Role of Stress Responsive Neuroendocrine Systems in the Environmental Programming of Life History Strategy in Humans

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List of Abbreviations

ACM: Adaptive calibration model of stress responsivity
ACTH: Adrenocorticotrophic hormone
ALHB: Arizona Life History Battery
ANOVA: Analysis of variance
AUC_G: Area under the curve with respect to ground
BDNF: Brain derived neurotrophic factor
BMI: Body mass index
CA: Cornu ammonis
CSES: Childhood socioeconomic status
CSF: Cerebral spinal fluid
DG: Dentate gyrus
CRH: Corticotrophin releasing hormone
CTQ: Childhood Trauma Questionnaire
ELA: Early life adversity
FDR: False discovery rate
FSH: Follicle stimulating hormone
FWHM: Full width at half maximum
GnRH: Gonadotrophin releasing hormone
GLM: General linear model
HC: Hippocampus
HPA: Hypothalamic-pituitary-adrenal axis
HPG: Hypothalamic-pituitary-gonadal axis
ICV: Intracranial volume
L: Left
LH: Luteinizing hormone
M: Mean
MAGeT: Multiple Automatically Generated Templates
MIST: Montreal Imaging Stress Test
MRI: Magnetic resonance imaging
NTS: Nucleus of the solitary tract
PBI: Parental bonding instrument
PHQ-9: Patient Health Questionnaire
PSNS: Parasympathetic nervous system
PVN: Paraventricular nucleus
R: Right
ROS: Reactive free oxygen species
SD: Standard deviation
SNS: Sympathetic nervous system
SOI-R: Sociosexual Orientation Inventory revised
STAXI: State-Trait Anger Expression Inventory
TSST: Trier Social Stress Test
VBM: Voxel-based morphometry
VIF: Variance inflation factor

Abstract

Early life adversity (ELA) can lead to various mental and physical health problems throughout the lifespan. Research suggests that the effects of ELA on behavior and health are largely mediated by alterations of stress responsive neuroendocrine systems including the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS) and the hypothalamic-pituitary-gonadal (HPG) axis. While extensive research has examined how ELA affects these stress responsive neuroendocrine systems, effects vary between studies, making it difficult to translate this research into treatments for individuals exposed to ELA. Understanding the adaptive significance of biological and behavioral responses to ELA, and the underlying features of early adverse conditions that trigger those responses may help identify factors that moderate effects of ELA on stress physiology and resolve inconsistent research findings. This thesis tests the theory that responsivity of the HPA axis, HPG axis and SNS to stress varies to adapt the individual's life history strategy according to events that predict premature mortality. Our findings suggest that adults with higher ELA exhibit a faster life history strategy, and faster life history strategy accompanies blunted HPA axis and SNS responsivity and elevated HPG axis responsivity to stress. We further found that individuals with ELA had blunted HPA axis responsivity, and briefly exposing participants to mortality cues (thoughts of one's own death) prior to the stress task mimicked certain effects of ELA on the HPA axis stress response. In conclusion, our findings are consistent with the notion that stress responsive neuroendocrine systems may have evolved partly to optimize life history strategy according to cues that predict premature mortality, and that mortality cues may moderate the effect of ELA on stress physiology. Controlling for events that remind individuals of their own mortality may reduce variability in findings among studies examining the effects of ELA on stress physiology.

Résumé

L'adversité de l'enfant peut entraîner divers problèmes de santé mentale et physique tout au long de la vie. La recherche suggère que les effets de l'adversité infantile sur le comportement et la santé sont largement médiés par des altérations des systèmes neuroendocriniens sensibles au stress, y compris l'axe hypothalamo-hypophyso-surrénalien (HPA), le système nerveux sympathique (SNS) et l'axe hypothalamo-hypophyso-gonadique (HPG). Bien que des recherches approfondies aient examiné comment l'adversité infantile affecte ces systèmes neuroendocriniens sensibles au stress, les effets varient d'une étude à l'autre, ce qui rend difficile la traduction de cette recherche en traitements pour les personnes exposées à l'adversité infantile. Comprendre l'importance adaptative des réponses biologiques et comportementales à l'adversité infantile et les caractéristiques sous-jacentes des conditions d'élevage défavorables qui déclenchent ces réponses peuvent aider à identifier les facteurs qui modèrent les effets de l'adversité infantile sur la physiologie du stress et à résoudre les résultats de recherche incohérents. Cette thèse teste la théorie selon laquelle la réactivité de l'axe HPA, de l'axe HPG et du SNS au stress varie pour adapter la stratégie du cycle de vie de l'individu en fonction des événements qui prédisent la mortalité prématurée. Nos résultats suggèrent que les adultes avec plus d'adversité infantile présentent une stratégie de cycle de vie plus rapide, et une stratégie de cycle de vie plus rapide accompagne l'axe HPA émoussé et la réactivité SNS et la réactivité élevée de l'axe HPG au stress. Nous avons en outre constaté que les personnes ayant plus d'adversité infantile avaient émoussé la réactivité de l'axe HPA, et exposer brièvement les participants à des indices de mortalité (pensées de sa propre mort) avant la tâche de stress imitait certains effets de l'adversité infantile sur la réponse au stress de l'axe HPA. En conclusion, nos résultats sont cohérents avec la notion selon laquelle les systèmes neuroendocriniens sensibles au stress peuvent avoir évolué

en partie pour optimiser la stratégie du cycle de vie en fonction d'indices prédisant la mortalité prématurée, et que les indices de mortalité peuvent modérer l'effet de l'adversité infantile sur la physiologie du stress. Le contrôle des événements qui rappellent aux individus leur propre mortalité peut réduire la variabilité des résultats entre les études examinant les effets de l'adversité infantile sur la physiologie du stress.

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Author's Contribution

Ellen Zakreski contributed the literature review, research questions, hypotheses, experimental design, statistical analyses, interpretation of the results, writing and coordinated data collection.

Originality of Contribution to Scholarship

The effects of early life adversity (ELA) on physiology and behavior are typically studied from the perspective that ELA disrupts development, leading to long-term physiological malfunction and subsequently illness. Recently, using life history theory, researchers have begun to consider the possibility that ELA, rather than purely disrupting development, may also guide development toward a phenotype (life history strategy) optimal in harsh conditions. This thesis contributes original knowledge about the potential physiological mechanisms by which ELA and possibly other conditions program or adapt life history strategy for harsh conditions. For the first time in humans, using a validated multi-trait measure of life history strategy, we found that life history strategy is independently related to the function of multiple stress responsive neuroendocrine systems (the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis and sympathetic nervous system (SNS)) between individuals. Past studies on the physiological correlates of life history strategy were either largely limited to animals, examined only one or two stress responsive neuroendocrine systems at a time, or examined only a narrow subset of life history strategy characteristics. Our research suggests HPA axis, HPG axis and SNS responsivity to stress independently covary with life history strategy (not just specific aspects of life history strategy) in humans, like animals, adding empirical support to the theory that the HPA axis, HPG axis and SNS may have evolved partly to regulate life history strategy. Furthermore, past research on the physiological correlates of life history strategy examines the *output* of the HPA axis, HPG axis and SNS but not the function or structure of brain regions that regulate these neuroendocrine systems. This thesis is the first to test the association between life history strategy and the volume of the hippocampus—a structure that influences and is influenced by the HPA axis, HPG axis and SNS. Finally, this thesis contributes novel

information about the underlying properties of ELA that trigger adaptive changes in stress physiology and subsequently life history strategy. Life history theorists have argued that ELA alters life history strategy partly because ELA over the course of human history predicts higher premature mortality in the individual's environment and the level of premature mortality determines the optimal life history strategy. This could mean that other stimuli related to premature mortality could affect life history strategy, similar to the effects of ELA. We found that exposing adults to non-stressful mortality cues (death thoughts) can momentarily blunt the HPA axis stress response in low ELA individuals. A novel implication of this finding is that questionnaires and other stimuli that invoke death thoughts potentially contribute to heterogeneous finding among studies examining effects of ELA on stress physiology, and these stimuli should therefore be controlled for in studies examining the effects of ELA on the stress response.

General Introduction

1 Effects of early life adversity (ELA) on health and development

In the context of biomedical research, ELA is exposure to (presumably) harsh, uncontrollable or unpredictable conditions prior to adulthood (Del Giudice, Ellis, & Shirtcliff, 2011; French & Carp, 2016) such as socioeconomic disadvantage, placement in institutional rearing facilities, parental loss/separation, insensitive caregiving, emotional or physical abuse or neglect, sexual abuse, or exposure to violence. While different individuals respond differently to ELA, extensive research in humans and animals suggests that ELA has an enduring impact on cognition, behavior, physiology and health. Cognitively, ELA is associated with impaired memory (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Bremner et al., 1995; Hulshof et al., 2011; Sousa et al., 2014), impaired attention (Shields & Cicchetti, 1998), difficulties regulating emotion (Dvir, Ford, Hill, & Frazier, 2014; Pechtel & Pizzagalli, 2010), impulsivity and delay discounting (Kamkar, Lewis, van den Bos, & Morton, 2017; Lovallo et al., 2013), altered reward processing (Dillon et al., 2009; Matthews, Wilkinson, & Robbins, 1996) and insecure attachment style (Hill, Young, & Nord, 1994; Oshri, Sutton, Clay-Warner, & Miller, 2015). These effects are observed in childhood (Bremner et al., 1995; Hill et al., 1994; Kamkar et al., 2017; Shields & Cicchetti, 1998) and may persist into adulthood (Bremner et al., 2004; Dillon et al., 2009; Lovallo et al., 2013; Matthews et al., 1996; Oshri et al., 2015; Sousa et al., 2014). Behaviorally, ELA survivors are prone to aggression (Doom, Vanzomeren-Dohm, & Simpson, 2015; Haller, Harold, Sandi, & Neumann, 2014; Lu & Chang, 2019; Shields & Cicchetti, 1998; Simmons et al., 2019), delinquency (Simpson, Griskevicius, Kuo, Sung, & Collins, 2012; Smith & Thornberry, 1995), substance use (Anda et al., 1999; Hampson, Andrews, Barckley, Gerrard, & Gibbons, 2016; Schwandt et al., 2010; Shin, Miller, & Teicher, 2013) and risk taking (Belsky,

Steinberg, Houts, Halpern-Felsher, & Network, 2010; Griskevicius, Tybur, Delton, & Robertson, 2011; Hampson et al., 2016; Ivan & Bereczkei, 2006; Kogan et al., 2014; Lu & Chang, 2019; Simpson et al., 2012). These effects are observed both in childhood (Shields & Cicchetti, 1998; Smith & Thornberry, 1995), adolescence (Hampson et al., 2016; Lu & Chang, 2019; Schwandt et al., 2010; Shin et al., 2013) and persist into adulthood (Anda et al., 1999; Griskevicius, Tybur, et al., 2011; Ivan & Bereczkei, 2006; McMahon et al., 2018; Simpson et al., 2012). Physiologically, ELA exerts complex effects on the structure and function of the brain, particularly the frontal cortex and limbic system (Luby, Barch, Whalen, Tillman, & Belden, 2017; Thomason & Marusak, 2017), which may contribute to aforementioned changes in cognition and behavior. Besides the nervous system, ELA affects physiological processes throughout the body, altering the immune system (Fagundes, Glaser, & Kiecolt-Glaser, 2013), metabolism (Bentley & Widom, 2009; Spann et al., 2014) and reproduction (Belsky et al., 2010; Ellis et al., 2003; Kogan et al., 2015; Pesonen et al., 2008; Sheppard, Pearce, & Sear, 2016). These physiological alterations, in addition to changes in behavior and cognition can lead to long-term health problems in ELA survivors. Evidence shows that ELA increases the risk of numerous health problems, including cardiovascular, autoimmune and metabolic disorders, sexually transmitted infections, addiction, psychosis and depression (Felitti et al., 1998; Luby et al., 2017; Shonkoff, Garner, Fa, Depe, & Pediat, 2012). ELA thus appears to exert a global effect on the phenotype that persists into adulthood. To improve interventions that help treat or prevent health and behavior problems in ELA survivors, researchers seek to understand the physiological mechanisms by which ELA alters behavior and health.

2 Stress responsive neuroendocrine systems may mediate some effects of ELA

Research on humans and animals suggests that the effects of ELA on health and behavior largely depend on alterations of stress responsive neuroendocrine systems, including the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS) and hypothalamic-pituitary-gonadal (HPG) axis (Agorastos, Pervanidou, Chrousos, & Baker, 2019; Danese & McEwen, 2011; Del Giudice, Ellis, et al., 2011; Doom & Gunnar, 2013; Ehlert, 2013; Koss & Gunnar, 2018; Young, 2002). As Sections 2.1–2.3 review, these neuroendocrine systems exert a broad range of effects on growth, reproduction, metabolism, inflammation, learning, motivation and various other processes. Understanding how ELA affects the HPA axis, SNS and HPG axis may help develop interventions for problems arising from ELA, however inconsistencies in research examining the impact of ELA on these neuroendocrine systems has hindered intervention development. Sections 2.1–2.3 provide an overview of the anatomy and physiology of the HPA axis, SNS and HPG axis, how these systems respond to stress and how these systems are impacted by ELA.

2.1 The hypothalamic-pituitary-adrenal (HPA) axis

2.1.1 HPA axis overview

The HPA axis, highly conserved across vertebrates, helps coordinate adaptive responses to stress by affecting metabolism, inflammation, learning, motivation and various other processes (Charmandari, Tsigos, & Chrousos, 2005; de Kloet, Joëls, & Holsboer, 2005; Del Giudice, Ellis, et al., 2011; Denver, 2009; Zakreski et al., 2019). As reviewed elsewhere (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Herman et al., 2016; Ulrich-Lai & Herman, 2009), the HPA axis is a feedforward-feedback controlled circuit between the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary and the adrenal glands. The feedforward

component begins with activation of the PVN and culminates in the release of glucocorticoid hormones (e.g. cortisol) from the adrenal glands. Glucocorticoids then provide negative feedback to the HPA axis, acting on the adrenals, pituitary and hypothalamus to inhibit further HPA axis activity.

The PVN receives input throughout the brain (Herman et al., 2016). Brain stem regions such as the nucleus of the solitary tract (NTS) and circumventricular organs provide the PVN with information about homeostasis, while higher-order brain regions such as the hippocampus, medial prefrontal cortex and amygdala provide more complex information about internal conditions (e.g. goals, past experience) and information about the external environment (Dedovic et al., 2009; Ulrich-Lai & Herman, 2009). This integrates information about internal and external conditions in the determination of the stress response. The detection of threat triggers specialized neurons in the PVN to secrete CRH and argenine vassopressin into the portal blood supply. These hormones stimulate the cleavage of the pro-opiomelanocortin into beta endorphin and ACTH. ACTH acts on the adrenal glands, stimulating the zona fasicularis to secrete steroid hormones known as glucocorticoids. In some animals (e.g. humans, fish) cortisol is the physiologically important glucocorticoid while in other organisms (e.g. rodents, birds), corticosterone is the primary glucocorticoid. Once in the blood, most glucocorticoids are bound to transporter proteins (Siiteri et al., 1982). Free (unbound) glucocorticoids are capable of penetrating cell membranes where they bind highly conserved nuclear glucocorticoid receptors (type I or type II) and subsequently regulate gene expression (Evans, 1988). Free glucocorticoids, and to an extent transporter bound glucocorticoids, can also interact with receptors on the cell membrane to induce non-genomic effects, which are generally faster and shorter lasting than the effects of binding nuclear receptors (Makara & Haller, 2001). These

nuclear and membrane glucocorticoid receptors exert a range of short-term and long-term effects on a wide range of tissue including the brain. Since glucocorticoids are lipid soluble, free glucocorticoids may cross the blood brain barrier, binding glucocorticoid nuclear and membrane receptors distributed throughout the brain particularly in the limbic system and frontal cortex (de Kloet et al., 2005).

Across species, the HPA axis helps individuals survive challenge. Glucocorticoids for instance increase energy available for immediate use by stimulating lipolysis (Djurhuus et al., 2002) and gluconeogenesis (Exton, 1979). Glucocorticoids also ensure that the brain receives sufficient energy during stress by inhibiting glucose uptake in peripheral tissues, reserving it for the brain (Baron, Wallace, & Brechtel, 1987; Munck, 1971). Furthermore, glucocorticoids play a critical role in suppressing inflammation during stress (Cupps & Fauci, 1982; Franchimont, 2004; Webster Marketon & Glaser, 2008). Glucocorticoids also inhibit processes that would otherwise divert resources away from immediate survival (e.g. growth, reproduction) (Charmandari et al., 2005). In the brain, glucocorticoids affect learning and motivation in ways that can help organisms deal with threat. For example, a moderate surge in glucocorticoid levels during stress affects the hippocampus, amygdala and other limbic structures to facilitate consolidation of threat related information (Joëls & Baram, 2009) and desensitize individuals to reward (Kinner, Wolf, & Merz, 2016). If ELA alters HPA axis function, the effects of glucocorticoids on limbic structures may be relevant to impaired learning and reward processing seen in ELA survivors (Section 1).

The HPA axis activates in response to physiological stressors (e.g. intense exercise) or psychological stressors, particularly those that are uncontrollable, unpredictable or involve social evaluation (Dickerson & Kemeny, 2004). In response to standardized psychosocial stress tasks

such as the Trier Social Stress Task (Kirschbaum, Pirke, & Hellhammer, 1993), cortisol levels typically peak approximately 15 minutes following stressor onset and last for approximately an hour (Goodman, Janson, & Wolf, 2017). The timing and magnitude of the cortisol stress response varies considerably between individuals and has been associated with various stress-related health problems that are also prevalent in ELA survivors including cardiovascular disease, metabolic disorders, autoimmune disorders and psychiatric illness (Hellhammer, Wust, & Kudielka, 2009; Zorn et al., 2017). While higher cortisol responsivity to stress can increase risk of stress-related illness, blunted cortisol responsivity is also associated with a wide range of health and behavioral problems as reviewed elsewhere (Carroll, Ginty, Whittaker, Lovallo, & de Rooij, 2017; Susman, 2006).

2.1.2 ELA affects HPA axis function

The effects of ELA on HPA axis function has been researched more than the HPG axis and SNS. In humans, numerous studies have examined the impact of ELA on cortisol responsivity to stress. There is nonetheless significant heterogeneity in research findings (Bunea, Szentagotai-Tatar, & Miu, 2017). According to a recent meta-analysis (Bunea et al., 2017), most studies associate higher ELA with *blunted* cortisol responsivity to stress (Cărnuţă, Crişan, Vulturar, Opre, & Miu, 2015; Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2010; Dietz et al., 2012; Kraft & Luecken, 2009; Lovallo, 2013; McLaughlin et al., 2015; Negriff, Saxbe, & Trickett, 2015; Schalinski, Elbert, Steudte-Schmiedgen, & Kirschbaum, 2015; Voellmin et al., 2015). Numerous studies however associate ELA with *heighted* cortisol responsivity (Bugental, Martorell, & Barraza, 2003; Heim et al., 2000; Ivanov et al., 2011; Pesonen et al., 2010; Pruessner, Champagne, Meaney, & Dagher, 2004; Sullivan, Bennett, & Lewis, 2013). A few studies report no significant effect of ELA on cortisol responsivity (Moran-

Santa Maria et al., 2010; Murali & Chen, 2005). To explain these mixed findings, several individual differences have been proposed to moderate the effects of ELA on HPA axis function including genotype (Buchmann et al., 2013; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014), the type of ELA (Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015), severity of ELA (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009) and when adversity occurred in development (Bosch et al., 2012; Lupien, McEwen, Gunnar, & Heim, 2009). Nonetheless, even among studies investigating highly similar populations (Gunnar et al., 2009; McLaughlin et al., 2015), observed associations between ELA and cortisol responsivity still vary inexplicably. Identifying additional factors that moderate relations between ELA and cortisol responsivity may help to resolve discrepant research findings and consequently provide a clearer picture of how ELA affects HPA axis function with the aim of improving treatments for ELA survivors.

2.2 The sympathetic nervous system (SNS)

2.2.1 SNS overview

The SNS, a branch of the autonomic nervous system, is a highly conserved neuroendocrine system (Wang, 2012) that regulates growth, reproduction, metabolism, inflammation and initiates the fight-or-flight response (Del Giudice, Ellis, et al., 2011; Zakreski & Pruessner, 2019). SNS activity is primarily regulated by the ventrolateral medulla, NTS and other parts of the brain stem (Card & Sved, 2011; Dampney, 1994). The SNS also receives input from forebrain regions such as the medial prefrontal cortex and central amygdala (Card & Sved, 2011) as well as receiving excitatory input from CRH secreting cells in the PVN (Kenney, Weiss, & Haywood, 2003). The SNS is therefore regulated by many of the brain regions that regulate the HPA axis (e.g. medial prefrontal cortex, PVN) (Ulrich-Lai & Herman, 2009). Like the HPA axis,

activity of the SNS changes in response to both homeostatic input primarily from brain stem regions as well as perceptions of threat conveyed from higher-order forebrain and limbic regions.

The anatomy and physiology of the SNS has been reviewed in detail elsewhere (Shields, 1993; Wehrwein, Orer, & Barman, 2016) so is only summarized here. The SNS consists of two types of motor neurons: preganglionic cells and postganglionic cells. Preganglionic cell bodies exist primarily in the interomediolateral cell column of the spine and receive either excitatory or inhibitory input from the brainstem. Preganglionic axons exit the spine transversely. A minority of preganglionic axons project to the adrenal medulla where they stimulate chromaffin cells to release epinephrine into the blood supply. Most sympathetic preganglionic axons synapse with postganglionic neurons in sympathetic ganglia that are connected in a chain running parallel to the spine. Postganglionic axons project to organs throughout the body, including radial pupillary muscles, saliva glands, thyroid glands, bronchi, heart, liver, kidneys, pancreas, intestines, sex organs, adipose tissue, blood vessels, bone and sweat glands. Postganglionic fibers innervating sweat glands release acetylcholine, while those innervating the kidneys release dopamine. Most postganglionic axon terminals however release norepinephrine. The catecholamines norepinephrine and epinephrine bind alpha or beta adrenergic receptors on target tissue. Exposure to physical or psychological stressors activates the SNS, increasing cardiac output, heart rate, blood pressure, respiration, lipolysis, perspiration among other effects.

