239: 87-99

Schooler JW, Mauss IB. 2010. To be happy and to know it: The experience and meta-awareness of pleasure. *Pleasures of the brain*: 244-54

Schultz W. 2015. Neuronal Reward and Decision Signals: From Theories to Data. *Physiological reviews* 95: 853-951

Schwabe L, Haddad L, Schachinger H. 2008. HPA axis activation by a socially evaluated cold-pressor test. *Psychoneuroendocrinology* 33: 890-95

Schwabe L, Schächinger H. 2018. Ten years of research with the Socially Evaluated Cold Pressor Test: Data from the past and guidelines for the future. *Psychoneuroendocrinology* 92: 155-61

Schwartz B. 2004. The paradox of choice. Harper Collins New York, NY

Seery MD. 2011. Challenge or threat? Cardiovascular indexes of resilience and vulnerability to potential stress in humans. *Neuroscience & Biobehavioral Reviews* 35: 1603-10

Seligman ME. 1971. Phobias and preparedness. *Behavior therapy* 2: 307-20

Seligman ME. 1974. *Depression and learned helplessness*. John Wiley & Sons.

Seligman ME. 1975. *Helplessness: On depression, development, and death*. WH Freeman/Times Books/Henry Holt & Co.

Seligman ME, Maier SF, Geer J. 1979. Alleviation of learned helplessness in the dog In *Origins of Madness*, pp. 401-09: Elsevier

Seligman ME, Rosellini RA, Kozak MJ. 1975. Learned helplessness in the rat: time course, immunization, and reversibility. *Journal of comparative and physiological psychology* 88: 542

Selye H. 1975. Stress and distress. *Comprehensive therapy* 1: 9-13

Selye H. 1976. Stress without distress In *Psychopathology of human adaptation*, pp. 137-46: Springer

Sethi-Iyengar S, Huberman G, Jiang W. 2004. How much choice is too much? Contributions to 401 (k) retirement plans. *Pension design and structure: New lessons from behavioral finance* 83: 84-87

Seward JP, Humphrey GL. 1967. Avoidance learning as a function of pretraining in the cat. *Journal of Comparative and Physiological Psychology* 63: 338

Shabel SJ, Janak PH. 2009. Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proceedings of the National Academy of Sciences* 106: 15031-36

Shafiei N, Gray M, Viau V, Floresco SB. 2012. Acute stress induces selective alterations in cost/benefit decision-making. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 37: 2194

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. 2003. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* 168: 3-20

Shenhav A, Botvinick Matthew M, Cohen Jonathan D. 2013. The Expected Value of Control: An Integrative Theory of Anterior Cingulate Cortex Function. *Neuron* 79: 217-40

Shenhav A, Cohen JD, Botvinick MM. 2016a. Dorsal anterior cingulate cortex and the value of control. *Nature neuroscience* 19: 1286

Shenhav A, Straccia MA, Botvinick MM, Cohen JD. 2016b. Dorsal anterior cingulate and ventromedial prefrontal cortex have inverse roles in both foraging and economic choice. *Cognitive, Affective, & Behavioral Neuroscience* 16: 1127-39

Shima K, Tanji J. 1998. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282: 1335-38

Shumake J, Gonzalez-Lima F. 2003. Brain systems underlying susceptibility to helplessness and depression. *Behavioral and cognitive neuroscience reviews* 2: 198-221

Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. 2011. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 36: 529-38

Singer T, Critchley HD, Preuschoff K. 2009. A common role of insula in feelings, empathy and uncertainty. *Trends in cognitive sciences* 13: 334-40

Sinha R. 2001. How does stress increase risk of drug abuse and relapse? *Psychopharmacology* 158

Skinner EA. 1995. *Perceived control, motivation, & coping*. Sage Publications.

Skinner EA. 1996. A guide to constructs of control. *Journal of personality and social psychology* 71: 549

Skoluda N, Strahler J, Schlotz W, Niederberger L, Marques S, et al. 2015. Intra-individual psychological and physiological responses to acute laboratory stressors of different intensity. *Psychoneuroendocrinology* 51: 227-36

Smith SM. 2002. Fast robust automated brain extraction. *Human brain mapping* 17: 143-55

Smith SM, Brady JM. 1997. SUSAN—A new approach to low level image processing. *International journal of computer vision* 23: 45-78

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, et al. 2004. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* 23: S208-S19

Smyth JM, Sliwinski MJ, Zawadzki MJ, Scott SB, Conroy DE, et al. 2018. Everyday stress response targets in the science of behavior change. *Behaviour research and therapy* 101: 20-29