Like the HPA axis, the SNS enables organisms to survive potential perturbations to homeostasis by mobilizing stored energy (e.g. lipolysis) (Hücking, Hamilton-Wessler, Ellmerer, & Bergman, 2003) and inhibiting inflammation (Kenney & Ganta, 2014). Epinephrine, while not capable of crossing the blood brain barrier, can also facilitate behavioral and cognitive adaptations to threat. For example, epinephrine can facilitate memory consolidation by binding

adrenergic receptors on vagal afferents projecting to the NTS (McGaugh, 2000), thus like the HPA axis, moderate activation of the SNS during stress may facilitate learning of threat related information. Also like the HPA axis, the SNS is highly sensitive to unpredictability, uncontrollability and social evaluative threat (Bosch et al., 2009). Compared to the HPA axis, the SNS however responds to a wider range of stressors than the HPA axis, such as mental challenge (Peters et al., 1998) and the SNS stress response is faster and of shorter duration (Engert et al., 2011). The HPA axis and SNS therefore represent functionally distinct yet overlapping systems that prepare organisms to deal with threats. Like the HPA axis, SNS responsivity to stress varies considerably between individuals and has been implicated in the etiology of various stress-related disorders including cardiovascular disease, metabolic syndrome, autoimmune disorders and various psychiatric disorders (Carroll et al., 2017; Zakreski & Pruessner, 2019).

2.2.2 ELA affects SNS function

Individuals exposed to ELA show altered SNS responsivity to stress. As is the case for the HPA axis, research on ELA and SNS responsivity is inconsistent (Zakreski & Pruessner, 2019). Some studies associate ELA with *greater* SNS responsivity (Cărnuţă et al., 2015; Kuras, McInnis, et al., 2017; Lucas-Thompson & Granger, 2014; Oosterman, Schipper, Fisher, Dozier, & Schuengel, 2010) while other studies associate ELA with *blunted* SNS responsivity (Bernstein, Measelle, Laurent, Musser, & Ablow, 2013; Busso, McLaughlin, & Sheridan, 2016; McLaughlin et al., 2015; Mielock, Morris, & Rao, 2017; Winzeler et al., 2016). Various factors may moderate relations between ELA and SNS responsivity. This includes genotype (Allegrini, Evans, de Rooij, Greaves-Lord, & Huizink, 2017; Esposito et al., 2017) and the type of stress task (McLaughlin, Sheridan, Alves, & Mendes, 2014) as reviewed elsewhere (Zakreski & Pruessner, 2019).

2.3 The hypothalamic-pituitary-gonadal (HPG) axis

2.3.1 HPG axis overview

The HPG axis is a highly conserved neuroendocrine system that regulates reproduction across vertebrates (Maruska & Fernald, 2011; Zakreski et al., 2019). The HPG axis involves a feedforward-feedback controlled circuit of hormones primarily produced by the arcuate and preoptic areas of the hypothalamus, the anterior pituitary and gonads, reviewed in detail elsewhere (Clarke, Campbell, Smith, Prevot, & Wray, 2012; Markee, 1951). Feedforward activation begins with the hypothalamus and culminates in the release of sex steroid hormones (e.g. testosterone, estradiol) from gonads. Gonadal sex hormones then provide either inhibitory or excitatory feedback on the HPG axis.

The hypothalamus receives input from multiple brain regions including the medial amygdala, bed nucleus of the stria terminalis and other parts of the hypothalamus allowing the HPG axis to alter reproduction and other processes in response to various internal and external events (e.g. internal energy supply, pheromones, photoperiod) (Maruska & Fernald, 2011). Cells in the hypothalamus secrete gonadotrophin releasing hormone (GnRH) into the portal blood supply which then stimulates the anterior pituitary to release gonadotrophins; follicle stimulating hormone (FSH) and luteinizing hormone (LH). The circulatory system then transports FSH and LH to the gonads. In testes, FSH stimulates spermatogenesis while LH triggers Leydig cells to produce testosterone. In ovaries, FSH helps prepare the oocyte for ovulation, while LH triggers ovulation and stimulates theca cells in the ovaries to synthesize testosterone. Unlike the testes however, ovaries contain higher levels of aromatase, the enzyme that converts testosterone to estradiol before secretion into the blood (Ryan, 1959). In both males and females, testosterone can be converted to estradiol within target tissue, such as the hippocampus (Fester et al., 2016).

Synthesis of estradiol from testosterone is therefore part of the mechanism by which testosterone affects physiology.

Blood caries testosterone and estradiol to targets throughout the body. Like glucocorticoids, most sex steroid molecules in blood are bound to transporter proteins (Siiteri et al., 1982). Sex steroids unbound to transporter proteins can bind highly conserved nuclear receptors within the cell to exert longer lasting, slower changes by influencing transcription. Testosterone binds nuclear androgen receptors (Gelmann, 2002) while estradiol binds alpha or beta nuclear estrogen receptors (Carroll & Brown, 2006). Like glucocorticoids, testosterone and estradiol also bind membrane receptors, capable of faster, briefer non-genomic effects (e.g. neural modulation) (Foradori, Weiser, & Handa, 2008; Prossnitz & Barton, 2011). In the brain, estradiol and testosterone provide feedback to the HPG axis by acting on the pituitary and hypothalamus. Estradiol provides positive or negative feedback (Herbison, 2008), while testosterone provides negative feedback (Nagayama, 1977).

Sex steroids influence a broad range of processes including body fat composition and metabolism (Buchanan, Evans, Goldsmith, Bryant, & Rowe, 2001; Wade & Gray, 1979), inflammation (Angele, Schwacha, Ayala, & Chaudry, 2000; Wichmann, Zellweger, DeMaso, Ayala, & Chaudry, 1996), growth and maintenance of bone (Nicks, Fowler, & Gaddy, 2010) and muscle (La Colla, Pronsato, Milanesi, & Vasconsuelo, 2015). Throughout the lifespan, gonadal sex steroids shape the structure and function of various parts of the brain. This includes organizing sexually dimorphic behaviors (e.g. lordosis, mounting) in some species (Arnold, 2009). Gonadal sex steroids also impact the development and function of brain systems implicated in reward and emotion (Sisk & Zehr, 2005). According to one review (Peper, van den Heuvel, Mandl, Hulshoff Pol, & van Honk, 2011), high levels of testosterone are associated with

reduced cortico-subcortical communication. For example, high testosterone levels overtime can attenuate white matter tracts between frontal and striatal regions, which may have chronic effects on reward and threat processing (e.g. increased impulsivity) (Peper et al., 2013). Testosterone may have acute in addition to chronic effects on reward and threat processing. Administering testosterone acutely increases reactivity of the striatum to monetary reward (Hermans et al., 2010; Op de Macks et al., 2011) and increases amygdala reactivity while reducing hippocampal reactivity to threat (Goetz et al., 2014; Heany, van Honk, Stein, & Brooks, 2016). Changes in testosterone levels may therefore partly explain altered threat and reward processing seen in ELA survivors as discussed earlier (Section 1).

While the HPG axis stress response has not been studied as extensively as the HPA axis or SNS stress response, HPG axis activity changes in response to stress. While chronic stress can inhibit sex steroid output (Rivier & Rivest, 1991; Zakreski et al., 2019), acute physical or psychological challenge temporarily increases sex steroid output (Chichinadze & Chichinadze, 2008). Higher circulating sex steroids may help organisms deal with challenge by releasing energy stored in fat (Mudali & Dobs, 2004), suppressing inflammation (Angele et al., 2000; Wichmann et al., 1996) or by facilitating competitive behavior (Archer, 2006; Muller, 2017).

2.3.2 ELA affects HPG axis function

A growing body of work suggests that ELA alters HPG axis function. Deprivation of maternal care programs reproductive behaviors in rodents, potentially by epigenetically modifying the expression of alpha type estrogen receptors in the brain (Toufexis, Rivarola, Lara, & Viau, 2014), suggesting that ELA impacts sensitivity to hormones regulated by the HPG axis. ELA also impacts the activity of the HPG axis. In zebra finches, exposure to ELA increased testosterone levels in adults (Zito, Hanna, Kadoo, & Tomaszycki, 2017). In humans, numerous

studies suggest that parental absence and other forms of ELA accelerate puberty (Ellis, 2004; Ellis & Essex, 2007; Ellis & Garber, 2000; Kogan et al., 2015; Wise, Palmer, Rothman, & Rosenberg, 2009), suggesting that ELA survivors have greater activation of the HPG axis at an earlier age (Belsky, 2012; Ellis, 2013). Early puberty increases risk of various health problems including testicular cancer (Forman et al., 1994), prostate cancer (Giles et al., 2003) and breast cancer (Peeters, Verbeek, Krol, Matthyssen, & de Waard, 1995) and may also lead to anxiety disorders and other mental health problems (Golub et al., 2008) experienced by ELA survivors. Early puberty has also been found to mediate the effect of ELA on risky sex (Belsky et al., 2010; Kogan et al., 2015) and other forms of risk taking (James, Ellis, Schlomer, & Garber, 2012). Similar to research on the relationship between ELA and the HPA axis and SNS, the relationship between ELA and markers of HPG axis function is also variable. For instance, the relationship between ELA and markers of HPG axis function was found to vary according to the activity of the SNS or HPA axis (Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011).

3 Limitations of research on how ELA affects stress responsive neuroendocrine systems

Numerous studies have examined how ELA impacts stress responsive neuroendocrine systems in both children and adults. Translating this research into treatment has proven difficult, largely because the effect of ELA on stress responsivity varies between studies. As discussed in the Sections 2.1–2.3, inconsistent findings may be due in part to individual differences such as genotype, sex or the activity of other stress response systems. Inconsistent findings may also arise from differences in the conditions where participants are tested, rather than differences between participants, especially since the physiological stress response is typically assessed on a single occasion in a specific context (e.g. a standardized laboratory stress task). Identifying situational factors that moderate the effects of ELA on stress physiology may therefore help to

resolve some of the inconsistent research findings. Using life history theory as a framework, this thesis explores how situational factors acutely moderate effects of ELA on stress responsive neuroendocrine systems.

4 Life history theory

A growing number of researchers have used life history theory as a framework for describing and explaining the effects of ELA on health and behavior (Belsky, 2012; Belsky, Steinberg, & Draper, 1991; Chisholm, 1993, 1996; Csatho & Birkas, 2018; Del Giudice, Ellis, et al., 2011; Ellis, Bianchi, Griskevicius, & Frankenhuis, 2017). The adaptive calibration model extends life history theory to explain the effects of ELA on the physiological stress response systems (Del Giudice, Ellis, et al., 2011). Life history theory (Ellis, Figueredo, Brumbach, & Schlomer, 2009; Roff, 1992; Stearns, 1992) is a mature branch of evolutionary biology that uses the notion of life history strategy to explain why phenotypes vary between safe and harsh conditions. Life history strategy varies between species and within species and is the way an organism strategically distributes finite time and energy among various conflicting fitness-related tasks (i.e. reproduction, growth and survival). Providing a basic review of life history theory, Sections 4.1–4.6 explain how different life history strategies are adaptive in different environments and how the biological and behavioral effects of ELA (and potentially the effects of other events that predict premature mortality) may constitute an adaptive shift in life history strategy.

4.1 Different life history strategies evolved to resolve trade-offs between fitness-related tasks

Different life history strategies represent different resolutions to inherent trade-offs between fitness-related tasks (Roff, 1992; Stearns, 1992). According to the principle of allocation, given the finite availability of time and energy, an organism's investment in one fitness-related task

comes at the expense of investing in another, thus creating inherent trade-offs between fitness-related tasks. A key trade-off is between somatic investment (long-term growth and survival) and reproductive investment (mating and parenting). Since somatic investment increases the resources an individual can invest in future reproduction, the trade-off between somatic effort and reproductive effort can be conceptualized as a trade-off between *future* reproduction and *current* reproduction (Hill & Kaplan, 1999). Within reproduction exists other trade-offs; mating effort vs. parental effort and offspring quality vs. offspring quantity. Organisms evolved to resolve these trade-offs as to optimize their reproductive fitness. How an organism resolves one trade-off impacts the optimal resolution to other trade-offs (Ellis et al., 2009). For instance, prioritizing parental effort over mating effort is more likely to enhance fitness when the organism also produces fewer offspring rather than producing many offspring. Since optimal resolutions to different trade-offs are interdependent, much of the variance in life history strategy reduces to single a dimension ranging from slow to fast.

4.2 Life history strategy varies on a continuum ranging from slow to fast

Organisms with a slower life history strategy prioritize somatic effort over reproductive effort (i.e. future reproduction over current reproduction), parenting over mating and offspring quality over offspring quantity. Organisms at the fast end do the opposite. Fast and slow life history strategy manifest as distinct clusters of attributes (Figueredo, Vásquez, Brumbach, & Schneider, 2007; Figueredo et al., 2006; Réale et al., 2010). Fast life history strategy manifests as early puberty and reproduction, more offspring, sexual promiscuity, impulsivity and aggression. Slow life history strategy manifests as the opposite (i.e. neoteny, later reproduction, fewer offspring, high self-control and secure, stable relationships).

4.3 Premature mortality determines whether a slow or fast life history strategy is optimal

Different life history strategies are optimal in different conditions (Ellis et al., 2009). In safe, stable conditions with low premature mortality rates, slow life history strategy enhances the resources parents can invest in future offspring, allowing them to produce more robust and competitive offspring. Alternatively, fast life history strategy helps organisms propagate in harsh conditions with high premature mortality because fast life history strategy organisms are more likely to reproduce even if they die prematurely. Consequently, slow life history strategy is generally optimal in safe environments where premature mortality is low while fast life history strategy is optimal in harsh environments where premature mortality is high.

Anthropological research suggests that throughout human history, premature mortality fluctuated rapidly due to famine, disease, conflicts and other factors (Kuzawa & Bragg, 2012). Genetically mediated adaptation is too slow to accommodate these rapid fluctuations, so human life history strategy is probably plastic (Kuzawa & Bragg, 2012). Humans likely evolved to detect cues that, over the course of human history, reliably predict premature mortality in the individual's environment (Chisholm, 1993, 1996; Del Giudice, Hinnant, Ellis, & El-Sheikh, 2011; Ellis et al., 2009; Nettle, Frankenhuis, & Rickard, 2013). Individuals then optimize their life history strategy according to the cues they detect. Theoretically, cues that signal high premature mortality in the individual's environment accelerate life history strategy, while cues that signal low premature mortality should slow life history strategy.

4.4 ELA accelerates life history strategy because ELA predicts higher premature mortality

Humans may have evolved to use ELA as a mortality cue since ELA tends to occur in environments where premature mortality is high (Belsky et al., 1991; Chisholm, 1993, 1996; Del Giudice, Ellis, et al., 2011; Ellis et al., 2009; Nettle et al., 2013). Consistent with this notion,

ELA survivors show signs of faster life history strategy such as earlier puberty (Belsky et al., 2010; Chisholm, Quinlivan, Petersen, & Coall, 2005; Ellis et al., 2011; James et al., 2012; Kogan et al., 2014), earlier reproduction (Chisholm et al., 2005; Gettler, McDade, Bragg, Feranil, & Kuzawa, 2015; James et al., 2012; Nettle & Cockerill, 2010), impulsivity and delay discounting (Kamkar et al., 2017; Lovallo et al., 2013), more risky behavior (Belsky et al., 2010; Griskevicius, Tybur, et al., 2011; Hampson et al., 2016; Ivan & Bereczkei, 2006; Kogan et al., 2014; Lu & Chang, 2019; Simpson et al., 2012), and more aggression (Doom et al., 2015; Simmons et al., 2019; Simpson et al., 2012), relative to individuals reared in safe conditions. As proposed by the adaptive calibration model (Del Giudice, Ellis, et al., 2011) faster life history strategy may be an evolved conditional adaptive response to harsh environments, triggered by cues that predict higher premature mortality (e.g. ELA).

4.5 Thinking about death may accelerate life history strategy because death thoughts predict higher premature mortality

Some authors (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012) argue that life history strategy plasticity is confined to critical developmental periods (predominately in childhood). Data however suggest that life history strategy may also change in adulthood. Spikes in mortality due to natural disasters or conflict are shortly followed by spikes in birth rate (baby booms) (Cohan & Cole, 2002; Rodgers, John, & Coleman, 2005) and risky behavior (Ben-Zur & Zeidner, 2009), potentially indicating faster life history strategy. Death thoughts reliably covary with actual mortality/harshness. Compared to individuals in safer circumstances, death thoughts are more prevalent among food-deprived adolescents (Alaimo, Olson, & Frongillo, 2002), terminally ill adults (Cox, Reid-Arndt, Arndt, & Moser, 2012; Robertson, Parsons, Van Der Horst, & Hall, 2006) and individuals living in war-stricken areas (Abdel-Khalek, 2003),

especially if they perceive their environment as dangerous (Shakil & Yousaf, 2015). In fact, perceived mortality (subjective life-expectancy) is a stronger predictor of life history strategy traits than objective measures of harshness (Davis, 2012; Wilson & Daly, 1997). Thinking about one's own death temporarily lowers subjective life-expectancy (Maxfield, Solomon, Pyszczynski, & Greenberg, 2010; Zhou, Lei, Marley, & Chen, 2009), and when subjective life-expectancy is acutely reduced, participants acutely express faster life history strategy (Dunkel, Mathes, & Decker, 2010a). Taken together, death thoughts meet the criteria of a mortality cue and like other mortality cues (e.g. ELA), death thoughts may promote fast life history strategy characteristics given results from various psychological experiments. For example, inducing death thoughts at least momentarily increased interest in sun tanning among adults primed to associate tanned skin with physical attractiveness (Routledge, Arndt, & Goldenberg, 2004). Prioritizing reproduction (physical attractiveness) over long-term survival (avoiding skin cancer) typifies fast life history strategy. Death thoughts also lead adults to desire more offspring (Fritsche et al., 2007; Mathews & Sear, 2008; Wisman & Goldenberg, 2005), compromise mate standards (Hirschberger, Florian, & Mikulincer, 2002), endorse casual sex (Birnbaum, Hirschberger, & Goldenberg, 2011; Lam, Morrison, & Smeesters, 2009; Taubman Ben-Ari, 2004) among other risky behaviors (Ben-Zur & Zeidner, 2009; Hart, Schwabach, & Solomon, 2010; Hirschberger, Florian, Mikulincer, Goldenberg, & Pyszczynski, 2002; Taubman Ben-Ari & Findler, 2003; Taubman Ben-Ari, Florian, & Mikulincer, 1999).

4.6 Physiological regulation of life history strategy

Physiological systems likely facilitate life history strategy by regulating trade-offs between longevity, mating and parenting. Numerous authors (Del Giudice, Ellis, et al., 2011; Korte, Koolhaas, Wingfield, & McEwen, 2005; Réale et al., 2010; Ricklefs & Wikelski, 2002; Wikelski

& Ricklefs, 2001; Wingfield, Hegner, Dufty, & Ball, 1990; Wingfield & Sapolsky, 2003) have hypothesized physiological correlates of life history strategy, although the data supporting these predictions comes largely from non-human animals. While various physiological systems likely regulate life history strategy, models of the physiological regulation of life history strategy, such as the pace of life model (Réale et al., 2010), emphasize the role of stress responsive neuroendocrine systems, particularly the HPA axis, HPG axis and SNS. These systems likely play a central role in regulating life history strategy given that 1) these systems are highly conserved across vertebrates, 2) they simultaneously control multiple life history strategy-relevant domains (energy expenditure, fertility, aggression, growth, impulsivity, etc.) and 3) they are responsive to shifts in ecological conditions that determine the optimality of individual life history strategies (i.e. adversity). Structural changes in brain regions such as the hippocampus, which influences and is influenced by activity of the HPA axis, HPG axis and SNS function, could also play a role in regulating life history strategy.

4.6.1 HPG axis regulation of life history strategy

Greater gonadal sex steroid output particularly of the hormone testosterone could promote a faster life history strategy by prioritizing reproductive effort over somatic effort and by prioritizing mating effort over parenting effort. Testosterone and its metabolite, estradiol, facilitate reproductive effort by promoting the development of primary sexual characteristics (e.g. development of the genitalia) and secondary sexual characteristics (e.g. breast enlargement, voice change) and by facilitating ovulation and spermatogenesis as reviewed in Section 2.3.1. Increased testosterone is associated with higher mating success in animals (Alatalo, Höglun, Lundberg, Rintamäki, & Silverin, 1996; Hau, Ricklefs, Wikelski, Lee, & Brawn, 2010) and humans (Peters, Simmons, & Rhodes, 2008). Correlational and experimental research suggests

that testosterone increases libido (Alexander & Sherwin, 1993; Alexander et al., 1997; Tuiten et al., 2000), intercourse frequency (Persky, Lief, Strauss, Miller, & O'Brien, 1978) and sexual promiscuity (Pollet, van der Meij, Cobey, & Buunk, 2011; van Anders, Hamilton, & Watson, 2007) in males and females.

Testosterone promotes numerous sexually selected characteristics that increase mating success but threaten survival, thus trading-off survival for reproduction. For example, in various bird species, testosterone facilitates the expression of brightly colored plumage, combs and other ornamental appendages in males that attract mates but require significant energy to maintain and make the male more vulnerable to predation (Martínez-Padilla, Pérez-Rodríguez, Mougeot, Ludwig, & Redpath, 2014). In addition to sexually selected physical characteristics, testosterone facilitates sexually selected behaviors that may increase mating success but interfere with long-term growth and survival. Sexually selected behaviors include aggression (Ainsworth & Maner, 2012; Archer, 2009) and risk taking (Baker & Maner, 2009; Greitemeyer, Kastenmüller, & Fischer, 2012). In both humans and animals, endogenous and exogenous testosterone is associated with aggression (Anestis, 2006; Archer, 2006; Book, Starzyk, & Quinsey, 2001; Ligon, Thornhill, Zuk, & Johnson, 1990; Rowe, Maughan, Worthman, Costello, & Angold, 2004; Welling, Moreau, Bird, Hansen, & Carré, 2016) and risk taking (Apicella et al., 2008; Halpern, Campbell, Agnew, Thompson, & Udry, 2002b; Nofsinger, Patterson, & Shank, 2018; Stanton, Liening, & Schultheiss, 2011).

Testosterone can also undermine longevity by accelerating aging at the cellular level. Drury et al. (2014) found that children with higher testosterone responsivity to stress had shorter buccal cell telomere lengths, a cellular marker of accelerated aging. Oxidative stress, a major contributor to aging, is increased by testosterone which promotes the production of reactive free

oxygen species (ROS) and prevents ROS clearance (Alonso-Alvarez, Bertrand, Faivre, Chastel, & Sorci, 2007). According to Herald et al. (2017), the effects of testosterone on oxidative stress in addition to testosterone-induced alterations of the heart and vasculature contribute to various cardiovascular diseases later in life. Hormones regulated by the HPG axis therefore promote reproduction potentially at the expense of long-term growth and survival, consistent with fast life history strategy.

HPG axis hormones, specifically testosterone, could also facilitate faster life history strategy by redirecting effort away from parenting toward mating. In humans, research conducted in various cultures has found that fathers with higher testosterone levels invest less care in their children (Gray, McHale, & Carré, 2017). Longitudinal research suggests that testosterone level also covaries with parental investment within individuals over time. Naturalistic research has found that testosterone declines once men become fathers (Gettler, McDade, Agustin, Feranil, & Kuzawa, 2013). In a laboratory simulation of parental care, testosterone also declined in men after they soothed a crying doll (van Anders, Tolman, & Volling, 2012). Change in testosterone levels may therefore facilitate trade-offs between mating and parenting, and potentially other life history strategy trade-offs within individuals in response to life history strategy relevant ecological cues.

4.6.2 HPA axis regulation of life history strategy

While chronic activation of the HPA axis may lead to "wear and tear" of various physiological systems (Charmandari et al., 2005; Chrousos, 2009; McEwen, 1998), momentary HPA axis activation enables organisms to survive challenge. As I reviewed in Section 2.1.1, glucocorticoids facilitate survival partly by enhancing learning of threat-related information and by providing the necessary bioenergetics resources to cope with challenge. Glucocorticoids also

help prevent toxic over-activation of the immune system (Section 2.1.1). Since glucocorticoids provide negative feedback to CRH secreting neurons, activation of the HPA axis helps to terminate both the HPA axis stress response and SNS stress response which could help promote long-term growth and survival by preventing toxic over-activation of the physiological stress response systems (Del Giudice, Ellis, et al., 2011). Simultaneously, the HPA axis inhibits processes that would otherwise divert resources away from immediate survival (e.g. growth, reproduction) (Charmandari et al., 2005). The HPA axis therefore activates and inhibits various central and peripheral processes in response to threat that enable the organism to survive challenge and accommodate their effects.

Activation of the HPA axis suppresses reproduction by inhibiting the HPG axis centrally and peripherally as reviewed in detail elsewhere (Rivier & Rivest, 1991; Whirledge & Cidlowski, 2010; Whirledge & Cidlowski, 2017; Zakreski et al., 2019). For example, glucocorticoids suppress gonadal sex steroid output (Bambino & Hsueh, 1981) by inhibiting GnRH secretion from the hypothalamus (Calogero et al., 1999) and by lowering cyclic adenosine monophosphate in Leydig cells of the testes (Dong et al., 2004). Increased glucocorticoids therefore generally suppress reproduction. Consistent with this observation, individuals with hypercortisolism due to Cushing's syndrome exhibit lower testosterone and libido, which return to normal once hypercortisolism is corrected (Keskin et al., 2018; Luton, Thieblot, Valcke, Mahoudeau, & Bricaire, 1977).

According to Wingfield and Sapolsky (2003), the capacity of HPA axis activation during stress to redirect resources away from reproduction toward survival enables organisms to selectively reproduce when conditions are more favorable (e.g. less predation, ample food supply, ample social support). This not only helps explain why glucocorticoids increase during

stress but can also help explain why the glucocorticoid stress response is attenuated in certain organisms. Delaying reproduction during stress only increases fitness when organisms have sufficient future reproductive potential (i.e. slow life history strategy organisms). For organisms with limited future reproductive potential (i.e. fast life history strategy organisms), delaying reproduction could result in no reproduction and consequently a loss of fitness. As Wingfield and Sapolsky (2003) argue, organisms with limited future reproductive potential may maintain reproductive capacity during stress by either mounting a blunted HPA axis response or by altering the communication between the HPG and HPA axes. Consequently, organisms with a faster life history strategy are expected to show blunted glucocorticoid output in response stress or altered HPA-HPG axis coupling.

Consistent with this idea, a review of research in birds, mammals and fish found that organisms with a faster life history strategy exhibit reduced glucocorticoid output particularly in response to stress (Carere, Caramaschi, & Fawcett, 2010). Likewise, in humans, blunted cortisol responsivity to stress has been associated with various characteristics of fast life history, including reduced parental care (Bos et al., 2018), earlier sexual debut (Brody, 2002), short-term mating orientation (Ponzi et al., 2015; Wilson et al., 2015), risk taking (Halpern, Campbell, Agnew, Thompson, & Udry, 2002a; Nofsinger et al., 2018) and impulsivity (Lovallo, 2013) which may partly result from disinhibition of the HPG axis (Zakreski et al., 2019). Taken together, evidence suggests that individuals with a faster life history strategy should exhibit blunted HPA axis activity particularly in response to stress.

4.6.3 SNS regulation of life history strategy

To compensate for blunted HPA axis responsivity to stress, organisms with a faster life history strategy may mount a larger SNS response to stress, since SNS activation, like HPA axis

activation, promotes processes that help organisms survive threat such as promoting energy release (e.g. lipolysis) (Hücking et al., 2003) and inhibiting inflammation (Kenney & Ganta, 2014). Unlike HPA activation, acute SNS activation does not suppress but rather facilitates reproduction, consistent with fast life history strategy. While glucocorticoids reduce gonadal steroid output, SNS activation up-regulates gonadal sex hormone secretion in part by sensitizing the gonads to gonadotropins (Engeland, 2013). SNS activation has also been found to enhance sexual arousal (Meston & Frohlich, 2000) Adrenergic receptor blockers inhibit sexual arousal in women (Meston, 2000) and in men reduce libido and inhibit erection (Fogari & Zoppi, 2002) suggesting that higher sympathetic outflow can facilitate mating effort. While findings are mixed, increased SNS activity has also been associated with various other markers of fast life history strategy including accelerated puberty (Cho, Mueller, Meininger, Liehr, & Chan, 2001; Lehmann, Eccard, Scheffler, Kurvers, & Dammhahn, 2018), impulsivity (Allen, Hogan, & Laird, 2009; Bennett, Blissett, Carroll, & Ginty, 2014; Bibbey, Ginty, Brindle, Phillips, & Carroll, 2016), and aggression (Hubbard et al., 2002; Sijtsema, Roon, Groot, & Riese, 2015).

4.6.4 Regulation of life history strategy by the hippocampus (HC)

Few studies explicitly examined relations between life history strategy and brain structure or function. Controlling for body size, Rushton (2004) found that species with slower life history strategies have larger brains. It is unclear however whether life history strategy is associated with any structural or functional differences in brain regions between individuals of the same species. While numerous brain regions likely affect or are effected by life history strategy, the hippocampus (HC) is a region of interest given 1) developmental factors (ELA) that theoretically entrain and empirically correlate with life history strategy are also known to alter the function and anatomy of the HC, 2) extensive research in humans and animals shows that changes in the

structure and function of the HC accompany changes in HPA axis, HPG axis and SNS activity, and 3) the behavioral correlates of life history strategy both affect and are affected by HC morphology.

4.6.4.1 HC and ELA

Research in humans and animals suggests that ELA alters the structure and function numerous brain regions (Luby et al., 2017; Thomason & Marusak, 2017). The HC is perhaps the most extensively studied in relation to ELA. In rodents (Hulshof et al., 2011; Ivy et al., 2010; Sousa et al., 2014) and humans (Lambert et al., 2017), ELA survivors show decreased performance on HC dependent cognitive task. ELA may affect the development and maintenance of the HC in various ways, (Frodl & O'Keane, 2013; Hoeijmakers, Lucassen, & Korosi, 2015; Korosi et al., 2012). For example, ELA can alter HC synaptogenesis and pruning during development by inhibiting axonal growth, mitochondrial activity, myelination and neurofilament formation (Wei et al., 2015). ELA also alters neurogenesis during development and in adulthood (Korosi et al., 2012). High glucocorticoid levels resulting from chronic stress can persistently modify the transcription of genes important for HC neurogenesis such as the gene encoding brain derived neuroprotective factor (BDNF), particularly if stress occurs early in life (Roth, Lubin, Funk, & Sweatt, 2009). ELA can also sensitize the HC to the effects of subsequent stress by epigenetically modifying the expression of glucocorticoid receptors within the HC (Champagne et al., 2008). Finally, chronic alterations of stress responsive neuroendocrine systems, including the HPA axis, SNS and potentially the HPG axis, may also mediate the long-term effects of ELA on HC development since the chemical messengers controlled by these neuroendocrine systems (e.g. glucocorticoids, CRH, sex steroids, inflammatory cytokines) are known to impact the function and structure of the HC (Chiang, Taylor, & Bower, 2015; Danese & McEwen, 2011;

Ehlert, 2013). By chronically altering the HPA, axis, SNS and HPG axis, ELA may have a cumulative effect on HC growth and maintenance over time.

Using MRI, numerous studies have examined the association between ELA and HC structure in humans, as reviewed in depth elsewhere (Frodl & O'Keane, 2013; Riem, Alink, Out, Ijzendoorn, & Bakermans-Kranenburg, 2015). Most of the studies published so far report an inverse association between ELA and HC volume (Bremner et al., 1997; Colle et al., 2017; Dahmen et al., 2018; Dannlowski et al., 2012; Gorka, Hanson, Radtke, & Hariri, 2014; Hanson et al., 2015; Janiri et al., 2017; Rao et al., 2010; Samplin, Ikuta, Malhotra, Szeszko, & DeRosse, 2013), although one study found larger HC volume in children exposed to ELA (Tupler & De Bellis, 2006). Several other studies, particularly in children, found no significant association between ELA and HC volume (Carrion et al., 2001; De Bellis et al., 1999; Gerritsen et al., 2012; Pederson et al., 2004; van Harmelen et al., 2010). While findings vary somewhat, MRI studies tend to finder smaller HC in ELA survivors, consistent with the effects of ELA on HC structure and function observed in animals.

4.6.4.2 HC and the HPA axis

The HC projects to the PVN of the hypothalamus via the lateral septal nucleus (Feldman, Conforti, & Weidenfeld, 1995) allowing the HC to control secretion of CRH and subsequently ACTH and glucocorticoids. Experiments in animals show that stimulating the HC inhibits glucocorticoid secretion (Casady & Taylor, 1976; Mueller, Dolgas, & Herman, 2004), while lesioning the HC increases glucocorticoid secretion (Ely, Greene, & Henry, 1977). This suggests that the HC inhibits HPA axis activity. Not all studies however support this conclusion. Buchanan, Tranel and Kirchbaum (2009) found that humans with HC lesions showed blunted (not greater) cortisol responsivity to stress compared to controls. Since the location and extent of

HC lesions vary between studies (particularly in humans), one potential explanation for the inconsistent association between HC structure and HPA axis activity is that different regions of the HC have different effects on HPA axis activity. Consistent with this idea, inhibition of the HPA axis largely arises from the ventral subiculum (Mueller et al., 2004; Ulrich-Lai & Herman, 2009). In contrast, in rodents, dorsal regions of the HC (equivalent to the human anterior HC (Gulyaeva, 2019)) appear to stimulate HPA axis activity (Umegaki, Yamamoto, Suzuki, & Iguchi, 2006). Since different regions of the HC have different effects on the HPA axis, it may be worthwhile to investigate the relationship between life history strategy and individual HC subfields.

HC structure and function are also affected by HPA axis activity. Cushing's syndrome patients who have abnormally high cortisol levels exhibit reduced performance on HC dependent cognitive tasks (Grillon, Smith, Haynos, & Nieman, 2004; Starkman, Gebarski, Berent, & Schteingart, 1992) and reduced HC volume (Starkman et al., 1992). Compared to the rest of the brain, the HC is rich with both type I and type II glucocorticoid receptors in humans (Seckl, Dickson, Yates, & Fink, 1991), rodents (Herman, Patel, Akil, & Watson, 1989; van Eekelen, Jiang, De Kloet, & Bohn, 1988) and non-human primates (Patel et al., 2000). Across these studies, the distribution of glucocorticoid receptors varies between HC subfields, with higher expression occurring in the dentate gyrus (DG). Different HC regions may therefore vary in sensitivity to the HPA axis, which further justifies the examination of life history strategy in relation to specific HC subfields. Acute and chronic activation of HC glucocorticoid receptors affects the function and structure of the HC. For example, glucocorticoid administration inhibits long term potentiation in the DG (Pavlides, Ogawa, Kimura, & McEwen, 1996) which could contribute to altered HC structure.

Numerous studies have used structural MRI to examine the relationship between HPA axis activity and HC volume in humans. A systematic review of this research (Frodl & O'Keane, 2013) associates lower HC volume with greater cortisol output at baseline and in response to stress. This is consistent with the idea that the HC is primarily involved in the inhibition of the HPA axis while increased HPA axis activity induces HC atrophy. Given that fast life history strategy potentially associates with blunted glucocorticoid responsivity to stress, one might expect fast life history strategy to have potentially protective effects of HC volume, at least for part of development; however, the consequences of prolonged hypocortisolism, which include heightened exposure to inflammatory cytokines and prolonged activation of the SNS, may lead to HC atrophy over time (Chiang et al., 2015).

4.6.4.3 HC and the SNS

The HC can affect autonomic tone via the NTS and medial prefrontal cortex (Ulrich-Lai & Herman, 2009). The HC may also reduce sympathetic outflow by inhibiting CRH secretion from the PVN. Animal research shows that stimulating the HC lowers heart rate, blood pressure, and respiratory rate (Ruit & Neafsey, 1988) while lesioning the HC increases heart rate and blood pressure during stress (Ely et al., 1977; Yokota, Sato, & Fujimori, 1963). These results could mean that the HC inhibits SNS activity, enhances parasympathetic nervous system activity or both, or acts on other systems (e.g. aldosterone). One study found that HC stimulation inhibited blood pressure in vagotomized cats treated with atropine (Yokota et al., 1963), suggesting that the HC does not exclusively regulate the parasympathetic nervous system and may inhibit SNS activity; however, other systems besides the SNS (e.g. aldosterone) may also mediate the effects of the HC on peripheral cardiovascular outcomes.

The HC may have excitatory effects on the SNS in addition to inhibitory effects. A few studies show that activation of cholinergic neurons within the dorsal HC increases markers of sympathetic outflow (Iguchi et al., 1992; Khookhor & Umegaki, 2013; Uemura et al., 1989) via excitation of the ventral medial hypothalamus (Iguchi et al., 1992). Thus, like HC regulation of the HPA axis, HC regulation of the SNS may vary between specific regions of the HC. This further justifies examining the relationship between life history strategy and specific HC subregions.

The HC, in addition to affecting SNS activity, is also affected by changes in SNS activity. The locus coeruleus, which activates sympathetic preganglionic fibers, also supplies the HC with noradrenergic input (Roth, Salzman, & Morgenroth, 1974). Changes in sympathetic outflow may therefore be coupled with changes in HC activity. Functional MRI studies have found that pressor challenges (e.g. the Valsalva maneuver), which activate the SNS, reduce BOLD signal within the HC (Harper, Bandler, Spriggs, & Alger, 2000; Macefield, Gandevia, & Henderson, 2006) further suggesting that acute changes in SNS activity lead to acute changes in HC activity. Individual differences in SNS function have also been associated with altered HC structure. Systolic blood pressure reactivity to stress predicted reduced HC volume one year later (Trotman, Gianaros, Veldhuijzen van Zanten, Williams, & Ginty, 2019) although this finding may be confounded by other systems affecting blood pressure (e.g. aldosterone). Over time, hyperactivity of the SNS increases risk of arthrosclerosis and other cardiovascular pathologies (Zakreski & Pruessner, 2019) which can lead to HC atrophy later in life (Koschack & Irle, 2005).

4.6.4.4 HC and the HPG axis

In both humans and animals, low levels of testosterone (Bimonte-Nelson et al., 2003; Moffat et al., 2002) or estradiol (Luine, Richards, Wu, & Beck, 1998; Resnick, Metter, & Zonderman,

1997) are associated with reduced performance on HC dependent cognitive tasks, suggesting that sex steroids may have neuroprotective effects with regards to the HC. The HPG axis may indirectly affect HC function and structure by acting on the HPA axis. As Viau reviews (2002), HPG axis hormones inhibit the HPA axis in multiple ways. Since hyperactivity of the HPA axis reduces the growth and maintenance of the HC, high levels of gonadal sex steroids may therefore exert neuroprotective effects on the HC in part by inhibiting the HPA axis. In addition to indirectly affecting the HC via the HPA axis, the HPG axis also directly affects the HC. The number of androgen receptors in the HC is on the same order of magnitude as in the prostate (Beyenburg et al., 2000). Estrogen receptors are also highly expressed in the HC relative to other parts of the brain (Gundlah et al., 2000; Mitra et al., 2003). Such abundant expression of HPG axis hormone receptors suggests that the HC is highly sensitive to changes in HPG axis activity. Research supports this notion. Sex steroids exert a broad range of effects on the HC reviewed in depth elsewhere (Vadakkadath Meethal & Atwood, 2005). For example, sex steroids promote HC growth and maintenance by enhancing neurogenesis (Galea, 2008) and by increasing regional blood flow to the HC (Maki & Resnick, 2000; Moffat & Resnick, 2007).

The HPG axis appears to affect the structure of the HC. In male vowels, higher plasma testosterone levels were associated with larger HC volume (Galea, Perrot-Sinal, Kavaliers, & Ossenkopp, 1999). Using voxel-based morphometry (VBM), Neufang et al. (2009) found that peri-pubertal children with higher testosterone levels exhibited larger HC gray matter volume, particularly boys. In contrast, other studies using whole brain VBM found no significant relationship between testosterone and gray matter volume anywhere in the brain, as reviewed elsewhere (Heany et al., 2016). Given the susceptibility of VBM to registration errors

(Bookstein, 2001), manual segmentation or multi-atlas based automated segmentation may be more sensitive to HC gray matter changes related to testosterone titers.

There is little research examining the effect sof HC structure or function on HPG axis activity. It is possible for the HC to affect HPG axis activity by acting on the various systems known to regulate the HPG axis such as the HPA axis. The HPA axis generally has an inhibitory effect on HPG axis activity at the level of the hypothalamus, pituitary and gonads (Rivier & Rivest, 1991; Whirledge & Cidlowski, 2010; Whirledge & Cidlowski, 2017; Zakreski et al., 2019). If the HC exhibits a predominately inhibitory effect on the HPA axis as reviewed in Section 4.6.4.2, the HC would likely disinhibit the HPG axis via inhibition of the HPA axis.

4.6.4.5 HC and behavioral correlates of life history strategy

The HC, along with other parts of the limbic system, regulate emotions and behaviors relevant to life history strategy. Bilateral lesions to the anterior temporal lobes can result in Kluever-Bucy syndrome, which is characterized by hypersexuality and impulsivity (Marlowe, Mancall, & Thomas, 1975), behavioral correlates of fast life history strategy. In children, Hanson et al. (2015) found that reduced HC volume mediated the relationship between ELA and externalizing problems (aggression, hyperactivity, etc.). Given the relationship between faster life history strategy and externalizing problems (Del Giudice, 2014), this suggests that HC volume may play a role in the development of fast life history strategy characteristics in ELA survivors.

On the other hand, behaviors related to life history strategy may also alter, in addition to being affected by, the function and structure of the HC. More aggressive mice exhibit higher BDNF levels in the HC (Lang et al., 2009), and male rats allowed to have positive fighting experiences showed increased neurogenesis in the dentate gyrus (Smagin et al., 2015). This may

suggest that certain behavioral characteristics of fast life history strategy (e.g. aggression) may have neuroprotective effects, at least with regard to the HC.

In conclusion, numerous lines of evidence suggest that facets of faster life history strategy including high testosterone output, reduced glucocorticoid output and potentially certain forms of behavior may at least initially promote the growth and maintenance of the HC, at least for part of development. Other factors such as chronic hyperactivity of the SNS or increased exposure to inflammatory cytokines may however lead to HC atrophy in individuals with a fast life history strategy later in development.

5 Objectives

Life history theory may explain why ELA and potentially other situational factors (e.g. death thoughts) affect the HPG axis, HPG axis and SNS stress response. Several limitations must be addressed (which are discussed in greater detail elsewhere in this thesis). First, as reviewed in Chapter 1, studies tend to focus on specific forms of ELA or focus on a narrow range of behaviors to indicate life history strategy. It is therefore important to replicate the association between ELA and life history strategy using validated measures of ELA and life history strategy that sample multiple forms of ELA and a wider range of characteristics that indicate life history strategy.

Second, while theories such as the pace of life model (Réale et al., 2010) associate life history strategy with activity of the HPA axis, HPG axis and SNS, research explicitly examining the physiological correlates of life history strategy has been predominately done on animals, tests only one or two physiological systems at a time, or examines only a narrow range of behaviors related to life history strategy. It is therefore important to replicate the associations predicted by

the pace of life model in humans, examining multiple physiological systems (the HPA axis, HPG axis and SNS) and using a valid multi-trait measure of life history strategy.

Research has related life history strategy to the *output* of the HPA axis, HPG axis and SNS (e.g. cortisol, testosterone, blood pressure), it is unclear how life history strategy relates to brain regions that regulate these neuroendocrine systems (i.e. the HC). Given that distinct HC subfields have distinct relationships with HPA axis, HPG axis and SNS, it is important to consider the relationship between life history strategy and individual HC subfield volumes in addition to the relationship between life history strategy and total HC volume.

If stress responsive neuroendocrine systems are associated with life history strategy, then conditions that theoretically program life history strategy (i.e. mortality cues) could potentially affect the physiological systems that regulate life history strategy. While studies have found that one mortality cue (priming thoughts of one's own death) induces *psychological* signs of faster life history strategy that are also seen in ELA survivors, no study has explicitly examined whether death thoughts also evoke *physiological* signs of faster life history strategy that are seen in ELA survivors.

To address these limitations, this thesis aims to 1) replicate past research showing a relationship between ELA and faster life history strategy, and to determine if 2) the association between life history strategy and activity of the HPA axis, HPG axis and SNS predicted by the pace of life model generalizes to humans, 3) if life history strategy covaries with the neuroanatomical features that regulate the HPA axis, HPG axis and SNS and respond to HPA axis, HPG axis and SNS activity and finally 4) to determine if the effect of ELA on the physiological stress response can at least be temporarily recapitulated by inducing death thoughts before exposing participants to a psychosocial stressor.