Solomon S, Rodin J. 1976. Control-seeking behavior: Are people motivated to attain control. *Unpublished manuscript, Yale University*

Sotres-Bayon F, Bush DE, LeDoux JE. 2004. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. *Learning & memory* 11: 525-35

Stephan KE, Penny WD, Moran RJ, den Ouden HE, Daunizeau J, Friston KJ. 2010. Ten simple rules for dynamic causal modeling. *NeuroImage* 49: 3099-109

Strait CE, Sleezer BJ, Hayden BY. 2015. Signatures of value comparison in ventral striatum neurons. *PLoS biology* 13: e1002173

Strong PV, Christianson JP, Loughridge AB, Amat J, Maier SF, et al. 2011. 5-hydroxytryptamine 2C receptors in the dorsal striatum mediate stress-induced interference with negatively reinforced instrumental escape behavior. *Neuroscience* 197: 132-44

Stuber GD, Sparta DR, Stamatakis AM, Van Leeuwen WA, Hardjoprajitno JE, et al. 2011. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature* 475: 377

Sunstein CR. 2017. Default rules are better than active choosing (Often). *Trends in cognitive sciences* 21: 600-06

Suzuki S. 1997. Effects of number of alternatives on choice in humans. *Behavioural Processes* 39: 205-14

Suzuki S. 1999. Selection of forced-and free-choice by monkeys (Macaca fascicularis). *Perceptual and motor skills* 88: 242-50

Tanaka SC, Samejima K, Okada G, Ueda K, Okamoto Y, et al. 2006. Brain mechanism of reward prediction under predictable and unpredictable environmental dynamics. *Neural Networks* 19: 1233-41

Tao R, Auerbach S. 1995. Involvement of the dorsal raphe but not median raphe nucleus in morphine-induced increases in serotonin release in the rat forebrain. *Neuroscience* 68: 553-61

Taub SI, Dollinger SJ. 1975. Reward and purpose as incentives for children differing in locus of control expectancies. *Journal of Personality* 43: 179-95

Thierry A, Tassin J, Blanc G, GLOWINSKI J. 1976. Selective activation of the mesocortical DA system by stress. *Nature* 263: 242

Thompson SC. 1981. Will it hurt less if I can control it? A complex answer to a simple question. *Psychological bulletin* 90: 89

Thornton JW, Jacobs PD. 1971. Learned helplessness in human subjects. *Journal of Experimental Psychology* 87: 367

Tomaka J, Blascovich J, Kibler J, Ernst JM. 1997. Cognitive and physiological antecedents of threat and challenge appraisal. *Journal of personality and social psychology* 73: 63

Trent F, Tepper J. 1991. Dorsal raphe stimulation modifies striatal-evoked antidromic invasion of nigral dopaminergic neurons in vivo. *Experimental brain research* 84: 620-30

Tricomi E, Fiez JA. 2012. Information content and reward processing in the human striatum during performance of a declarative memory task. *Cognitive, Affective, & Behavioral Neuroscience* 12: 361-72

Trusty ML, Macan TH. 1995. Personal control: Effects of reward contingency and locus of control. *Journal of Social Behavior and Personality* 10: 201

Tversky A, Kahneman D. 1981. The framing of decisions and the psychology of choice. *Science* 211: 453-58

Verardi V, Croux C. 2009. Robust regression in Stata. *The Stata Journal* 9: 439-53

Vohs KD, Baumeister RF, Schmeichel BJ, Twenge JM, Nelson NM, Tice DM. 2014. Making choices impairs subsequent self-control: a limited-resource account of decision making, self-regulation, and active initiative.

Vollmayr B, Gass P. 2013. Learned helplessness: unique features and translational value of a cognitive depression model. *Cell and tissue research* 354: 171-78

Walihagen MI, Brod M, Reimer M, Lindgren CL. 1997. Perceived control and well-being in Parkinson's disease. *Western Journal of Nursing Research* 19: 11-31

Wallston KA, Wallston BS, Smith S, Dobbins CJ. 1987. Perceived control and health. *Current Psychology* 6: 5-25

Wang KS, Delgado MR. 2019. Corticostriatal Circuits Encode the Subjective Value of Perceived Control. *Cerebral cortex*

Wang KS, Smith DV, Delgado MR. 2016. Using fMRI to study reward processing in humans: past, present, and future. *Journal of neurophysiology* 115: 1664-78

Weiner B. 1992. Attributional theories of human motivation. *Human motivation: metaphors, theories, and research. Newbury Park, CA: Sage*

Weiner B. 2012. *Human motivation*. Springer Science & Business Media.