Chapter 1: Association Between Early Life Adversity and Life History Strategy

As discussed in the General Introduction, the relationship between life history strategy and fitness is moderated by ecological factors (e.g. premature mortality) (Ellis et al., 2009; Roff, 1992; Stearns, 1992). We know that various outcomes of life history strategy (e.g. reproductive onset and frequency) closely track changes in premature mortality and other ecological factors that impact life history strategy optimality according to research in humans (Cohan & Cole, 2002; Nandi, Mazumdar, & Behrman, 2017; Rodgers et al., 2005; Wilson & Daly, 1997) and other animals (Promislow & Harvey, 1990). How then do organisms accurately predict these ecological factors?

Researchers theorize that humans evolved to detect cues that over the course of human evolution reliably predict premature mortality and other life history strategy relevant ecological factors, and to adjust their life history strategy according to these cues (Belsky et al., 1991; Chisholm, 1993, 1996; Del Giudice, Ellis, et al., 2011; Ellis et al., 2009; Nettle et al., 2013). Consistent with this notion, numerous studies have found that individuals exposed to various forms of early life adversity (ELA) show various signs of fast life history strategy as reviewed elsewhere (Belsky, 2012; Cabeza de Baca, Wahl, Barnett, Figueredo, & Ellis, 2016; Csatho & Birkas, 2018; Ellis, 2004; Webster, Graber, Gesselman, Crosier, & Schember, 2014). Replicating the association between ELA and faster life history strategy is particularly important here, since this association is used to justify and interpret results from other investigations in this thesis (see General Discussion), and because replication provides an opportunity to address some of the challenges and inconsistencies in how ELA and life history strategy have been quantified in the past as reviewed below. The purpose of this chapter therefore is to review the assessment of ELA

and life history strategy and to replicate the association between ELA and fast life history strategy reported in past studies.

Interest in the health effects of ELA may outweigh interest in what ELA is and how to measure it systematically. ELA encompasses an indefinite range of events or conditions that could occur over a long period of time (conception to adulthood). There is no standardized operational definition of ELA or formal rules for equating one type of ELA (e.g. sexual abuse) with another type of ELA (physical abuse). Most of the research linking ELA with faster life history strategy focuses on specific forms or markers of ELA, most frequently childhood socioeconomic disadvantage or fragmented family structure (Richardson, Guardia, & Klay, 2018), or a combination of these factors. Different forms or markers of ELA are not always interchangeable however and may differentially influence life history strategy (Belsky, 2012; Ellis et al., 2009). It is therefore challenging to choose which forms or markers of ELA to use when investigating how ELA affects life history strategy and other outcomes.

Numerous studies of human life history strategy development focus on low childhood socioeconomic status (CSES) on the grounds that individuals with lower socioeconomic status may live in harsher, less predictable conditions (e.g. crowding, crime, poor housing, negative family relations) (Daly, Wilson, & Vasdev, 2001; Evans, 2004). Consistent with the notion that ELA accelerates life history strategy, several studies report various signs of faster life history strategy in individuals with low CSES (Griskevicius et al., 2013; Griskevicius, Delton, Robertson, & Tybur, 2011; Griskevicius, Tybur, et al., 2011; Nettle, 2010; Richardson, Dariotis, & Lai, 2017; Sheppard et al., 2016). Some studies however failed to associate CSES with markers of faster life history strategy (Aronoff & DeCaro, 2019; Moffitt, Caspi, Belsky, & Silva, 1992b; Pettay, Helle, Jokela, & Lummaa, 2007; Richardson et al., 2018; Szepsenwol, Simpson,

Griskevicius, & Raby, 2015; Szepsenwol, Zamir, & Simpson, 2019). For example, in 19th century Finland, the poorest women had children later in life, not earlier, as would be expected if poorer women had faster life history strategies (Pettay et al., 2007). One possible explanation for this unexpected finding is that depending on various cultural and economic factors, participants with low CSES may experience extreme malnutrition which is known to inhibit both reproductive and somatic effort, leading to a form of life history strategy that does not fit on the fast-slow life history strategy continuum (Ellis et al., 2009). Another complication is that low socioeconomic status is an inconsistent proxy of adversity. The actual harshness experienced by lower socioeconomic strata varies with cultural and economic factors such as social welfare or discrimination. These complications can make the relationship between CSES and life history strategy potentially more difficult to interpret compared to other forms of ELA.

The relationship between low CSES and fast life history strategy may to an extent be mediated or overwhelmed by family relations. Resource depletion reduces maternal care in macaques (Rosenblum & Paully, 1984) and rodents (Ivy, Brunson, Sandman, & Baram, 2008; Rice, Sandman, Lenjavi, & Baram, 2008). Likewise, cross-cultural research in humans associates poverty and economic recession with reduced parental investment (Conger et al., 2002; Evans, 2004; Nettle, Coall, & Dickins, 2011) and harsher parenting (Evans, 2004; Lee, Brooks-Gunn, McLanahan, Notterman, & Garfinkel, 2013). More generally, increased premature mortality due to war, disease outbreaks, neighborhood danger, etc. reliably predicts lower parental care (Deater-Deckard et al., 2019; Quinlan, 2007; Quinlan, 2010). Quality of parental care may therefore be a more proximate predictor of harsh, unstable conditions then low CSES. Across cultures, various markers of fast life history strategy have been observed in individuals who experienced parental absence (Anderson, 2015; Belsky et al., 2007; Bogaert, 2008; Culpin et al.,

2014; Ellis et al., 2003; Ellis & Garber, 2000; Ellis, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999; Gaydosh, Belsky, Domingue, Boardman, & Harris, 2018; Hoier, 2003; Maestripieri, 2005a; Moffitt et al., 1992b; Pesonen et al., 2008; Quinlan, 2003; Schlomer, Murray, Yates, Hair, & Vandenbergh, 2019; Sheppard & Sear, 2011; Sheppard, Snopkowski, & Sear, 2014; Webster et al., 2014) or harsh or insensitive parental care (Belsky et al., 2010; Belsky et al., 2007; Bereczkei & Csanaky, 2001; Chisholm et al., 2005; Dunkel, Mathes, Kesselring, Decker, & Kelts, 2015; Ellis & Essex, 2007; Ellis et al., 1999; Ivan & Bereczkei, 2006; Lukazewski, 2015; Meckelmann, Pfeifer, & Rauh, 2013; Quinlan, 2003; Szepsenwol et al., 2015), even after controlling for CSES (Chisholm et al., 2005; Dunkel et al., 2015; Ellis & Essex, 2007; Moffitt et al., 1992b; Quinlan, 2003). Low parental care and other negative family relations have been found to *mediate* the effects of low CSES on various markers of life history strategy (Belsky, Schlomer, & Ellis, 2012; James et al., 2012; Lukazewski, 2015), and *overwhelm* the effects of low CSES (Richardson et al., 2018) such that sensitive and reliable parental care may buffer children from the effects of low CSES while even socioeconomically privileged children may develop faster life history strategies in response to harsh, insensitive or absent parenting. This parallels research on the physiological stress response systems that we hypothesize facilitate life history strategy (see General Introduction). Maternal care and other negative family relations have been found to mediate or overwhelm the effects of low CSES on the function of the hypothalamic-pituitary-adrenal (HPA) axis (Blair et al., 2008; Chen, Cohen, & Miller, 2010) and the autonomic nervous system (Johnson et al., 2017; Lucas-Thompson & Granger, 2014) just as these factors mediate and overwhelm the effects of CSES on life history strategy. Given that parental care may buffer the effects of other forms of ELA, parental care should be included when assessing ELA and its effects on life history strategy.

Like CSES, relations between parental care and life history strategy may be confounded by differences in cultural or social factors. According to Anderson et al. (2015), for white South African children, who tend to live in nuclear families, father absence significantly predicted early puberty (a sign of fast life history strategy). In contrast, father absence did not significantly predict pubertal timing in black South African children, who tend to live with their extended family (e.g. uncles, grandparents) which may or may not involve the father. Indeed, the role of fathers in child rearing varies considerably between cultures (Sear, 2016) which may make relations between father-care and life history strategy more difficult to interpret. The role of mothers in child rearing also varies with social and cultural factors but is arguably more consistent and greater across species and cultures then the role of fathers. Cross-culturally and across species, mothers spend more time caring for their offspring than fathers (Bowlby, 1953; Lamb, Pleck, Charnov, & Levine, 1985; Sear, 2016). From an evolutionary perspective, differences in parental investment between mothers and fathers may occur partly because females have a greater fitness incentive than males to parent their offspring since females have fewer reproductive opportunities, and can guarantee their maternity (Trivers, 1972). While both fathers and mothers play an important role in rearing their children, the relationship between mother-care and life history strategy may be easier to interpret than the relationship between father-care and life history strategy. Indeed, numerous studies associate low mother-care with various markers of life history strategy (Belsky et al., 2010; Dunkel et al., 2015).

Forms of interpersonal adversity not specific to parent-child relations have also been associated with signs of fast life history strategy, including childhood sexual abuse (Boynton-Jarrett et al., 2013; Mendle, Leve, Ryzin, Natsuaki, & Ge, 2011; Negriff, Blankson, & Trickett, 2015; Vigil, Geary, & Byrd-Craven, 2005; Wise et al., 2009) and physical abuse (Mendle et al.,

2011; Wise et al., 2009). More recently, studies have examined the relationship between life history strategy and a broader range of adverse events/experiences that include physical, sexual and emotional adversity in addition to harsh family environments (Anderson, 2017; Brumbach, Figueredo, & Ellis, 2009; Chang & Lu, 2018; Dinh, Pinsof, Gangestad, & Haselton, 2017; James et al., 2012; Kogan et al., 2015; Patch & Figueredo, 2017; Simpson et al., 2012). For example, Patch and Figueredo (2017) associated life history strategy with a composite index of ELA based on physical, sexual and emotional abuse and low parental care. Examining a combination of mother-care in addition to physical, emotional and sexual maltreatment, may therefore capture the factors theorized to directly program life history strategy.

Like ELA, life history strategy is a broad construct without a gold standard measure. Life history strategy is after all a latent bias toward prioritizing one broad set of fitness components (e.g. mating, parenting, longevity) over another. Studies tend to associate ELA with specific signs of fast life history strategy, such as risk taking (Griskevicius et al., 2013; Griskevicius, Tybur, et al., 2011; Hampson et al., 2016; Ivan & Bereczkei, 2006; Wang, Kruger, & Wilke, 2009), aggression and other externalizing problems (Chang et al., 2019; Doom et al., 2015; Griskevicius, Tybur, et al., 2011; Ivan & Bereczkei, 2006; Simmons et al., 2019). More commonly, studies model the relationship between ELA and one or more reproductive outcomes such as early puberty (Belsky et al., 2007; Bogaert, 2008; Boynton-Jarrett et al., 2013; Chisholm et al., 2005; Culpin et al., 2014; Ellis, 2004; Ellis & Essex, 2007; Ellis & Garber, 2000; Ellis et al., 1999; Graber, Brooks-Gunn, & Warren, 1995; Hoier, 2003; James et al., 2012; Jean et al., 2011; Kogan et al., 2015; Mendle et al., 2011; Moffitt, Caspi, Belsky, & Silva, 1992a; Negriff, Blankson, et al., 2015; Pesonen et al., 2008; Quinlan, 2003; Richardson et al., 2018; Romans, Martin, Gendall, & Herbison, 2003; Sheppard et al., 2016; Vigil et al., 2005; Webster et al.,

2014), early sexual debut (Alvergne, Faurie, & Raymond, 2008; Ellis et al., 2003; James et al., 2012; Jorm, Christensen, Rodgers, Jacomb, & Easteal, 2004; Kogan et al., 2015; Međedović & Bulut, 2018; Quinlan, 2003; Vigil et al., 2005), having more sexual partners (Alvergne et al., 2008; Belsky et al., 2012; Quinlan, 2003), unrestricted sexuality (Anderson, 2017; Dinh et al., 2017; Lukazewski, 2015; Međedović & Bulut, 2018), early preferred or actual age at first birth or pregnancy (Chisholm et al., 2005; Gaydosh et al., 2018; Griskevicius, Delton, et al., 2011; Nettle et al., 2011; Pesonen et al., 2008; Quinlan, 2003; Sheppard et al., 2016; Sheppard & Sear, 2011; Sheppard et al., 2014; Vigil et al., 2005) and offspring quantity (Bereczkei & Csanaky, 2001; Pesonen et al., 2008; Sheppard et al., 2016).

While life history strategies evolved to influence reproductive outcomes, the relationship between reproductive outcomes and life history strategy in humans may be confounded by various social and economic factors such as social desirability, access to birth control and childcare services (Figueredo et al., 2015). Furthermore, it can be challenging to accurately measure certain reproductive outcomes in males, since sexual maturity and parental status are less conspicuous in males than in females. These limitations may *partly* explain why some studies fail to associate reproductive outcomes with ELA in males (Aronoff & DeCaro, 2019; Belsky et al., 2010; Bereczkei & Csanaky, 2001; Meckelmann et al., 2013; Negriff, Blankson, et al., 2015). Indeed, empirical evidence linking ELA with faster life history strategy predominately comes from girls and women (Belsky et al., 2010; Belsky et al., 2007; Bereczkei & Csanaky, 2001; Bogaert, 2008; Boynton-Jarrett et al., 2013; Chisholm et al., 2005; Culpin et al., 2014; Dinh et al., 2017; Ellis, 2004; Ellis et al., 2003; Ellis & Garber, 2000; Ellis et al., 1999; Graber et al., 1995; Hoier, 2003; Jean et al., 2011; Jorm et al., 2004; Maestripieri, 2005a; Meckelmann et al., 2013; Mendle et al., 2011; Moffitt et al., 1992a; Negriff, Blankson, et al., 2015; Nettle et al.,

2011; Quinlan, 2003; Richardson et al., 2018; Schlomer et al., 2019; Vigil et al., 2005; Webster et al., 2014; Wise et al., 2009).

Rather than focusing exclusively on reproductive *outcomes*, which may not be indicative of reproductive *effort* in humans, Figueredo and colleagues (Figueredo, de Baca, & Woodley, 2013; Figueredo et al., 2015; Figueredo et al., 2014) recommend measuring life history strategy by sampling a broad range of internal processes that mediate life history strategy trade-offs that go beyond reproductive outcomes (e.g. attachment security, impulsivity, prosocial behavior). Studies using broader measures of life history strategy that do not exclusively rely on reproductive outcomes have found significant associations between ELA and life history strategy in both males and females (Brumbach et al., 2009; Chang & Lu, 2018; Chua, Lukaszewski, Grant, & Sng, 2016; Dunkel et al., 2015; Lu & Chang, 2019; Patch & Figueredo, 2017). Some of these studies (Chang & Lu, 2018; Lu & Chang, 2019; Patch & Figueredo, 2017) however measured life history strategy with questionnaires that included items about received parental care which may have exaggerated the association between ELA and fast life history strategy in these studies since low parental care is not only a form of ELA but also moderates and mediates the effects of other forms of ELA (e.g. socioeconomic disadvantage) on life history strategy (Belsky et al., 2012; Lukazewski, 2015; Richardson et al., 2018). It is therefore important to use a broad multi-trait measure of life history strategy that excludes questions about received parental care in addition to a measure that does not exclusively depend on reproductive outcomes.

Given the above limitations, this study aimed to replicate the association between ELA and faster life history strategy in a sample of healthy young adults using self-report questionnaire measures of ELA and life history strategy. ELA was assessed based on retrospective mother-

care, sexual, physical and emotional maltreatment. Life history strategy was assessed using a broad multi-trait measure of life history strategy that does not depend exclusively on reproductive outcomes. To avoid inflating the relationship between ELA and life history strategy, we removed questions asking about parental care from our measure of life history strategy.

We measured ELA and life history strategy using retrospective self-report questionnaires. While self-report questionnaires are susceptible to recall errors and subjective biases, compared to other measurement methods (e.g. behavioral observation), self-report questionnaires enabled us to sample a relatively broad range of events and behaviors over a long period of time. Questionnaires were administered to two different samples. Study 1 was a pilot study consisting of a survey which participants completed over the Internet. This allowed us to recruit a large and diverse sample quickly but afforded less control over testing conditions. Study 2 tested a different sample of participants in a more controlled environment but recruited a smaller, less diverse sample since Study 2 participants needed to meet more specific inclusion criteria since these individuals provided endocrine and neuroanatomical data for other parts of this thesis.

Study 1 methods

Study 1 sample

We posted ads on Internet classifieds inviting adults between the ages of 18 and 30 to participate in an online psychological survey. The invitation was linked to an online survey made with FluidSurvey. The survey began with questions to assess inclusion and exclusion criteria followed by questionnaires assessing life history strategy and ELA. Participants were included if they were between 18 and 30 years old, lived with their mother between the ages of 0 and 16, and completed all the questions. Throughout the survey, participants were asked to enter a specific

number into a text field. Those who did not enter the number correctly were excluded. Of the 588 individuals who started the survey, 95 adults (53 women) were included in Study 1.

Study 1 questionnaires

The online survey included questionnaires to assess depression, ELA and life history strategy. A measure of depression, the Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001), was included since depression may confound associations between ELA and life history strategy by biasing recollection toward negative life events.

Early life adversity (ELA)

ELA was assessed using two retrospective self-report measures— the Parental Bonding Instrument (PBI) (Parker, Tupling, & Brown, 1979) and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The PBI measures mother-care during the first 16 years of life. The CTQ has 5 subscales: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect. We chose these questionnaires for several reasons. High test-retest reliability and validity evidence in young adults exposed to different forms of maltreatment has been demonstrated for both the PBI (Lancaster, Rollinson, & Hill, 2007; Mackinnon, Henderson, & Andrews, 1991; Wilhelm & Parker, 1990) and CTQ (Cammack et al., 2016; Forde, Baron, Scher, & Stein, 2012; Paivio & Cramer, 2004; Spinhoven et al., 2014). Furthermore, the PBI and CTQ have been used extensively to investigate the effects of ELA on the physiological stress response systems including the autonomic nervous system (Ali & Pruessner, 2012; Bernstein et al., 2013; Busso et al., 2016; Dale et al., 2018; Dalsant, Truzzi, Setoh, & Esposito, 2015; Kuras, McInnis, et al., 2017; McLaughlin et al., 2014) and the HPA axis (Carpenter et al., 2007; Carpenter et al., 2010; Engert, Buss, et al., 2010; Houtepen et al., 2016; Kawai et al., 2017; Kuras, Assaf, et al., 2017; Luecken, 2000; Narita et al., 2011; Vergara-Lopez, Chaudoir, Bublitz, Treter, & Stroud,

2016). The PBI and CTQ have also been used to study the effects of ELA on brain structures that regulate stress physiology, such as the hippocampus (Buss et al., 2007; Dannlowski et al., 2012; Gorka et al., 2014; Janiri et al., 2017; Narita et al., 2011). Furthermore, the CTQ and PBI have established norm based cutoffs for classifying participants as high or low on the various subscales (Bernstein et al., 2003; Parker & Lipscombe, 1979).

Participants were classified as high or low on mother-care relative to the recommended cutoff (Parker & Lipscombe, 1979). For each of the 5 CTQ subscales, participants were classified as low or high relative to the recommended cutoff for moderate to severe trauma (Bernstein et al., 2003). We classified participants as high ELA if they were low on mother-care, or high on at least one CTQ subscale. Participants were classified as low ELA if they were high on mother-care and low on all five CTQ subscales.

Life history strategy

The Mini-K is a 20 item self-report questionnaire measure of life history strategy. It is the short version of the 199 item Arizona Life History Battery (ALHB) (Figueredo et al., 2007). Items assess a broad range of psychological traits related to life history strategy including risk avoidance, social contact and preference for monogamy. The Mini-K is among the most commonly used questionnaire measures of life history strategy (Black, Figueredo, & Jacobs, 2017; Richardson, Chen, Dai, Brubaker, & Nedelec, 2017) and has demonstrated validity in young adults and other populations (Dunkel & Decker, 2010; Figueredo et al., 2014; Olderbak, Gladden, Wolf, & Figueredo, 2014). Since our sample consisted of young adults, we omitted items asking about the provision of parental care, as the test developer recommends. Since we were interested in the relationship between ELA and life history strategy, we omitted two items

about received parental care as this could inflate the association between ELA and life history strategy. This left 17 items. Higher scores on the Mini-K indicate slower life history strategy.

Study 1 data reduction and statistical analysis

Analyses were done using MATLAB 2017a (Mathworks, Inc. Natick, Massachusetts). We first examined correlations between study variables. For each variable, we tested whether it violated the normality assumption with the Anderson-Darling test then corrected violations with Box-Cox transformation. We then made a general linear model (GLM) regressing Mini-K onto dichotomized ELA. We repeated this analysis with PHQ-9 depression and gender as covariates.

Study 1 results

Table 1.1 reports descriptive statistics for Study 1. All ELA measures were significantly skewed even after Box-Cox transformation. 39 participants (48.15%) were classified as high ELA. Wilcoxon rank sum tests showed that low ELA and high ELA participants were significantly distant from each other on all ELA measures (all $|z|>4.6$, $p<0.001$). Table 1.2 shows the percentage of participants scoring high on PBI mother-care and each CTQ subscale.

Table 1.1 *Study 1 descriptive statistics of untransformed variables*

Variable	Low ELA (n=55)	High ELA (n=39)	Total (N=94)	High – low ELA
Sex (% female)	58	53.33	55.79	$\chi 2$=0.21, p=0.65
Age (years)	23.2 (2.88)	23.5 (3.04)	23.3 (2.95)	z=+0.54, p=0.59
PHQ-9 depression	6.28 (4.23)	12.5 (6.4)	9.21 (6.17)	z=+4.58, ***
ALHB Mini-K	1.08 (0.663)	0.599 (0.82)	0.854 (0.777)	t=-3.19, **
PBI mother-care	28.1 (5.11)	18.5 (10.1)	23.5 (9.2)	z=-4.62, ***
CTQ total	31.8 (5.74)	60.2 (17.9)	45.3 (19.3)	z=+7.83, ***
CTQ emotional abuse	7.38 (2.56)	14.6 (5.89)	10.8 (5.73)	z=+6.35, ***
CTQ physical abuse	5.52 (0.953)	10.9 (4.95)	8.05 (4.38)	z=+6.39, ***
CTQ sexual abuse	5.1 (0.463)	9.16 (5.37)	7.02 (4.21)	z=+5.11, ***
CTQ emotional neglect	8.12 (2.99)	15.8 (4.9)	11.8 (5.56)	z=+6.82, ***
CTQ physical neglect	5.7 (1.45)	9.73 (3.96)	7.61 (3.54)	z=+6.13, ***

Mean and standard deviation are reported as M (SD). Participants were classified as high or low ELA based on PBI and CTQ scores. For Gaussian variables, differences between high and low ELA groups were tested with an independent groups t-test. For non-Gaussian variables, differences between high and low ELA participants were tested with the Wilcoxon rank sum test and the distance of the difference from 0 is expressed as the z-static. ALHB=Arizona Life History Battery, CTQ=Childhood Trauma Questionnaire, ELA=early life adversity, PHQ-9=Patient Health Questionnaire, PBI=Parental Bonding Instrument, ***=p<0.001, **=p<0.01**,** *=p<0.05, T=p<0.01

Table 1.2 *Portion of Study 1 participants high on each ELA subscale*

ELA subscale	% of low ELA (n=55)	% of high ELA (n=39)
Low PBI mother-care	0	75.56
High CTQ emotional abuse	0	64.44
High CTQ physical abuse	0	66.67
High CTQ sexual abuse	0	51.11
High CTQ emotional neglect	0	71.11
High CTQ physical neglect	0	60

For each ELA subscale, participants were classified as high or low relative to the test developer's recommended cutoff. Participants were classified as high ELA if they were high on at least 1 CTQ subscale or low on PBI mother-care . CTQ=Childhood Trauma Questionnaire, ELA=early life adversity, ELA=early life adversity, PBI=Parental Bonding Instrument.

Table 1.3 reports zero-order correlations between study variables after Box-Cox transformation. Since CTQ subscale, CTQ total, and PBI mother-care scores were not normally distributed, even after Box-Cox transformation, we examined the association between dichotomized ELA and Mini-K total. As hypothesized, the GLM suggested that individuals categorized as high ELA reported significantly lower Mini-K scores (B=-0.243, SE=0.076, t[93]=-3.190, p=0.002). This association remained significant after controlling for PHQ-9 depression and sex (B=-0.197, SE=0.089, t[91]=-2.219, p=0.029).

Table 1.3 *Zero order correlations between Study 1 variables*

	1	2	3	4	5	6	7	8	9
1. Age									
2. PHQ-9 depression	-0.097								
3. ALHB Mini-K	+0.132	-0.21*							
4. PBI mother-care	+0.074	-0.375***	+0.502***						
5. CTQ total	-0.01	+0.559***	-0.422***	-0.753***					
6. CTQ emotional abuse	-0.033	+0.44***	-0.344***	-0.744***	+0.862***				
7. CTQ physical abuse	-0.045	+0.453***	-0.209*	-0.473***	+0.786***	+0.661***			
8. CTQ sexual abuse	-0.013	+0.358***	-0.114	-0.197T	+0.538***	+0.308**	+0.435***		
9. CTQ emotional neglect	+0.03	+0.551***	-0.509***	-0.761***	+0.914***	+0.745***	+0.602***	+0.371***	
10. CTQ physical neglect	-0.103	+0.38***	-0.336***	-0.593***	+0.788***	+0.548***	+0.604***	+0.421***	+0.702***

Measures of early life adversity (PBI mother-care, CTQ total and CTQ subscale scores were Box-Cox transformed).
ALHB=Arizona life history strategy, CTQ=Childhood Trauma Questionnaire, PBI=Parental Bonding Instrument, PHQ-9=Patient health questionnaire, ***=p<0.001, **=p<0.01, *=p<0.05, T=p<0.10.

Study 2 methods

Study 2 administered the same questionnaires as Study 1 but in a more controlled laboratory environment. The long version of the Mini-K was used to assess life history strategy. Study 2 also included additional questionnaires to validate our measure of life history strategy.

Study 2 sample

We recruited 62 healthy men between the ages of 18 and 30 via posts on Internet classifieds. Prospective participants completed a prescreening survey and phone interview to assess inclusion and exclusion criteria described for Study 1. Since Study 2 participants provided endocrine and neuroanatomical data analyzed in Chapters 2, 3 and 4, additional inclusion and exclusion criteria were applied (see Chapters 2 and 3). Only men were included in Study 2 because we did not have the resources required to control for both menstrual cycle phase, pregnancy or hormone contraceptives, all of which are known to affect the endocrine variables we assessed (Kudielka, Hellhammer, & Wust, 2009).

Study 2 questionnaires

Participants completed questionnaires alone in a quiet office space. Like Study 1, Study 2 included the PBI and CTQ to assess ELA and the PHQ-9 to assess depression. Study 2 included the long version of the Mini-K (the Arizona Life History Battery) to assess life history strategy. To assess the validity of the ALHB, we administered additional questionnaires to measure unrestricted sexuality and anger expression as theory and evidence suggest these characteristics should correlate with a valid measure of life history strategy.

ELA

ELA was measured and using the same method as Study 1 described above.

Life history strategy

Study 2 included the long version of the Mini-K, the Arizona Life History Battery (ALHB) (Figueredo et al., 2007), a 199 item self-report measure of life history strategy that examines a broad range of psychological traits associated with life history strategy including impulsivity, attachment security, altruism, social contact and support, and religiosity. Each of these traits is assessed by a different subscale. The Mini-K is also included as a subscale of the ALHB. The ALHB has been validated in a wide range of populations, and shows high internal-consistency and test-retest reliability as described elsewhere (Figueredo et al., 2013; Figueredo et al., 2015; Figueredo et al., 2014; Olderbak et al., 2014). Consistent with Study 1, we removed questions asking about received or provided parental care, leaving 162 items. For each participant, each ALHB subscale was scored by averaging his responses to that subscale. The ALHB total score was calculated by averaging the standardized subscale scores. Higher ALHB total scores indicate slower life history strategy.

Unrestricted sexuality

The revised Sociosexual Orientation Inventory (SOI-R) (Penke & Asendorpf, 2008) is a 9-item self-report questionnaire assessing sexual attitudes, beliefs and behaviors. Total scores on the SOI-R reflect unrestricted sexuality, a component of fast life history strategy. Past research shows that SOI-R scores correlate with various markers of life history strategy (Dunkel, Mathes, & Decker, 2010b; Kruger, 2017; Patch & Figueredo, 2017). Since higher total scores on the SOI-R predict a more unrestricted sexuality, we expected a negative correlation between SOI-R and ALHB total scores.

Trait anger expression

Hostility and aggression facilitate trade-offs between survival and mating in a manner consistent with fast life history strategy in both humans (Figueredo et al., 2018; Figueredo & Jacobs, 2010; Lu & Chang, 2019; Simmons et al., 2019) and animals (Biro & Stamps, 2008; Réale et al., 2010; Wolf, van Doorn, Leimar, & Weissing, 2007). While the ALHB assesses pro-social behavior, it does not directly assess aggression or hostility. Participants completed the trait subscale of the State-Trait Anger Expression Inventory-2 (STAXI) which assesses the tendency to express and experience hostile emotions (Spielberger, 1999). STAXI trait scores have been found to correlate with other measures of fast life history strategy (Giosan & Wyka, 2009). We therefore expected a negative correlation between STAXI trait and ALHB total scores.

Study 2 data reduction and statistical analysis

Analyses were similar to those in Study 1 only ALHB total was used as a measure of life history strategy instead of the Mini-K and Study 2 did not include sex as a covariate in any GLM since Study 2 included only male participants. To establish validity, Study 2 also examined whether ALHB total scores inversely correlated with two measures that theory and evidence suggest should be associated with fast life history strategy: SOI-R unrestricted sexuality and STAXI trait anger expression.

Study 2 results

Table 1.4 reports descriptive statistics for Study 2. 33 participants (53.3%) were classified as high ELA. Like Study 1, CTQ subscales, CTQ total and PBI mother-care scores were not normally distributed even after Box-Cox transformation. Like Study 1, Wilcoxon rank sum tests showed that low ELA and high ELA participants were significantly different on all measures of ELA (all $p<0.05$). Table 1.5 shows the percentage of participants scoring high on each subscale.

Table 1.4 *Study 2 descriptive statistics of untransformed variables*

Variable	Low ELA (n=55)	High ELA (n=39)	Total (N=94)	High – low ELA
Age (years)	24.09 (3.28)	24.8 (3.82)	24.47 (3.57)	t=+0.78
PBI mother-care	32.24 (2.56)	17.52 (7.4)	24.4 (9.31)	z=-6.23, ***
CTQ total	36.66 (2.89)	56.7 (11.85)	47.32 (13.39)	z=+6.48, ***
CTQ emotional abuse	6.39 (1.37)	14.33 (6.2)	10.61 (6.09)	z=+5.56, ***
CTQ physical abuse	5.55 (0.83)	9.61 (5.04)	7.71 (4.22)	z=+3.66, ***
CTQ sexual abuse	5.03 (0.19)	6.15 (2.48)	5.64 (1.88)	z=+2.57, *
CTQ emotional neglect	6.72 (2)	16.76 (4.46)	12.06 (6.14)	z=+6.35, ***
CTQ physical neglect	5.31 (0.71)	9.45 (3.33)	7.52 (3.22)	z=+5.78, ***
PHQ-9 depression	4 (5.72)	8.33 (3.62)	6.31 (5.28)	z=+3.24, **
ALHB total	0.32 (0.38)	-0.28 (0.59)	0 (0.62)	t=-4.75, ***
ALHB Mini-K	1.39 (0.61)	0.47 (0.77)	0.9 (0.84)	t=-5.15, ***
ALHB insight	1.84 (0.58)	1.49 (0.80)	1.65 (0.72)	t=-1.91, T
ALHB family contact support	1.83 (0.52)	1.02 (0.62)	1.4 (0.72)	t=-5.58, ***
ALHB friends contact support	1.93 (0.52)	1.69 (0.62)	1.8 (0.58	t=-1.66
ALHB attachment security	0.54 (0.85)	0.13 (0.85)	0.32 (0.87)	t=-1.9, T
ALHB altruism	0.39 (0.76)	0.27 (0.92)	0.33 (0.85)	t=-1.04
ALHB religiosity	-1.24 (1.5)	-1.92 (1.11)	-1.6 (1.34)	t=-2.04, *
SOI-R short-term mating	35.28 (15.41)	47.28 (14.52)	41.67 (16)	t=+3.16, **
STAXI trait anger	16.48 (4.14)	17.64 (5.07)	17.1 (4.65)	z=+1

Mean and standard deviation for each variable are reported as M (SD). Participants were classified as high or low ELA based on PBI and CTQ scores. For Gaussian variables, differences between high and low ELA groups were tested with an independent groups t-test. For non-Gaussian variables, differences between high and low ELA participants were tested with the Wilcoxon rank sum test and the distance of the difference from 0 is expressed as the z-statistic. ALHB=Arizona Life History Battery, CTQ=Childhood Trauma Questionnaire, ELA=early life adversity, PHQ-9=Patient Health Questionnaire, PBI=Parental Bonding Instrument, ***=$p<0.001$, **=$p<0.01$, *=$p<0.05$, T=$p<0.01$

Table 1.5 *Portion of Study 2 participants high on each ELA subscale*

ELA subscale	% of low ELA (n=55)	% of high ELA (n=39)
Low PBI mother-care	0	90.84
High CTQ emotional abuse	0	51.3
High CTQ physical abuse	0	36.33
High CTQ sexual abuse	0	18.28
High CTQ emotional neglect	0	64.06
High CTQ physical neglect	0	45.68

For each ELA subscale, participants were classified as high or low relative to the test developer's recommended cutoff. Participants were classified as high ELA if they were high on at least one CTQ subscale or low on PBI mother-care. CTQ=Childhood Trauma Questionnaire, ELA=early life adversity, PBI=Parental Bonding Instrument.

Table 1.6 reports zero-order correlations between variables after Box-Cox transforming variables that were not normally distributed. Like Study 1, ELA measures were inter-correlated with the exception of sexual abuse. As expected, ALHB total and ALHB subscale scores were inter-correlated with each other. ALHB total correlated most strongly with the Mini-K compared to the other ALHB subscales, consistent with other work (Figueredo et al., 2007). The ALHB had high internal consistency for this sample, with a coefficient alpha of 0.93. ALHB total scores were also significantly negatively correlated with other measures of fast life history strategy related traits. As expected, men with higher ALHB total scores had significantly lower SOI-R total ($r=-0.462$, $p<0.001$) and lower STAXI trait scores ($r=-0.378$, $p=0.003$).

Table 1.6 *Zero order correlations between Study 2 variables*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. ALHB total																
2. ALHB Mini-K	+0.845***															
3. ALHB insight	+0.686***	+0.565***														
4. ALHB family contact support	+0.565***	+0.484***	0.132													
5. ALHB friends contact support	+0.474***	+0.309*	0.179	0.205												
6. ALHB attachment	+0.458***	+0.311*	+0.298*	+0.215T	0.0604											
7. ALHB altruism general	+0.719***	+0.596***	+0.469***	0.18	+0.308*	0.134										
8. ALHB religiosity	+0.478***	+0.301*	+0.236T	+0.274*	0.0279	-0.15	+0.405**									
9. PBI mother-care	+0.66***	+0.612***	+0.353**	+0.585***	+0.246T	+0.318*	+0.301*	+0.336**								
10. CTQ total	-0.612***	-0.64***	-0.264*	-0.589***	-0.255*	-0.33**	-0.199	-0.297*	-0.843***							
11. CTQ emotional abuse	-0.559***	-0.647***	-0.29*	-0.422***	-0.18	-0.34**	-0.198	-0.272*	-0.718***	+0.881***						
12. CTQ physical abuse	-0.255*	-0.29*	-0.149	-0.338**	-0.118	-0.354**	0.127	0.112	-0.492***	+0.635***	+0.573***					
13. CTQ sexual abuse	-0.18	-0.173	-0.00134	-0.208	-0.139	-0.232T	0.081	0.0366	-0.434***	+0.457***	+0.343**	+0.485***				
14. CTQ emotional neglect	-0.69***	-0.675***	-0.348**	-0.655***	-0.29*	-0.363**	-0.302*	-0.308*	-0.849***	+0.887***	+0.782***	+0.479***	+0.327**			
15. CTQ physical neglect	-0.55***	-0.527***	-0.233T	-0.57***	-0.279*	-0.197	-0.244T	-0.252*	-0.777***	+0.796***	+0.612***	+0.379**	+0.43***	+0.734***		
16. SOI-R total	-0.462***	-0.636***	-0.203	-0.373**	-0.0553	-0.143	-0.229T	-0.235T	-0.375**	+0.461***	+0.485***	0.171	0.15	+0.471***	+0.372**	
17. STAXI trait anger	-0.378**	-0.326**	-0.149	-0.255*	-0.281*	-0.365**	-0.247T	-0.003	-0.318*	+0.247T	+0.315*	0.137	0.105	+0.368**	0.178	+0.292*

Measures of early life adversity (PBI mother-care, CTQ total and CTQ subscale scores were Box-Cox transformed). ALHB=Arizona life history strategy, CTQ=Childhood Trauma Questionnaire, PBI=Parental Bonding Instrument, PHQ-9=Patient health questionnaire, ***=p<0.001, **=p<0.01, *=p<0.05, T=p<0.10.

We made a GLM regressing ALHB total onto dichotomized ELA. As expected, the GLM suggested that individuals categorized as high ELA showed significantly lower ALHB total scores (B=-0.227, SE=0.077, t[79]=-2.970, p=0.004). This association remained significant after controlling for PHQ-9 depression (B=-0.199, SE=0.093, t[77]=-2.150, p=0.035).

Discussion

With a combined sample of 157 young adults, two studies examined the association between ELA (in the form of low maternal care, or high emotional, physical or sexual maltreatment) and a multi-trait based measure of life history strategy (the short and long versions of the ALHB), that did not exclusively rely on reproductive outcomes. As hypothesized, individuals exposed to higher ELA exhibited a faster life history strategy (lower Mini-K and ALHB scores). This association remained significant after controlling for sex and depression. Furthermore, our measures of ELA and life history strategy demonstrated good psychometric properties in this investigation. The inter-correlation between ELA measures matches findings from past research using other measures of mother-care, emotional, physical and sexual abuse (Herrenkohl & Herrenkohl, 2007), such that with the exception of sexual abuse, measures of ELA were collinear. Furthermore, the ALHB showed high internal consistency between items and between subscales, and significantly negatively correlated with variables that are theoretically and empirically related to fast life history strategy, i.e. unrestricted sexuality and the tendency to experience or express anger, such that men with faster life history strategies exhibited more unrestricted sexuality and a greater tendency to experience and express anger.

The association we observed between high ELA and faster life history strategy replicates results from past studies reviewed in the introduction of this chapter while adjusting for a few limitations in past research. First, our findings replicate results from studies associating ELA

with specific characteristics of fast life history strategy (e.g. risk taking, aggression, pubertal timing, sexual debut, number of offspring). While these specific traits or outcomes are empirically and theoretically relevant to life history strategy, life history strategy is a pattern of traits not a specific trait. Aggregating scores across multiple traits may therefore provide a more reliable estimate of life history strategy than a single trait or outcome. Since we used a broad measure of life history strategy based on multiple traits that mediate life history trade-offs, our findings suggest that ELA is related to a pattern of traits consistent with life history strategy, not just specific outcomes or characteristics related to life history strategy. Furthermore, our findings replicate past research using reproductive outcomes as markers of life history strategy. Reproductive outcomes may not always accurately reflect life history strategy given various social and cultural factors (Figueredo et al., 2015). Furthermore, reproductive outcomes may be particularly difficult to interpret in males since males have less conspicuous paternity and sexual maturity compared to females, which may partly explain why some studies fail to associate ELA with life history strategy in males, as reviewed in the introduction of this chapter. While Study 2 found that ALHB total correlated with unrestricted sexuality, the ALHB is not exclusively based on reproductive outcomes which may partly explain why we were able to find effects in both females (Study 1) and males (Studies 1 and 2).

Another limitation of past research addressed in the current investigation is that studies linking ELA with faster life history strategy have often focused on specific markers or forms of ELA (e.g. low childhood socioeconomic status (CSES) or father-care). As stated earlier in this chapter, the relationship between life history strategy and CSES may be difficult to interpret given variable discrepancies in nutrition and health between the rich and the poor. The effects of father-care may also be difficult to interpret given cultural variation in the role of fathers. Often

studies focused on ELA within the context of parental relations without considering more general forms of interpersonal adversity (emotional, physical or sexual maltreatment) which should also theoretically convey information about premature mortality in the individual's environment (Belsky et al., 1991). Here we used a composite measure of ELA that captures key events believed to shape life history strategy (low mother-care or high levels of either physical, sexual or emotional abuse, or physical or emotional neglect). Our results are therefore consistent with other studies that used different measures of ELA reviewed earlier in this chapter suggesting that various forms of early adverse experiences likely have similar effects on life history strategy.

Limitations

This investigation had several limitations that should be addressed in future research. The first concerns our assessment of ELA. Since in both Study 1 and 2 our measures of ELA (PBI mother-care, CTQ subscales) were highly collinear, we could not assess the effects of different forms of childhood abuse and neglect independently of each other. Future research should attempt to recruit individuals exposed to specific forms of ELA and not others to see if specific forms of maltreatment have differential effects on life history strategy.

While the ALHB, CTQ and PBI are routinely used questionnaires that have been validated in numerous populations (see methods section), like any retrospective self-report questionnaire, they are susceptible to subjective bias, recall error or factors present in the testing environment. Nonetheless, retrospective self-report questionnaires, compared to alternative measures (e.g. behavioral observation) were not only more practical and less expensive to administer but enabled us to sample a broad range of phenomena relevant to life history strategy and ELA over a wide range of time. To obtain a more reliable measure of life history strategy or

ELA that is less likely influenced by situational factors, future research may administer self-report questionnaires repeatedly across a range of situations and average scores across situations (Moskowitz, Russell, Sadikaj, & Sutton, 2009).

Conclusion

In conclusion, this investigation reviewed research on the relationship between ELA and life history strategy in humans. Studies tend to associate ELA with faster life history strategy. Since there is no gold standard measure for either ELA or life history strategy, researchers have used a diverse range of measures to assess these phenomena. The present study replicated the association between ELA and faster life history strategy using validated measures of ELA that captures key interpersonal experiences believed to influence life history strategy, and a broad multi-trait based measure of life history strategy. This suggests that exposure to various forms of interpersonal ELA is associated with a general pattern of traits consistent with a faster life history strategy not just specific, individual traits.

Chapter 2: Life History Strategy Covaries with Adrenocortical, Gonadal and Sympathetic Activity During Stress

Chapter 1 suggests that life history strategy can account for various behavioral effects of ELA but can life history strategy account for some of the physiological effects of ELA? As reviewed in the General Introduction, numerous effects of ELA on health and development are partly mediated by alterations of stress responsive neuroendocrine systems including the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG) axis, and the sympathetic nervous system (SNS). While the physiological mechanisms of life history strategy remain relatively unclear, especially in humans, the HPA axis, HPG axis and SNS exhibit several properties that theoretically make them probable regulators of life history strategy, as reviewed in the General Introduction and elsewhere (Korte et al., 2005; Ricklefs & Wikelski, 2002; Wikelski & Ricklefs, 2001; Wingfield et al., 1990; Wingfield & Sapolsky, 2003). The HPA axis, HPG axis and SNS are highly conserved across vertebrates and exert numerous pleiotropic effects on metabolism, growth, reproduction and other life history relevant processes. Furthermore, both the acute and chronic activity of these neuroendocrine systems changes in response to ecological conditions that are hypothesized to alter life history strategy (e.g. harsh, unpredictable or uncontrollable conditions). Synthesizing research on animals, the pace of life model (Réale et al., 2010) hypothesizes that faster life history strategy is facilitated by reduced HPA axis activity, increased HPG axis activity and increased SNS activity.

Past research explicitly examining the association between life history strategy and physiology is limited in the following way. First, most studies explicitly examining the physiological correlates of life history strategy are limited to animals (Dammhahn, Dingemanse, Niemelä, & Réale, 2018). These findings may not generalize to humans however. Compared to

other vertebrates, humans have unique life history strategies (e.g. humans have extremely slow and potentially more plastic life history strategies) (Del Giudice, Gangestad, & Kaplan, 2015; Hill & Kaplan, 1999). Since different physiological systems may regulate life history strategy in humans, it is important to empirical test whether HPG axis, HPA axis and SNS function correlate with life history strategy in humans in a manner similar to animals.