Weissenbacher A, Kasess C, Gerstl F, Lanzenberger R, Moser E, Windischberger C. 2009. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. *NeuroImage* 47: 1408-16

Wemm SE, Wulfert E. 2017. Effects of acute stress on decision making. *Applied psychophysiology and biofeedback* 42: 1-12

White RW. 1959. Motivation reconsidered: the concept of competence. *Psychological review* 66: 297

Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SMJN. 2004. Multilevel linear modelling for FMRI group analysis using Bayesian inference. 21: 1732-47

Worsley K. 2001. Statistical analysis of activation images. *Functional MRI: An introduction to methods* 14: 251-70

Wortman CB, Brehm JW. 1975. Responses to uncontrollable outcomes: An integration of reactance theory and the learned helplessness model. *Advances in experimental social psychology* 8: 277-336

Wright CI, Beijer A, Groenewegen HJ. 1996. Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. *Journal of Neuroscience* 16: 1877-93

Appendix

Supplementary material for Chapter II

Sample size determination

We conducted an one-tailed power analysis using G*Power (version 3.1; Faul et al 2007) for logistic regression according to the guidelines established by Lipsey (1990). We conducted a one-tailed test because we had an *a priori* hypothesis that participants would show a bias towards the SELF-option. For the logistic regression, to achieve an alpha of 0.05, a power of 0.80 and a large effect size (using odd ratio = 3.8 based on criteria suggested by Chen and colleagues (2010)), the desired sample size was 26. We added 5 participants in recruitment (final count of 31) to account for potential participant dropout during data collection.

Questionnaire results

Four questionnaires were collected during the experiment. We had an *a priori* hypothesis about the Locus of Control (LOC) questionnaire, reported in the main manuscript, and exploratory hypotheses about the other three questionnaires. Specifically, we probed whether each of the additional questionnaires was correlated with our POE measure using Bonferroni-adjusted significance level. For the Mini mood and anxiety symptom questionnaire (MASQ) anhedonic depression score, participants scored an average of 25.93 +/- 6.71. For the Desirability of control (DOC) scale, participants scored an average of 99.43 +/- 14.28. For the BIS/BAS scale, participants scored an average of 11.62 +/- 2.35 for behavioral activation system (BAS) drive, 11.38 +/- 2.30 for BAS fun seeking, and 17.62 +/- 1.92 for BAS reward responsiveness. We found no significant correlation between any of the questionnaire scores and the POE measure

(MASQ: r = -0.12, p = 1.00; DOC: r = 0.076, p = 1.00; LOC: r = -0.11 p = 1.00; BAS drive: r = -0.39, p = 1.00; BAS fun seeking: r = -0.15, p = 1.00; BAS reward responsiveness: r = -0.50, p = 0.20).

Activation tables for all contrasts

Activation tables for all neuroimaging contrasts are depicted below for completeness. The tables include areas of activation identified that met the threshold of $p_{uncorrected} < 0.001$, their peak MNI coordinates and peak z-scores (an "*" signifies an ROI that survives correction). All contrasts maps are available in NeuroVault (Gorgolewski et al 2015).

Conjunction of controllable and uncontrollable

Region	**MNI coordinates**			***z*-stats**
	X	Y	Z	
*R. Anterior Cingulate Cortex**	3	11	43	5.53
*R. Lateral Occipital Cortex**	30	-58	50	5.75
*R. Lingual Gyrus**	18	-55	-1	3.91
*R. Occipital Pole**	18	-91	11	6.99
*R. Orbitofrontal Cortex**	37	22	-12	3.54
L. Posterior Cingulate Gyrus	-3	-31	26	3.45
*L. Precentral Gyrus**	-42	2	26	4.53
R. Precentral Gyrus	45	8	26	3.31
*L. Ventral Striatum**	-20	16	-4	3.64

Controllable (SELF) – uncontrollable (COMP)

Region	**MNI coordinates**			***z*-stats**
	X	Y	Z	
*L. Anterior Midcingulate Cortex**	-2	10	43	4.20
R. Hippocampus	15	-10	-22	3.35
*R. Inferior Lateral Occipital Cortex**	54	-73	2	3.99
*L. Nucleus Accumbens**	-6	6	-8	3.93
R. Occipital Pole	33	-94	11	3.32
*L. Postcentral Gyrus**	-36	-28	50	6.36
*L. Precentral Gyrus**	-60	5	26	4.38
L. Superior Parietal Lobule	-30	-52	62	3.82