A second limitation is that studies typically examine one or two physiological systems at a time, such as the HPG axis alone, or the HPG and HPA axes. Given extensive cross-talk between the HPA and HPG axes (Viau, 2002; Zakreski et al., 2019), and between the HPA axis and SNS (Zakreski & Pruessner, 2019), the relationship between life history strategy and one system may depend on the relationship between life history strategy and another system. It would therefore be useful to model the effects of HPA axis, HPG axis, and SNS function simultaneously to see if these systems relate to life history strategy independently of each other.

Third, studies tend to examine specific markers of life history strategy, typically reproductive outcomes, such as pubertal timing (Lehmann et al., 2018; Negriff, Saxbe, et al., 2015), parental investment (Kuo et al., 2018) or short-term mating orientation (Gettler et al., 2018). As discussed in Chapter 1, since life history strategy is a broad and latent construct, examining a broader range of characteristics may be more accurate than measuring one marker. The risk of a single outcome misrepresenting life history strategy is particularly high in studies that rely exclusively on reproductive or sex-related outcome (e.g. number of sexual partners, age at first pregnancy), as the relationship between reproductive outcomes and life history strategy may be confounded by social and cultural factors (see Chapter 1 Introduction). It is therefore important to measure a broad range of characteristics related to life history strategy, not just a single aspect and to use a measure that does not rely exclusively on reproductive outcomes.

To address these limitations, the current study tested whether HPA axis, HPG axis and SNS activity during stress independently covary with life history strategy, as assessed by a comprehensive and well-validated battery of psychological traits (see Chapter 1). We exposed 63 healthy young men from Chapter 1 (Study 2) to a standardized psychosocial stress task. HPA axis, HPG axis and SNS activity were indexed by salivary cortisol, testosterone and alpha-amylase. As hypothesized by the pace of life theory (Réale et al., 2010), we predicted that men with faster life history strategies output less cortisol, more testosterone and more alpha-amylase during stress.

Methods

Sample

We recruited 63 healthy young men from the Montreal community, the same sample described in Study 2, Chapter 1. We tested only men since we did not have sufficient resources to control for menstrual cycle phase and chemical contraceptives which are known to affect steroid hormone levels (Kudielka et al., 2009). Exclusion criteria were past or current mental illness, a BMI less than 18 kg/m^2 or greater than 28 kg/m^2, prior exposure to a standardized psychosocial stress task, more than three alcoholic beverages per day, using marijuana or tobacco more than twice weekly, or using prescription or other drugs.

Procedure

Figure 2.1 provides a timeline of the procedure and indicates when saliva samples were taken. Before testing, we told participants to avoid drugs and alcohol for at least 24 hours before testing, and on testing day, to avoid caffeine and physical exertion, and to eat breakfast. To correct for circadian cortisol rhythms, testing occurred between 12:30 PM – 3:30 PM. The procedure lasted roughly 2.25 hours and consisted of habituation, a psychosocial stressor, and

recovery. Cortisol and alpha-amylase were assessed throughout the procedure. Testosterone was assessed before and after the stressor. As part of a separate investigation (Chapter 4), prior to the psychosocial stressor, participants were exposed to either a mortality cue or a control cue as part of the death thought manipulation. Since the effect of the cue was not relevant to the present investigation, to control for the effects of cue on cortisol, alpha-amylase and testosterone levels, cue was included as a categorical covariate in the general linear models (GLMs) we used to test our hypotheses.

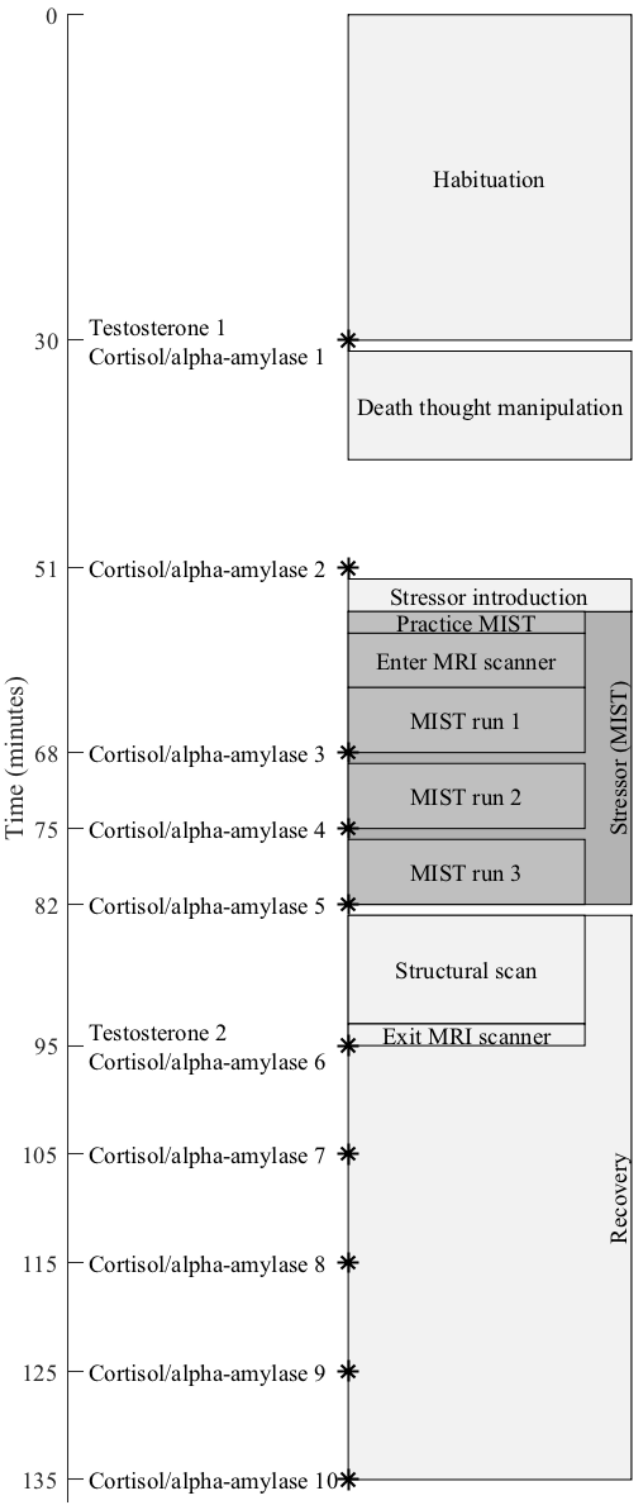

Figure 2.1. Time in minutes of each saliva sample relative to participants' arrival. Salivary cortisol and alpha-amylase were measured 10 times using the swab method. Salivary testosterone was assessed twice using the passive drool method. The death thought manipulation was performed as part of a separate project and controlled for in our statistical analysis.

Habituation

Upon arrival, participants were told to wash their mouth thoroughly with water then habituated to the laboratory environment for 30 minutes while completing questionnaires. Baseline testosterone, cortisol, and alpha-amylase were assessed after habituation.

Psychosocial stressor

As part of a separate project, participants performed the stress task inside the magnetic resonance imaging (MRI) scanner. We used the Montreal Imaging Stress Test (MIST) (Dedovic et al., 2005) which is designed for neuroimaging environments. The MIST is a computer task done inside the MRI scanner where participants perform mental arithmetic under time pressure and negative social evaluation. Although participants are urged to do their best, the task covertly adjusts difficulty so that participants perform poorly. Participants practiced the MIST for 2 minutes to habituate to the interface. Once inside the scanner, participants performed the MIST for 18 minutes (1 minute in control mode, 2 minutes in experimental mode, repeated 6 times). Every 6 minutes, participants received negative performance feedback from an opposite-sex confederate while a saliva sample was taken.

Recovery

After the stressor, there was a 1 hour recovery period. This involved a 9 minute structural MRI scan. After exiting the scanner, participants completed questionnaires, colored in coloring books, or read magazines before debriefing.

Salivary cortisol

HPA axis activity was indexed by salivary cortisol. We collected saliva throughout the experiment using Salivette® collection devices (Sarstedt Inc., Quebec City, Canada). Figure 2.1 indicates the time of each saliva sample. To collect one sample, participants placed the cotton

swab in their mouth for 2 minutes without chewing. Saliva samples were frozen immediately at -20 degrees C until analysis. Cortisol levels (nmol/L) were measured in duplicate by time-resolved fluorescence immunoassay with 0.179 nmol/L sensitivity and intra-assay and inter-assay variability below 10% and 12% respectively (Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992).

Salivary alpha-amylase

Alpha-amylase, a peptide that breaks down starch and kills bacteria, is a relatively new marker of SNS activity (Chatterton, Vogelsong, Lu, Ellman, & Hudgens, 1996; Nater et al., 2006; Zakreski & Pruessner, 2019). Alpha-amylase was examined in the same saliva samples as cortisol. The concentration of alpha-amylase (enzyme units per milliliter; U/mL) in each sample was measured in duplicates using an enzyme kinetic method described elsewhere (Engert et al., 2011) with intra-assay and inter-assay variability around 6.3% and 7.6% respectively.

Salivary testosterone

Salivary testosterone, a marker of HPG axis activity, was collected after habituation, and after the stress task (Figure 2.1). Saliva for testosterone was collected by the passive drool method which more closely approximates free testosterone levels in blood than other methods of saliva collection (Fiers et al., 2014). For each sample, participants were instructed to drool into an empty Salivette® collection device providing 2 mL of saliva per sample. Since testosterone is highly unstable at room temperatures, samples were put on dry ice immediately then stored at -20 degrees C until analysis. Testosterone concentration for each sample was measured in duplicates using the expanded range enzyme-linked immunoassay (Salimetrics, LLC.), with intra-assay and inter-array variability below 10% and sensitivity at 1 pg/mL.

Life history strategy

As described in Chapter 1, Study 2, life history strategy was assessed using the Arizona Life History Battery (ALHB) (Figueredo et al., 2007). Higher ALHB total scores indicate slower life history strategy.

Data reduction and statistical analysis

Cortisol and alpha-amylase output following the stress task were quantified by area under the curve with respect to ground (AUC_G) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). To isolate stress-induced elevations in cortisol and alpha-amylase, we used only the samples collected after stressor induction. AUC_G is advantageous over alternative approaches (e.g. repeated measures ANOVA, growth curve analysis) because AUC_G is simple to compute, makes fewer statistical assumptions and is routinely used to quantify cortisol, alpha-amylase and testosterone output during stress. To capture stress-induced activity of the HPG axis, only the post-stress testosterone sample was used.

To test the hypothesized association between life history strategy and activity of the HPA axis, HPG axis and SNS during stress, we made a general linear model (GLM) regressing ALHB total onto cortisol output, alpha-amylase output and post-stress testosterone. To ensure the relationship between ALHB total and each biomarker was independent of the effect of cue, we included cue (mortality vs. control) as a dichotomous covariate. Violations of the normality assumption were checked with Anderson-Darling tests and corrected for by Box-Cox transformation. Multicollinearity was quantified by the variance inflation factor (VIF). The influence of specific observations on overall model fit was quantified by Cook's distance (Belsley, Kuh, & Welsch, 1980). DFBETAS quantified the influence of an observation on the estimated effect of each predictor (Belsley et al., 1980). Recommended cutoffs for Cook's

distance and DFBETAS were respectively 4 times the mean Cook's distance, and 3/√N as specified in the MATLAB 2017a user manual (Mathworks, Inc. Natick, Massachusettes).

Results

Table 2.1 provides descriptive statistics. Additional descriptive statistics and correlations between variables (e.g. age, ALHB subscales) are reported in Chapter 1 Study 2. Cortisol output and post-stress testosterone levels were significantly positively correlated (r=+0.344, p=0.009). Since both variables are predictors in the same regression formula, we examined multicollinearity by calculating VIF. For cortisol output and post-stress testosterone, VIF was 1.129 and 1.130 respectively, below the recommended limit of 5 (Craney & Surles, 2002). Alpha-amylase output was not significantly correlated with either cortisol output or post-stress testosterone (p>0.550) and according to point-biserial correlations, neither cortisol output, alpha-amylase output or post-stress testosterone differed significantly between the control cue and mortality cue conditions (p>0.439).

Table 2.1. *Sample descriptive statistics*

Variable	**Low ELA (n=29) M (SD)**	**High ELA (n=33) M (SD)**	**Total (N=62) M (SD)**
BMI (kg/m2)	22.73 (2.37)	23.13 (2.17)	22.94 (2.25)
ALHB total	0.32 (0.48)	-0.28 (0.59)	0 (0.62)
Cortisol AUCG	523.31 (332.34)	410.80 (196.58)	463.43 (272.35)
Alpha-amylase AUCG	22243.83 (3814.55)	18461.29 (5319.39)	20230.54 (5014.30)
Post-stress testosterone	132.52 (39.23)	141.08 (47.75)	137.07 (43.83)
Testosterone AUCG	11193.40 (2884.89)	12230.96 (3882.55)	11745.65 (3464.15)

Mean and standard deviation including those for ALHB subscales are based on raw data. ALHB subscale scores were standardized only for computation of ALHB total. Higher ALHB total scores indicates slower life history strategy. ALHB=Arizona life history strategy.

GLM regressed ALHB total onto cortisol, testosterone and alpha-amylase AUC_G. Cue (mortality vs. control) was included as a dichotomous covariate. Overall, the model explained a significant portion of the variance in ALHB total ($F[1,57]=4.52$, $p=0.003$, $R^2=0.241$). Table 2.2

provides regression coefficients and related statistics. Higher ALHB total (indicative of a slower life history strategy) was associated with significantly greater cortisol and alpha-amylase output and lower post-stress testosterone levels. These effects remained significant after controlling for 3 comparisons with the Bonferroni-Holm method. We also repeated the analysis, replacing post-stress testosterone with testosterone AUC_G (using both pre and post stress testosterone samples) and results were similar (effect of testosterone AUC_G on ALHB total was t[57]=-2.791, p=0.007).

Table 2.2. *Effects of cortisol, testosterone and alpha-amylase output on life history strategy*

Term	Estimate	SE	t[57]	p	Adjusted p
Cortisol AUC_G	$+6.431 \times 10^{-4}$	2.790×10^{-4}	+2.305	0.025	0.025
Post-stress testosterone	-4.656×10^{-3}	1.735×10^{-3}	-2.683	0.010	0.029
Alpha-amylase AUC_G	$+3.568 \times 10^{-5}$	1.441×10^{-5}	+2.475	0.016	0.033
Mortality – Control cue	+0.090	0.071	+1.265	0.211	
Intercept	-0.379	0.389	-0.974	0.334	

Total score on the Arizona Life History Battery (ALHB) was regressed onto cortisol AUC_G, post-stress testosterone, and alpha-amylase AUC_G and cue (mortality vs. control). Adjusted p values are p values after using the Bonferroni-Holm method for 3 comparisons. We corrected for three comparisons because three coefficients (cortisol, testosterone and cue) were of theoretical interest. ALHB total scores indicate slower life history strategy. AUC_G = area under the curve with respect to ground.

Figure 2.2 shows the adjusted response plot for cortisol output (A), post-stress testosterone (B), and alpha-amylase output (C). While the effect of cortisol AUC_G was in the hypothesized direction, visual inspection of Figure 1.2 (A) suggests the effect of cortisol AUC_G is driven by an influential observation. DFBETA for this participant and term, and Cook's distance for this participant did not exceed the cutoffs described in the methods section. There was no procedural or other known abnormality to justify exclusion of this participant. Nonetheless, after removing this observation, the effect of cortisol output was no longer statistically significant (t[56]=1.518, p=0.135). Model fit was similar although slightly lower (R^2

= 0.217, p=0.008) and the effects of alpha-amylase and post-stress testosterone were also similar (t[56]=2.441, p=0.018 and t[56]=-2.583, p=0.012, respectively).

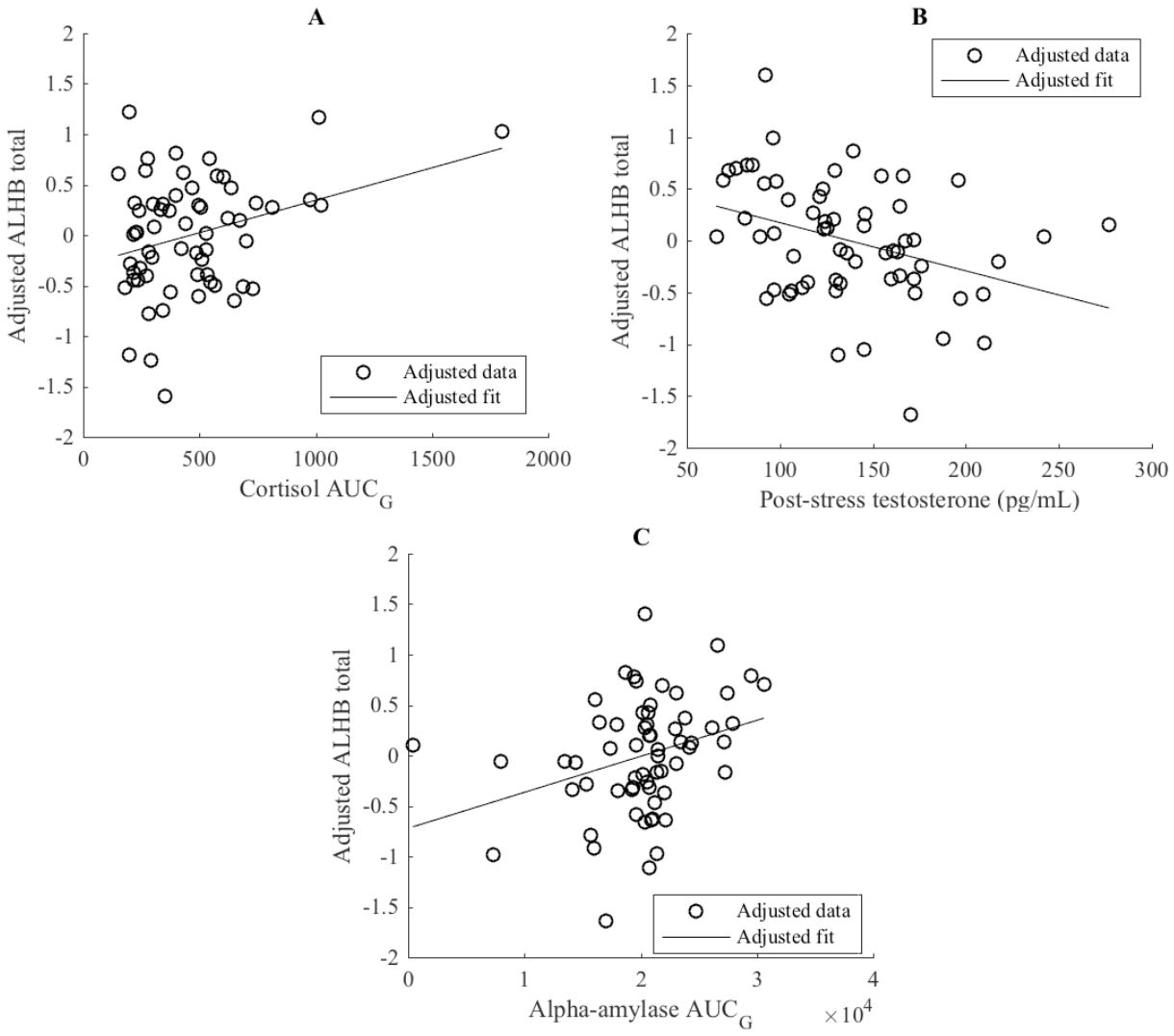

Figure 2.2. Effects of cortisol output (A), post-stress testosterone (B) and alpha-amylase output (C) on ALHB total. Higher ALHB total indicates slower life history strategy. Each adjusted response plot shows the effect of the predictor (X-axis) on ALHB total, controlling for other predictors in the model. For instance, A shows the effect of standardized cortisol output on ALHB total controlling for cue, post-stress testosterone, and alpha-amylase output. ALHB = Arizona Life History Battery, AUC_G = area under the curve with respect to ground.

Discussion

This study examined how life history strategy relates to the function of neuroendocrine systems implicated in the health and developmental effects of ELA, specifically, HPA axis, HPG

axis and SNS activity following acute psychological stress. Cortisol output, post-stress testosterone, and alpha-amylase output each independently contribute to the variance in life history strategy which was measured by a comprehensive battery of questionnaires (the ALHB). Participants with a slower life history strategy released more cortisol and less testosterone following stress. Unexpectedly, slower life history strategy was associated with greater, as opposed to lower, alpha-amylase output.

As hypothesized by the pace of life model (Réale et al., 2010), participants with faster life history strategies had higher post-stress testosterone levels indicating greater HPG axis activity. This is consistent with research in humans and animals which associate higher testosterone levels with specific markers of fast life history strategy such as reduced parental care (Alvergne et al., 2008; Gettler, McDade, & Kuzawa, 2011; Gray et al., 2017; Onyango, Gesquiere, Altmann, & Alberts, 2013), more sexual partners (Alatalo et al., 1996; Bogaert & Fisher, 1995; Peters et al., 2008; Pollet et al., 2011), unrestricted sexuality (Booth & Dabbs, 1993; Gettler et al., 2018; Hooper, Gangestad, Thompson, & Bryan, 2011; Puts et al., 2015), risk taking (Apicella, Carré, & Dreber, 2015; Apicella et al., 2008; Nofsinger et al., 2018) and aggression and hostility (Anestis, 2006; Archer, 2006; Girdler, Jammer, & Shapiro, 1997).

Also as hypothesized, men with a slower life history strategy exhibited higher cortisol levels during stress. This effect however is difficult to interpret since it was no longer statistically significant after removing what appears visually to be an influential observation. To resolve uncertainty in this effect, future research should attempt to replicate our findings. Nonetheless, the association we observed between slower life history strategy and greater cortisol output is in the direction hypothesized by the pace of life model (Réale et al., 2010), and is consistent with results from past studies examining the association between life history strategy and

glucocorticoid regulation. A review of research in birds, mammals and fish (Carere et al., 2010) found that studies tend to associate reduced glucocorticoid output with faster life history strategy. Likewise, in humans, reduced cortisol responsivity to stress has been associated with specific markers of fast life history strategy such as accelerated puberty (Saxbe, Negriff, Susman, & Trickett, 2014), short-term mating orientation (Ponzi et al., 2015; Wilson et al., 2015), younger age at first intercourse (Brody, 2002), more sexual partners (Halpern et al., 2002a), risk taking (Brown et al., 2016), impulsivity (Lovallo, 2013) and aggression (Almeida, Lee, & Coccaro, 2010).