Uncontrollable (COMP) – controllable (SELF)

Region	**MNI coordinates**			***z*-stats**
	X	Y	Z	
L. Frontal Pole	-15	56	23	3.30
R. Frontal Pole	48	41	-1	3.60
L. Superior Lateral Occipital Cortex	-42	-73	32	3.43
R. Middle Frontal Gyrus	27	32	47	3.26
R. Middle Temporal Gyrus	63	-46	-10	3.45
R. Orbitofrontal Cortex	27	23	-19	3.43
L. Precentral Gyrus	-45	5	29	3.34
R. Precentral Gryus	42	5	32	3.89
L. Superior Frontal Gyrus	-15	11	65	3.52

$Mixed_{SELF}$ – $Mixed_{COMP}$ with POE covariate

Region	**MNI coordinates**			***z*-stats**
	X	Y	Z	
L. Frontal Medial Cortex	-3	41	-25	3.34
L. Frontal Pole	-27	53	35	3.79
R. Inferior Lateral Occipital Cortex	51	-70	5	3.37
*R. Parietal Operculum Cortex**	45	-28	20	4.17
R. Pallidum	24	-13	-1	3.75
*R. Postcentral Gyrus**	6	-40	68	3.98
L. Precentral Gyrus	-18	-28	65	3.46
R. Precentral Gyrus	48	-10	56	3.77
*L. Superior Lateral Occipital Cortex**	-54	-73	20	3.81
*Supplementary Motor Cortex**	0	-13	59	3.87
*R. Supplementary Motor Cortex**	9	-7	47	3.93
*R. Ventromedial Prefrontal Cortex**	-6	32	-14	3.87

Additional behavioral experiment

In the current paper, we observed a bias towards the SELF-option in the *mixed* condition when we varied the reward magnitude of the COMP-option while keeping the SELF-option constant. To investigate whether this bias towards the SELF-option could be potentially driven by a nonlinear value function because only the COMP-option was varied, we conducted an additional behavioral

experiment. Specifically, we adapted the *Value of Control* task to vary the reward magnitude of the SELF-option while keeping the COMP-option constant. By doing so, we hypothesize that participants would still demonstrate a bias towards the SELF-option and thus allow us to conclude that the derived subjective value associated with perceived control (i.e., our POE measure) was most likely a result of participants' preference for seeking and exercising control in the task.

Participants

We recruited 29 participants (12 Males and 17 Females) between the ages of 18 and 25 (M = 19.7, SD = 1.73) from the Rutgers University community. Participants were given research credit for their voluntary participation in the experiment. In addition, they could also earn up to $5 of bonus monetary reward based on task performance. All participants provided written informed consent in accordance with the experimental protocol approved by the Rutgers University Institutional Review Board. Two participants' data were excluded from behavioral analyses due to failure to understand task instructions, yielding a final participant count of 27 (11 Males and 16 Females; M = 19.8, SD = 1.73).

Experimental design

In the mixed condition, instead of manipulating the magnitude of the COMP option (0 to 20 points in increments of 2 points) and keeping the SELF option constant at 10 points (as we did so in the main text), we manipulated the magnitude of the SELF option (0 to 20 points in increments of 2 points) and kept the COMP option constant at 10 points. All other task parameters and descriptions were identical to that described in the main text.