Men with slower life history strategies also exhibited significantly *greater* SNS activity during stress as indexed by alpha-amylase output while fast life history strategy was associated with blunted SNS activity. Although this effect is opposite to what the pace of life model predicts (Réale et al., 2010), it is in line with results from other studies. Corsican blue tits with faster life history strategies exhibited reduced heart rate during restraint stress (which could mean blunted SNS responsivity), consistent with what was observed here (Dubuc-Messier, Réale, Perret, & Charmantier, 2017). In humans, various markers of blunted SNS responsivity have been associated with specific behaviors related to life history strategy, such as aggressive, delinquent and other externalizing behaviors (de Vries-Bouw et al., 2012; Susman et al., 2010). On the other hand, contrary to this study, but consistent with the pace of life model, several studies have associated specific facets of fast life history strategy with *greater* SNS activity at rest or under stress. Early puberty, a sign of fast life history strategy, has been associated with higher resting blood pressure (Cho et al., 2001; Dreyfus et al., 2015; Lehmann et al., 2018) and greater alpha-amylase reactivity to stress (Weichold, Büttig, & Silbereisen, 2008).

It is challenging to explain the mixed associations between life history strategy and SNS responsivity since only a few studies explicitly examine relations between life history strategy and SNS function. One possibility is that SNS function may differentially relate to different components of life history strategy although this would seem unlikely since different components of life history strategy (e.g. mating effort, somatic effort) and their various subdomains supposedly function as cohesive whole. The relationship between SNS function and specific facets of life history strategy (e.g. pubertal timing) may also be less reliable across studiers compared to the relationship between SNS function and a more comprehensive measure of life history strategy based on multiple traits such as the measure we used here.

It is also possible that the association between life history strategy and SNS function varies between studies depending on how SNS activity is measured. There are numerous markers of SNS activity and different markers are susceptible to different confounds and methodological complications (Zakreski & Pruessner, 2019). For example, the relationship between blood pressure and SNS activity is confounded by mineralocorticoid activity, while cardiac parasympathetic outflow confounds associations between SNS activity and heart rate. Consequently, studies using different markers of SNS activity may therefore find different associations between life history strategy and SNS activity. In line with this idea, Lehmann and colleagues (2018), found that blood pressure correlated with *faster* life history strategy while a different SNS marker (heart rate) correlated with *slower* life history strategy. Future studies should examine multiple markers of SNS activity to see if they consistently relate to life history strategy.

Limitations

This study had several limitations that should be addressed in future research. First, we cannot establish whether altered responsivity of the HPA axis, HPG axis or SNS caused or was a consequence of life history strategy. A longitudinal design may allow one to determine whether changes in stress responsive neuroendocrine precede or follow changes in life history strategy. Alternatively, the HPA axis, HPG axis or SNS could be pharmacologically manipulated to see if this produces acute changes in life history strategy related characteristics (e.g. reproductive and risk-taking preferences).

Another limitation is that only men were tested since we had insufficient resources to control for menstrual cycle phase or hormonal contraceptives which are known to impact strongly the HPA and HPG axes (Kudielka et al., 2009). We also tested only young adults to avoid the confounding effects of age on neuroendocrine function (Kudielka, et al., 2009). Future studies should try to replicate our findings in females especially since there may be sex differences in how life history strategy is expressed and physiologically regulated (Del Giudice, Ellis, et al., 2011). Our findings may also not generalize to other developmental periods. Activity and responsivity of the HPA and HPG axes change over development (Zakreski et al., 2019), yet life history strategy is assumed to be stable in adulthood (Simpson et al., 2012). Future research should also determine whether the relationship between life history strategy and the function of stress responsive neuroendocrine systems changes over development.

There was only one post-stress testosterone sample per participant. More testosterone samples would have provided a more reliable estimate of HPG axis activity. We could have measured testosterone, cortisol and alpha-amylase simultaneously at multiple time points if all saliva samples were collected by the passive drool method. This method however was

incompatible with our neuroimaging protocol, which required participants to remain in a specific posture for the duration of the stressor. We therefore chose to use the swab method for cortisol and alpha-amylase, which is compatible with the neuroimaging protocol, so that we could sample cortisol and alpha-amylase throughout the entire procedure. This however reduced the amount of resources available to collect samples by the passive drool method. Despite this limitation, there was still a significant effect of post-stress testosterone on life history strategy in the hypothesized direction.

This study could also be improved upon by assessing additional physiological systems that are theorized to play a role in the regulation of life history strategy. The pace of life model hypothesizes that the parasympathetic nervous system (PSNS), along with the HPA axis, HPG axis and SNS, helps regulate life history strategy (Réale et al., 2010). While the current investigation attempted to include PSNS activity via respiratory sinus arrhythmia, due to equipment problems we did not have enough data to include PSNS activity in our analysis. Since there is significant cross-talk between the PSNS and the other neuroendocrine systems investigated here (Zakreski et al., 2019), future research should examine the PSNS, along with the HPG axis, HPG axis and SNS to see if the function of these systems contribute independently to life history strategy.

Conclusion

In conclusion, this study showed that life history strategy covaries with stress induced activity of the HPA axis, HPG axis and SNS. Our findings with regards to HPA axis and HPG axis responsivity, but not SNS responsivity, are consistent with the pace of life model which is based on data from non-human vertebrates. Our results are also consistent with data from human studies that were limited because they examined specific behavioral characteristics related to life

history strategy and/or because they examined only one or two of the multiple physiological systems believed to regulate life history strategy. Our findings suggest that certain physiological correlates of life history strategy (HPA axis, HPG axis and SNS responsivity) observed in animals likely generalize to humans, and that, since we used a broad multi-trait measure of life history strategy, HPA axis, HPG axis and SNS responsivity relate not just to one specific facet of life history strategy but rather relate to a general pattern of traits consistent with life history strategy.

Chapter 3: Volumetric Differences in the Hippocampus Between Men with Slow and Fast Life History Strategies

Chapter 2 suggests that individuals with different life history strategies exhibit varied levels of HPA axis, HPG axis, and SNS activity during stress. According to the adaptive calibration model, genes and environment interact to calibrate stress responsive neuroendocrine activity, subsequently calibrating life history strategy for levels of adversity specific to the individual's environment (Del Giudice, Ellis, et al., 2011). This process is predicted to occur gradually and at sensitive periods in development, particularly early in life (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012). Since activity of the HPA axis, HPG axis and SNS is related to the structural integrity of numerous brain regions, as reviewed in the General Introduction, the volume of these brain regions may covary with life history strategy, especially if, as others propose (Del Giudice, Ellis, et al., 2011), ones' life history strategy is dependent on gradual changes in the HPA axis, HPG axis and SNS that emerge predominantly in early life. To expand on Chapter 2, Chapter 3 examines whether volumetric differences in brain regions related to the HPA axis, HPG axis and SNS covary with life history strategy between individuals.

To date, research has examined the relationship between life history strategy and total brain size between species. Controlling for body weight and length, mammals with slower life history strategies tend to have larger brains (Rushton, 2004). To the best of our knowledge, no study has explicitly investigated whether life history strategy correlates with brain morphology between individuals of the same species, nor has any study explicitly investigated whether life history strategy is associated with volumetric differences in specific brain regions.

Figueredo and colleagues (2006) hypothesize that life history strategy depends on alterations of various frontal and temporal lobe structures including the hippocampus (HC). This

study focused on the HC for three reasons: 1) As discussed in the General Introduction, the HC both influences and is influenced by the HPA axis, HPG axis, and SNS activity. 2) The HC is implicated in physical, cognitive and behavioral processes that mediate life history trade-offs. HC morphology should also covary with life history strategy given that 3) ecological conditions (i.e. ELA) that theoretically calibrate life history strategy have also been shown to affect HC volume. Specifically, ELA has been shown to alter HC function and morphology in humans and animals as reviewed in the General Introduction and elsewhere (Frodl & O'Keane, 2013; Hoeijmakers et al., 2015; Lupien et al., 2009).

The HC is composed of structurally and functionally distinct subfields. Recent research suggests that ELA affects specific HC subfields, such as the dentate gyrus (DG) or cornu ammonis (CA) 3, more strongly than others (Dahmen et al., 2018). The relationship between HC function and structure and the activity of the HPA axis, HPG axis and SNS also varies between HC subfields (see General Introduction). Since life history strategy is theoretically programmed by ELA and life history strategy is facilitated by HPA axis, HPG axis and SNS activity, the effects of life history strategy may also vary between different HC subfields. We therefore examined relations between life history strategy and the volume of different HC subfields in addition to examining the relationship between life history strategy and total HC volume. Using structural magnetic resonance imaging (MRI), we investigated this relationship in three ways: manual segmentation of the HC, voxel-based morphometry, and multi-atlas based automated segmentation of HC subfields. We used multiple approaches because each approach has its own strengths and weakness.

Neuroanatomical regions of interest (ROI) can be isolated by either manual or automated segmentation protocols. Manual segmentation is considered the gold standard but is time

consuming, requires specific training, and is susceptible to inter-rater variability (Chakravarty et al., 2013), making it more difficult to replicate results. Protocols for manually segmenting total HC volume (head, body and tail) are established (e.g. Pruessner et al. (2000)), and are compatible with standard imaging procedures (e.g. *in vivo* imaging with a 3 T MRI scanner). Manual segmentation of individual HC subfields is also possible with *in vivo* MRI. Manual HC subfield segmentation protocols, however, either exclude large parts of the HC (La Joie et al., 2010; Mueller et al., 2007), and/or require more sophisticated imaging protocols (4 T or 7 T MRI scanner) (Mueller et al., 2007; Wisse et al., 2012). Manual segmentation of multiple HC subfields also requires considerably more time than segmenting a single structure. Manual segmentation was therefore used to isolate total HC volume while an automated method, Multiple Automatically Generated Templates (MAGeT) (Chakravarty et al., 2013; Winterburn et al., 2013), was employed to isolate HC subfields.

MAGeT can segment HC subfields using images from commonly available MRI scanners (e.g. 3 T scanners) and is faster and less subjective than manual segmentation but may be less accurate. In cross-validation studies, MAGeT achieves high similarity with manual segmentation, outperforming alternative automated segmentation protocols such as FreeSurfer (Herten, Konrad, Krinzinger, Seitz, & von Polier, 2018; Pipitone et al., 2014). To achieve more accurate registration, MAGeT uses five expertly segmented atlases of adult HC subfields labels. Five atlases accommodate a wider range of anatomical variability than a single atlas. To further improve registration, atlases are first registered to a representative subset of 21 participants to form a template library. Template library images are then registered to each participant. Labels are then propagated along each registration pathway creating 105 (21*5) possible segmentations. The best segmentation for each participant is decided by a voxel-wise majority voting algorithm.

Determining the volume of ROI by ether manual or automated segmentation cannot determine whether volumetric differences are confined to the ROI, a specific part of the ROI, or extend to other parts of the brain. Voxel-based morphometry was therefore used in addition to ROI analyses described above.

Voxel-based morphometry (VBM) is an automated method that estimates differences in the amount of brain matter by determining the deformation field required to warp each participant's brain to a standardized brain, then comparing brains on a voxel-by-voxel basis after applying the deformation field. Like other automated methods, VBM is faster and less subjective than manual segmentation. VBM is also advantageous because it reveals whether volumetric differences are confined to specific anatomical regions like the HC. VBM however is highly sensitive to registration errors (Bookstein, 2001). This issue is partly addressed by spatially smoothing data prior to statistical analysis. Smoothing however obfuscates differences in relatively small structures such as individual HC subfields. We therefore used VBM to see if life history strategy is associated with volumetric differences in the HC relative to the rest of the brain.

The present study therefore used manual segmentation to determine if life history strategy covaried with total left or right HC volume, while automated segmentation was used to determine the association between life history strategy and different HC subfields. Finally whole brain VBM was used to see if life history strategy had effects anywhere in the brain (including the HC).

Methods

Sample

This study used the same sample as described in the methods section of Chapter 1, Study 2 and Chapter 2. Two participants were excluded due to excessive head movement during neuroimaging leaving a total of 61 participants. All participants reported no prior head injury resulting in loss of consciousness. 57/61 subjects were right-handed.

Life history strategy

As described in Chapter 1, Study 2, life history strategy was assessed using the Arizona Life History Battery (ALHB). Higher ALHB scores reflect slower life history strategy.

Magnetic resonance imaging (MRI)

Participants were scanned in a 3-Tesla Siemens Trio MRI scanner at the Douglas Mental Health Institute using a 32-channel head coil. A high-resolution (1 mm isotropic voxel) T1-weighted image of the entire brain was acquired along the sagittal plane using a 3D magnetization-prepared rapid gradient-echo sequence (MPRAGE) with the following acquisition parameters: repetition time=2300 ms; echo time=2.98 ms; slice number=176; flip angle=9 degrees; field-of-view=256 mm. Total scan time was 554 seconds.

Manual segmentation of the hippocampus (HC)

The HC was segmented by blind raters following the protocol described by Pruessner and colleagues (2008). First, raw anatomical images were denoised (Coupé et al., 2010; Coupé et al., 2008) and corrected for non-uniform intensity (Sled, Zijdenbos, & Evans, 1998). Images were normalized to the ICBM 152 T1 average brain template by a 12-parameter linear transformation (Collins, Neelin, Peters, & Evans, 1994). Using the MINC toolkit Display function, raters then

segmented the HC head, body and tail which includes the CA subfields, DG, subiculum and parts of the alveus and fimbria.

The volume of manually segmented HC labels were determined by voxel count. Using MATLAB 2017a, we made a general linear model regressing HC volume onto mean centered ALHB total. Left and right HC volume were modeled separately. Anderson-Darling tests were performed on model residuals to test for violations of the normality assumption.

Automated segmentation of HC subfield volumes

HC subfields were segmented using an automated segmentation protocol: Multiple Automatically Generated Template (MAGeT)-Brain (Chakravarty et al., 2013; Winterburn et al., 2013). MAGeT estimates the volume of the CA1, CA2-CA3, CA4-dentate gyrus (DG), alveus, fimbria, subiculum and stratum (stratum moleculare, stratum lacunosum, and stratum lucidium).

MAGeT works by propagating 5 expertly segmented atlases to a template library from a representative subset of 21 participants. The 21 template participants were selected so that the mean and variance in age, BMI, and life history strategy were as similar as possible to the whole sample. Before running MAGeT, raw anatomical images were preprocessed using a pipeline recommended by the developers of MAGeT, bpipe (https://github.com/CobraLab/minc-bpipe-library/). The pipeline corrects for non-uniform intensity, crops images to improve registration on brain tissue, and performs brain extraction using the BEaST extraction method (Eskildsen et al., 2012). For each participant, MAGeT HC subfield labels were inspected manually.

Using MATLAB 2017a, for each HC subfield volume, a general linear model (GLM) was made regressing the volume of that subfield onto mean centered ALHB total with intracranial volume (ICV) included as a covariate. Left and right subfields were modelled separately, making for a total of 14 comparisons (7 per hemisphere). To test for violations of the

normality assumption, the Anderson-Darling test was performed on model residuals. False discovery rate (FDR) was corrected using the Benjamini-Hochberg method which is valid when variables in comparisons are independent or positively correlated. Comparisons surviving 5% FDR were considered statistically significant. Both uncorrected and FDR corrected p-values are reported.

Voxel-based morphometry (VBM)

VBM was performed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) package in SPM12 (Ashburner, 2007, 2009). Images were preprocessed following the recommended guidelines for DARTEL. Raw anatomical images were reoriented to the anterior commissure, bias corrected and voxels were classified as gray matter, white matter, cerebral spinal fluid (CSF), bone, air or non-brain tissue. DARTEL then created a study-specific gray matter template. During this step, each participant's tissue probability map was warped into alignment with the DARTEL template producing a flow field for each participant. Images were normalised to MNI space, then modulated by their respective flow fields. Modulated gray and white matter images were then smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel. We repeated our analyses using 4 mm, 8 mm and 12 mm FWHM smoothing kernels, yielding similar results.

Using the SPM12 group-level factorial design toolbox, we made a general linear model regressing each voxel onto mean-centered ALHB total score. To correct for differences in intracranial volume (ICV; gray matter + white matter + CSF), global correction was applied using proportional scaling. An absolute mask with a threshold of 0.20 was used to eliminate background voxels. Results are reported after correcting for FDR. Comparisons surviving 5% FDR were considered statistically significant.

Results

Descriptive statistics and correlations among study variables

Sample characteristics in addition to the internal consistency of the ALHB and correlations between the ALHB subscales are reported in Chapter 1 Study 2. Total ICV was not significantly correlated with ALHB total ($r=+0.069$, $p=0.585$). Using partial correlation to adjust for ICV, manually segmented HC volume was significantly correlated with total HC volume calculated from MAGeT HC subfields both for the right HC ($r=+0.801$, $p<0.001$) and left HC ($r=+0.723$, $p<0.001$).

Volumetric differences in manually segmented HC total volume

We tested whether ALHB total was related to manually segmented left or right HC volume controlling for ICV. Left and right sides were modelled separately. Table 3.1 reports the estimated effect and related statistics of ALHB total in each model. There was no significant effect of ALHB on either left or right HC volume.

Table 3.1 *Effect of life history strategy on manually segmented hippocampal volume*

Dependent variable	Estimate of ALHB total effect	SE	t[58]	p
R HC	168.48	135.34	1.245	0.218
L HC	139.91	59.469	0.156	0.348

Effect of life history strategy (ALHB total) on right and left manually segmented HC volume correcting for intracranial volume. ALHB = Arizona Life History Battery; FDR = false discovery rate; HC = hippocampus; L = left; R= right.

Volumetric differences in MAGeT segmented HC total volume and HC subfield volume

Similar to results from manual segmentation, total HC volume calculated from MAGeT labels was not significantly correlated with ALHB total. Table 3.2 reports the estimated effect of ALHB total on total HC volume calculated from MAGeT segmented HC subfield volumes.

Table 3.2 *Effect of life history strategy on MAGeT hippocampal volume*

Dependent variable	Estimate of ALHB total effect	SE	t[58]	p
R HC	135.34	62.577	0.852	0.397
L HC	9.262	59.469	0.156	0.877

Effect of life history strategy (ALHB total) on right and left MAGeT segmented HC volume correcting for intracranial volume. Total HC volume was calculated by adding the volume of the subiculum, CA1, CA2-CA3, CA4-DG, alveus and fimbria. ALHB = Arizona Life History Battery; FDR = false discovery rate; HC = hippocampus; L = left; R= right.

We then tested whether individual HC subfield volumes covary with ALHB total. As Table 3.3 shows, before FDR correction, most subfield volumes were not significantly related to ALHB total; however participants with a slower life history strategy (higher ALHB total score) exhibited a larger left alveus (t[58]=2.044, p=0.046). There was a trend such that higher ALHB was associated with a larger right alveus (t[58]=1.932, p=0.058). There was no significant effect or trend however after adjusting for 5% FDR (adjusted p>0.4).

Table 3.3 *Effect of life history strategy on each hippocampal subfield*

Dependent variable	Estimate of ALHB total effect	SE	t[58]	p	5% FDR corrected p
R CA1	25.477	26.695	1.329	0.189	0.814
R CA2-CA3	0.885	6.507	0.136	0.892	0.892
R CA4-DG	-5.513	15.357	-0.359	0.721	0.814
R subiculum	8.489	8.455	1.004	0.320	0.814
R stratum	13.185	16.399	0.804	0.425	0.814
R alveus	20.578	10.651	1.932	0.058	0.406
R fimbria	-1.667	3.025	-0.551	0.584	0.814
L CA1	8.706	18.213	0.478	0.635	0.814
L CA2-CA3	-2.723	6.318	-0.431	0.668	0.814
L CA4-DG	-6.979	15.205	-0.459	0.648	0.814
L subiculum	6.459	8.465	0.763	0.449	0.814
L stratum	5.008	16	0.313	0.756	0.814
L alveus	19.319	9.452	2.044	0.046	0.406
L fimbria	-2.983	3.022	-0.987	0.328	0.814

Effect of life history strategy (ALHB total) on each hippocampal subfield volume controlling for intracranial volume. For each subfield, a general linear model regressed ALHB total and total brain volume onto that subfield's native volume. No effects were statistically significant at the 0.05 level after correction for multiple comparisons. ALHB = Arizona Life History Battery; CA = cornu ammonis, DG: dentate gyrus, FDR = false discovery rate; L = left, R = right, stratum = stratum moleculare + stratum lucidium + stratum lacunosum.

VBM

Gray matter VBM analyses revealed no significant effect of ALHB total on any voxels after correcting for 5% FDR. Changing the size of the smoothing kernel (4 vs. 6 vs. 8 vs. 12 mm FWHM) did not impact results.

Discussion

This study examined whether individuals with different life history strategies exhibit volumetric differences in the HC, a region that both influences and is influencedc by the activity of the HPA axis, HPG axis and SNS. HC volume was assessed using three different methods with different advantages: manual HC segmentation, automated HC subfield segmentation using MAGeT and VBM. VBM found no significant gray matter differences within the HC or anywhere in the brain. Manually segmented total HC volume strongly correlated with HC volume derived from MAGeT but total HC volume was not related to life history strategy. While individuals with a slower life history strategy exhibited a significantly larger right alveus and a trend toward a larger left alveus, there were no trends or significant effects after controlling for multiple comparisons. This study therefore found no evidence that the volume of the HC or part of the HC differs between individuals with fast and slow life history strategies within a sample of healthy young men.

While our study may have simply lacked the sensitivity required to detect a significant relationship between life history strategy and HC total or subfield volume, it is surprising that life history strategy was not significantly related to HC volume given that Chapter 2, which used the same participants and measure of life history strategy, found that life history strategy was significantly associated with HPA axis, HPG axis and SNS activity, and the activity of these

systems influences and is influenced by HC volume (see General Introduction). Since life history strategy is believed to emerge largely in the first 5 years of life (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012) and involves gradual changes in stress responsive neuroendocrine systems (Del Giudice, Ellis, et al., 2011), one would expect a significant association between life history strategy and HC volume to be evident in young adults like our participants, especially since ELA (a determinate of life history strategy) has been associated with HC volume in children and adolescence (Dahmen et al., 2018; Hanson et al., 2015) although findings in children have not been consistent (Frodl & O'Keane, 2013). Researchers have found significant differences in HC volume between low and high ELA participants even with relatively small samples. For example, in a sample of 34 adults, Bremner et al. (1997) found that those with a history of childhood abuse had significantly smaller (12 % smaller) left HC volumes compared to the low ELA group.