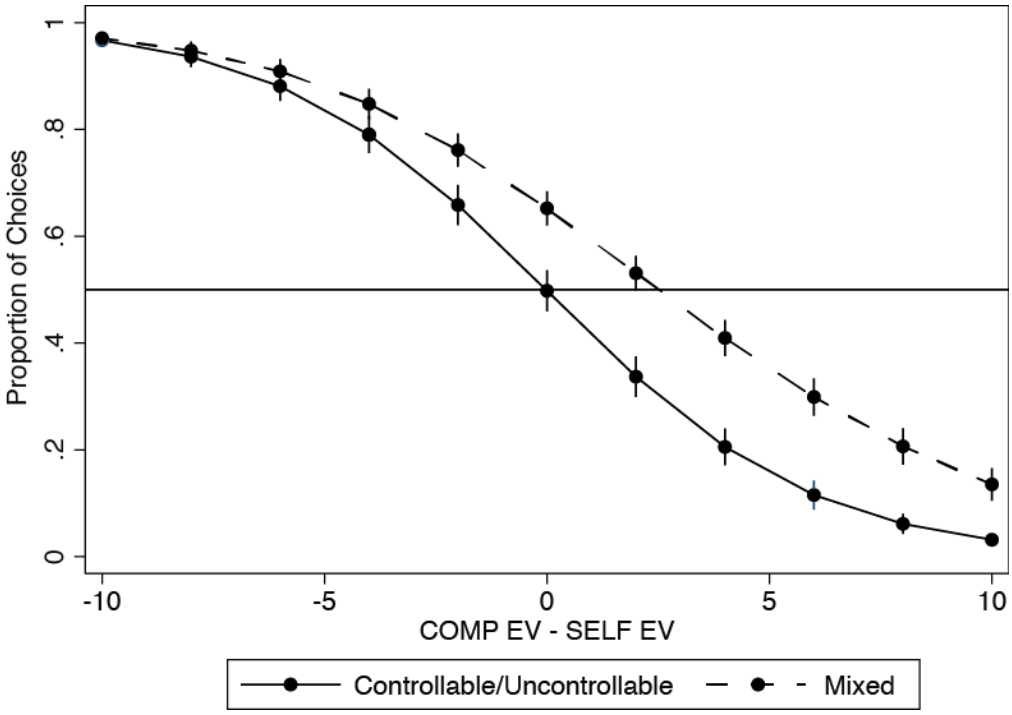
Behavioral results

We conducted the same behavioral analysis described the subsection "Behavioral analyses of choices in the *VoC* task" of the Data Analysis methods section. First, participants' choice behavior in the *mixed* condition showed a significant bias towards the SELF-option (M: 55.2%; SD: 10.65; $t(26) = 2.53$, $p = 0.018$). In contrast they showed no bias towards either option in the baseline condition (i.e., they chose COMP1 51.5% [SD: 7.24] of the time in *uncontrollable* trials [$t(26) = 0.89$, $p = 0.38$] and SELF1 48% [SD: 8.81] in *controllable* trials [$t(26) = -1.54$, $p = 0.14$]).

Next, we performed a logistic regression analysis on participants' trial-by-trial data to extract individual participants' POE measures. We pooled the two baseline trial types (i.e., *controllable* and *uncontrollable*) and the regression analysis yielded a mean participant POE of 0.036 (Supplementary Fig. 1, solid line; SD: 1.67; Range = -3.98 to 3.43) and this was found to be not significantly different from the expected POE of 0 ($t(26) = 0.11$, $p = 0.91$). In contrast, for the *mixed* condition, the regression analysis yielded an average participant POE of 2.61 (Supplementary Fig. 1, dashed line; SD = 5.48, Range = -2.74 to 21.8), which was significantly different from the expected POE of 0 ($t(26) = 2.47$, $p = 0.020$). In addition, using a paired t-test, we found that participants' POEs differed significantly between the *mixed* and baseline conditions ($t(26) = 2.50$, $p = 0.019$). Comparing the POE derived from this behavioral dataset to that of the imaging dataset in the main text, we found that the POEs in the *mixed* condition was not significantly different between the two cohorts of participants ($t(52) = 0.26$, $p = 0.79$).

Finally, we also quantified participants' RT during the *Choice* phase across conditions (*mixed*- M = 1.12, SD = 0.21; pooled baseline- M = 1.12; SD = 0.19) and this RT observation was comparable to the RT found for the imaging dataset in the main text (refer to *Behavioral Results* section titled "Reaction Time").

Taken together, the results replicated the main behavioral results reported in the main text, suggesting that the bias we observed in the original experiment was most likely not influenced by the nonlinearity of the value function. Importantly, we observed similar subjective value of control irrespective of whether the magnitude of the SELF- or COMP-option was independently manipulated, in support of the idea of a subjective value of perceived control.



Supplementary Fig. 1. Logistic regression findings. Regression analysis conducted on participants' choice patterns revealed that the POE for the *mixed* condition was significantly greater than 0 (POE = 2.61) in contrast to the POE of

0.036 for the two baseline trial types (i.e., *controllable* and *uncontrollable*). The x-axis indicates the reward expected value difference between each choice pair. The y-axis indicates the proportion of choices which for the *mixed* condition would be proportion of SELF-choices and for the baseline condition would be proportion of fixed choices. The horizontal line indicates a choice proportion of 0.5 and intersections with the curved lines represent the POE for each condition.