Several methodological modifications may yield a stronger relationship between life history strategy and HC volume. Since HC subfields are relatively small structures, imaging at a higher spatial resolution may reduce errors in models relating life history strategy with HC subfield volumes. Although MAGeT is compatible with 1 mm^3 resolution, more accurate HC subfield segmentation can be obtained with a higher spatial resolution and this reduction in measurement error could strengthen the effect of life history strategy on the right alveus to the point of statistical significance.

The current study tested hypotheses about volume. Other aspects of HC structure besides volume, such as shape, may be more strongly related to life history strategy. Voineskos and colleagues (2015) describe how differences in HC shape can be measured using MAGeT. Furthermore, the hippocampal to ventricle volume ratio (Schoemaker et al., 2019) may be used

as an alternative to total HC volume. This recently proposed marker of HC structural integrity was found to more strongly correlate with age and memory than HC volume alone (Schoemaker et al., 2019). The hippocampal to ventricle volume ratio however requires segmenting specific regions of the lateral ventricle that supposedly reflect the loss of HC tissue although no empirical data has yet been provided to support this assumption.

Moreover, the age and sex of our participants may have impacted our results since we tested only young men. Age and sex have both been shown to moderate the impact of ELA (a determinant of life history strategy; Chapter 1) on neurogenesis in the DG (Loi, Koricka, Lucassen, & Joels, 2014) and on HC volume (Colle et al., 2017; Samplin et al., 2013). For example, Loi and colleagues (2014) found that male rats but not female rats exposed to ELA exhibited increased neurogenesis prior to puberty but decreased neurogenesis after puberty. If the correlation between ELA and DG neurogenesis switches from positive to negative in adolescence or early adulthood, then the relationship between ELA (or life history strategy) and HC volume may also be difficult to detect. Since our sample was limited to young men, our findings may not generalize to other ages or other sexes/genders. Future research should explore whether the relationship between HC volume and life history strategy may change with age or vary between men and women.

Our measure of lisfe history strategy (the ALHB) encompasses a broad range of psychological characteristics (e.g. impulsivity, social contact, attachment). It could be that specific components of life history strategy (e.g. impulsivity) relate to specific brain structures rather than all components loading onto one neuroanatomic structure. It may be worthwhile to separate the individual components of life history strategy (e.g. specific ALHB subscales) and analyze their relationships with HC volume separately. However, examining the association

between measures of HC volume and various, more specific components of life history strategy would have greatly increased the number of statistical comparisons performed, thus reducing our statistical power.

Other brain regions, besides the HC, may covary with life history strategy since changes in HPA axis, HPG axis and SNS activity correlate with structural changes in various brain regions including other parts of the limbic system (e.g. the amygdala) as well as cortical areas (e.g. medial prefrontal cortex) (Dedovic et al., 2009; Ulrich-Lai & Herman, 2009). While VBM analysis showed no volumetric differences anywhere in the brain, whole-brain analysis is less sensitive than ROI analysis. ROI analysis targeting brain structures other than the HC, such as the amygdala may reveal a significant association between life history strategy and volume. Future research may use what is known about the psychological, developmental or neuroendocrine correlates of life history strategy to select ROI's *a priori*.

Conclusion

In conclusion, this study did not find any significant volumetric differences in the HC, HC subfields or anywhere in the brain between men with fast and slow life history strategies. This was unexpected since in the same sample we found significant associations between life history strategy and ELA, HPA axis, HPG axis and SNS activity. Given the paucity of research examining the neuroanatomical correlates of life history strategy, future research should examine the relationship between life history strategy and other parts of the brain and/or examine aspects of HC structure besides volume, such as shape and examine the neuroanatomical correlates of life history strategy in a more diverse sample (men and women across the lifespan).

Chapter 4: Death Thoughts and Early Life Adversity Interact to Affect Cortisol Responsivity to Stress

Environment is believed to shape life history strategy slowly during sensitive periods of development, mostly in early life (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012). Consistent with this idea, studies have found that adverse conditions (e.g. father absence, changes in family structure) early in life (the first 5 years), but not necessarily later, affect life history strategy markers (Sheppard & Sear, 2011; Simpson et al., 2012). The idea that early life experience has a lasting impact on *life history strategy* is consistent with the idea that early life experience has a lasting impact on *stress responsive neuroendocrine systems* like the hypothalamic-pituitary-adrenal (HPA) axis (Lupien et al., 2009; van Oers, de Kloet, & Levine, 1998), since these neuroendocrine systems theoretically facilitate individual differences in life history strategy— a prediction supported by Chapter 2 and other research (see Chapter 2 and General Introduction).

While ELA may be an important influence on life history strategy and the physiological systems that regulate life history strategy (e.g. the HPA axis), other experiences may influence life history strategy as well. This possibility seems particularly likely since, as discussed in the General Introduction, the relationship between ELA and cortisol responsivity to stress varies considerably between studies (Bunea et al., 2017) as does the relationship between ELA and SNS responsivity to stress (Zakreski & Pruessner, 2019).

Life history strategy may also be influenced by other ecological cues that predict premature mortality since this predictive capacity is at least theoretically the reason why ELA entrains life history strategy (Chisholm, 1993, 1996; Del Giudice, Ellis, et al., 2011; Nettle et al., 2013). While various cues may convey information about mortality (e.g. death of siblings),

contemplation of one's own death, like ELA, has been found to correlate with actual mortality (Abdel-Khalek, 2003; Alaimo et al., 2002; Cox et al., 2012; Robertson et al., 2006; Shakil and Yousaf, 2015), which may be why death thoughts have been found to induce effects similar to ELA. In adults, Byrd-Craven et al. (2015) showed that inducing death thoughts shortly before a psychosocial stressor lead to blunted cortisol responsivity to stress—the more commonly observed effect of ELA in humans (Bunea et al., 2017). Byrd-Craven et al. (2015) however did not interpret their findings with regards to life history theory, nor did they assess ELA. Additional behavioral experiments suggest that inducing acute death thoughts in the laboratory, like ELA, evokes fast life history strategy psychological characteristics such as increased risk taking and short-term mating orientation (Fritsche et al., 2007; Gillath et al., 2011; Hart et al., 2010; Hirschberger et al., 2002a; Hirschberger et al., 2002b; Kelley and Schmeichel, 2015; Lam et al., 2009; Mathews and Sear, 2008; Routledge et al., 2004; Silveira et al., 2013; Taubman Ben-Ari, 2004; Taubman Ben-Ari et al., 1999; Wisman and Goldenberg, 2005). Thus, we hypothesize that ELA and death thoughts have similar effects on HPA axis function and life history strategy, however we speculate that the effects of death thoughts are momentary, whereas the effects of ELA are chronic.

Research also shows that death reminders temporarily interact with ELA to affect various life history strategy related behaviors (Griskevicius et al., 2011a; Griskevicius et al., 2011b). While these studies create precedence for combining acute death thoughts with varying ELA, no study has investigated how death thoughts affect the cortisol stress response in interaction with ELA. If death thoughts moderate effects of ELA on cortisol responsivity, this may partly explain why studies examining effects of ELA on cortisol responsivity yield mixed results. Given our theoretical rationale, we hypothesized that participants with high ELA would show blunted

cortisol responsivity to an acute stressor. Since death thoughts signal premature mortality, we further hypothesized that acute death thoughts would also blunt cortisol responsivity in low ELA individuals. We also hypothesized that death thoughts would not affect cortisol responsivity in high ELA participants since they should already present with blunted cortisol responsivity.

To test these hypotheses, we recruited healthy young men who were low or high on ELA and assigned them to death thoughts or no death thoughts conditions before exposing them to a psychosocial stressor. The main dependent variable was salivary cortisol output as a marker of HPA axis responsivity to the stressor. Subjective stress was also assessed to see if the effects of the death thought manipulation were independent of changes in subjective stress levels.

Methods

Participants (N=128) from two different studies were pooled together to increase statistical power. Study 1 (N=65) and Study 2 (N=63) tested different samples drawn from the same population: healthy young men low or high in ELA. Study 2 participants are the same sample described in Chapter 1 (Study 2), Chapter 2 and Chapter 3. Study 1 participants are from a preliminary investigation on the effects of ELA and cortisol responsivity with a similar protocol and recruitment process. Study 1 participants were included only in this chapter and not in the previous chapters of this thesis because Study 1 participants did not complete the Mini-K or Arizona Life History Battery nor did they provide other physiological data (e.g. neuroimaging data, salivary testosterone). In both studies, men were classified as low or high ELA using retrospective self-report questionnaires. To manipulate death thought accessibility, men were exposed to either a mortality cue (described below) or a control condition before a psychosocial stressor. Study 1 participants performed the Trier Social Stress Test (Kirschbaum et al., 1993).

Study 2 used the Montreal Imaging Stress Test (Dedovic et al., 2005). In both studies, cortisol and subjective stress were sampled repeatedly.

Sample

We recruited 128 participants in Montreal by advertising on Internet classifieds using the recruitment protocol and inclusion/exclusion criteria described in Chapter 1 Study 2 and Chapter 2.

Early life adversity (ELA)

As described in Chapter 1, ELA was assessed using two retrospective measures, the Parental Bonding Instrument (PBI) and Childhood Trauma Questionnaire (CTQ). Participants were classified as high or low ELA based on the recommended cutoffs (see Chapter 1). There are several reasons why we chose to dichotomize ELA rather than use a continuous score. First, statistical simulation studies have found that dichotomizing variables does not increase type I error unless there is extremely high multicollinearity (Iacobucci et al., 2015). Dichotomous variables can be more robust than continuous predictors when data are skewed or when the independent variable has both linear and nonlinear effects (Farrington and Loeber, 2000; Iacobucci et al., 2015). This advantage is significant for our purposes since Anderson-Darling tests found that CTQ total scores and PBI scores in our sample were significantly skewed even after Box-Cox transformation. Furthermore, several studies suggest the relationship between ELA and HPA function may contain quadratic and other nonlinear components in addition to linear components that, unless corrected for, increase noise (Ellis et al., 2005; Engert et al., 2010; Gunnar et al., 2009; Hagan et al., 2014). Modeling quadratic and higher-order effects of ELA would help control for these non-linear effects while keeping ELA as a continuous variable. This would however greatly increase model complexity and subsequently reduce statistical power,

particularly in our situation since we are interested in the interaction between ELA and another variable (death thoughts). Finally, there is a well-established precedence in research for treating ELA as a categorical variable. Many of the studies that used the PBI or CTQ to examine effects of ELA on HPA function categorized participants as high or low ELA using the recommended cutoffs we used here (Ali and Pruessner, 2012; Carpenter et al., 2007; Carpenter et al., 2010; Cook et al., 2012; Kawai et al., 2017; Kuras et al., 2017).

Procedure

Study 1 and 2 involved habituation, death thought manipulation, psychosocial stress task and recovery as described in Chapter 2. Figure 4.1 compares the procedures of the two studies.

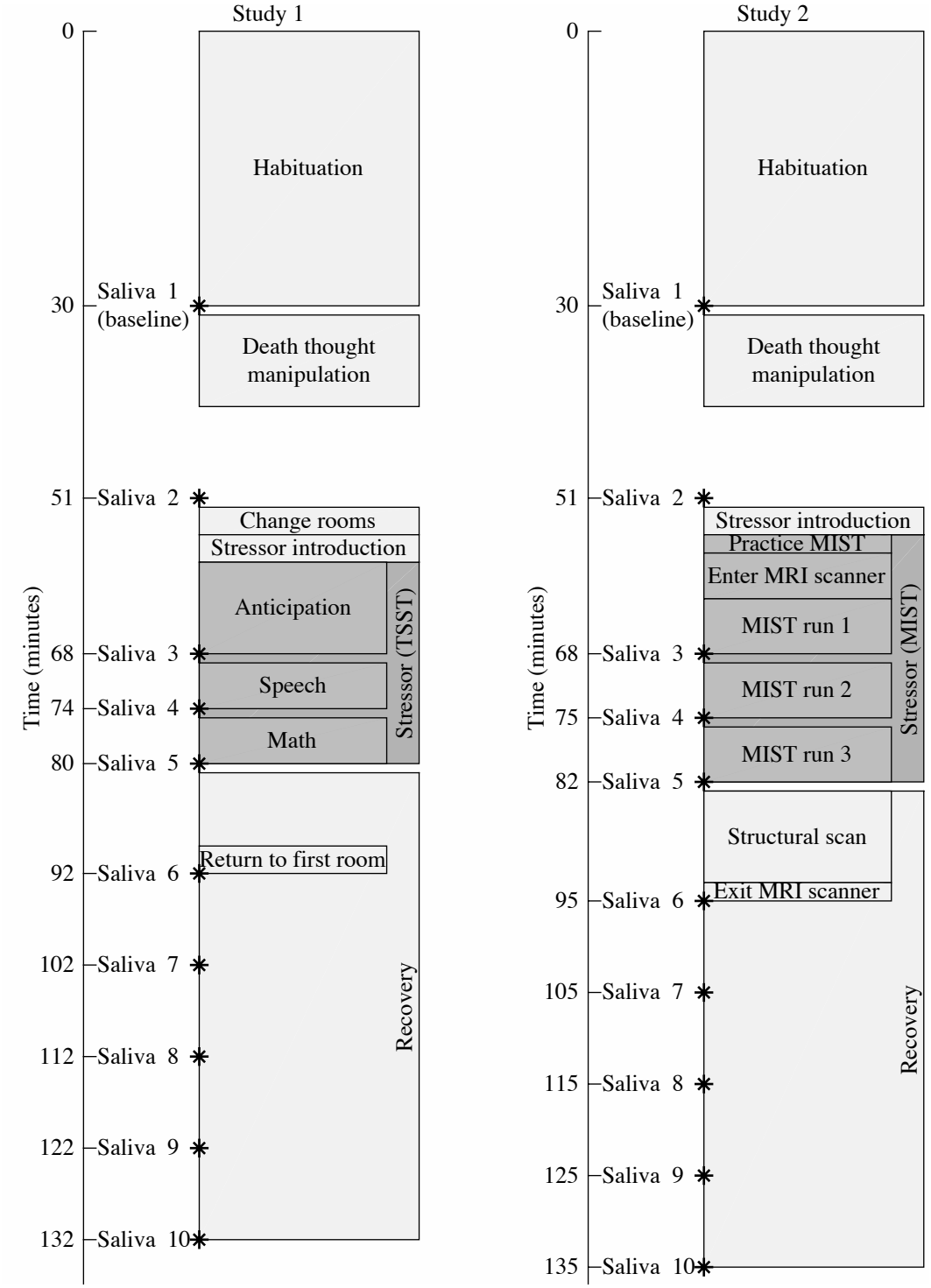

Figure 4.1. Salivary cortisol sampled throughout the procedure. Asterisks indicate the time of each saliva sample in minutes relative to participant's arrival for Study 1 and Study 2. Since Study 2 included functional magnetic resonance imaging, saliva samples were taken at slightly different time points relative to Study 1 to accommodate the neuroimaging protocol. In Study 1, momentary subjective stress was measured with each saliva sample. In Study 2, subjective stress was measured with samples 1, 2, 6, 7, 8, 9 and 10 but was not assessed while participants were in the MRI scanner.

Death thought manipulation

After sampling baseline cortisol and subjective stress, we exposed participants to either a mortality cue or control condition for 10 minutes. Condition was assigned so that age, BMI, PBI mother-care, CTQ scores, and PHQ-9 depression were balanced.

Mortality condition

We used the Mortality Attitudes Personality Survey (MAPS) (Rosenblatt et al., 1989), the most common method of experimentally inducing death thoughts (Burke et al., 2010). The MAPS instructs participants to write two brief essays. Participants were asked to "briefly describe the emotions that the thought of your own death arouses in you" and to "jot down, as specifically as you can, what you think will happen to you as you physically die and once you are physically dead". We chose this stimulus as a mortality cue because it has been repeatedly shown to acutely induce fast life history characteristics (e.g. interest in casual sex, risk taking) (Gillath et al., 2011; Hart et al., 2010; Hirschberger et al., 2002a; Hirschberger et al., 2002b; Kelley and Schmeichel, 2015; Lam et al., 2009; Routledge et al., 2004; Taubman Ben-Ari, 2004; Taubman Ben-Ari et al., 1999; Wisman and Goldenberg, 2005).

Control condition

Participants that did not receive the mortality cue received one of three control stimuli: sleep, dental pain, or non-death related questionnaires, all of which have been used in past experiments manipulating death thought accessibility (Burke et al., 2010). The sleep and dental pain cues were essay questions identical to the MAPS except the word death was replaced with "sleep" and "dental pain", respectively. For instance, the sleep cue asked participants to "briefly describe the emotions that the thought of sleeping induces in you", and "jot down, as specifically as you can, what you think happens to you as you fall asleep and once you are sleeping". Participants in the

neutral questionnaire condition completed personality questionnaires unrelated to death, sleep or dental pain. Study 1 control participants completed either the sleep condition or questionnaire condition. Study 2 control participants only completed the dental pain condition. We did not observe any difference in physiological or psychological outcomes between the three control conditions, thus we merged them into one control condition to maximize statistical power.

Psychosocial stressor

Ten minutes after the death thought manipulation ended, participants were introduced to the stress task. Study 1 used the Trier Social Stress Task (TSST) in a laboratory environment (Kirschbaum et al., 1993). The TSST is used widely in stress research since it elicits robust physiological and psychological responses. The TSST involves anticipation (10 minutes), public speaking (5 minutes), and mental arithmetic (5 minutes). During anticipation, participants prepared an oral presentation for a mock job interview. After anticipation, participants presented their speech and performed mental arithmetic before a panel of two trained confederates of mixed gender.

Study 2 used the Montreal Imaging Stress Task (MIST), (Dedovic et al., 2005) described in Chapter 2. Like the TSST the MIST involves performing mental arithmetic under time pressure and negative social evaluation.

Recovery

After the stressor, there was a 1 hour recovery period where participants completed questionnaires, colored in coloring books, or read magazines before debriefing.

Salivary cortisol and subjective stress

Salivary cortisol, a marker of HPA axis activity, was sampled according to the protocol in Chapter 2. Figure 4.1 indicates the time of each saliva sample. In Study 1, with each saliva

sample, participants rated their current stress levels on a visual analogue scale, placing an "X" on a 10 cm line anchored from 0 (not at all stressed) to 10 (extremely stressed). In Study 2, with each saliva sample (except those taken during the MRI session), momentary subjective stress was assessed using the affect grid (Russell, 1989). Participants indicated their current feelings by placing an "X" on a 10 X 10 grid. The grid's horizontal axis is valence (unpleasant vs. pleasant feelings). The vertical axis is arousal (low vs. high). Subjective stress is calculated as arousal minus valence for that time point. Since Study 1 and 2 measured subjective stress on different scales, subjective stress scores were z-transformed within studies. Two participants had no subjective stress data.

Data reduction and statistical analysis

Missing cortisol and subjective stress samples were estimated with linear interpolation. As described in Chapter 2, cortisol responsivity to stress was quantified as area under the curve with respect to ground (AUC_G). Since we were interested in the effects of death thoughts on cortisol responsivity to the psychosocial stressor, AUC_G calculation was restricted to samples occurring after the death thought manipulation. Violations of the normality assumption were checked with Anderson-Darling tests, and corrected by Box-Cox transformation. Violations of the equal variance assumption were checked with Brown-Forsynthe tests. To ensure a balanced experimental design, we performed an ELA (low vs. high) by death thoughts (yes vs. no) by Study (1 vs. 2) chi-squared test of unequal proportions which showed group sizes were not significantly disproportionate $\chi^2[4] = 2.358$, $p = 0.670$. We compared demographic and outcome variables between Studies 1 and 2 to confirm that data were similar enough to merge the studies. After merging the studies, to control for any differences between studies (e.g. different stress tasks), Study was also included as a categorical covariate.

Before testing our primary hypothesis, we performed separate mixed analyses of variance (ANOVA) to see if cortisol and subjective stress levels changed after the death thought manipulation, or after the psychosocial stressor. ELA, death thoughts and Study were between-subject factors while Time was the within-subject factor. Cortisol and standardized subjective stress were the dependent variables and were Box-Cox transformed to correct for violations of the normality assumption.

To test our primary hypothesis that death thoughts and ELA interact to affect cortisol responsivity, we made a general linear model (GLM) regressing cortisol AUC_G onto the formula: ELA*Death thoughts + ELA + Death thoughts + Study + Intercept. The categorical variables death thoughts (yes vs. no) and Study (1 vs. 2) were coded so coefficients would sum to 0. Type III sum of squares was assumed. A sensitivity power analysis with alpha set to 0.05 and power set to 0.80 was performed with the R "pwr" package (Champely, 2018). The analysis showed that our experimental design, with one degree of freedom in the numerator per term, and 123 error degrees of freedom is sufficient to detect an effect size greater than $f^2 = 0.064$ which is between small and medium (Cohen, 1988).

Results

Demographic and baseline differences between groups

Table 4.1 summarizes sample characteristics. Among low ELA participants (n=61), 27 were primed with death thoughts and 34 were in the control group. Among high ELA participants (n=67), 29 were in the death thought condition and 38 were in the control condition. Figure 4.2 shows the relationship between cortisol AUC_G and scores on each of the CTQ and PBI subscales. Before testing our primary hypothesis, to assess potential confounds, GLM performed on baseline cortisol and standardized baseline subjective stress revealed no significant main effects

or interactions ($F[1,123]<2.28$, $p>0.133$), suggesting that basal cortisol and basal standardized subjective stress were comparable across groups. Likewise, additional GLM's showed no significant differences between groups in age, BMI, and depression although Study 2 had higher CTQ scores and lower mother-care scores.

Table 4.1 *Study 1 and 2 sample characteristics*

Study	ELA	Death thoughts	N	Age (years)	BMI	PHQ-9 depression	PBI mother-care	CTQ emotional trauma	CTQ physical trauma	CTQ sexual abuse	CTQ total
				M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
1	Low	Yes	12	25.58 (3.92)	22.81 (1.25)	3.17 (3.13)	33.33 (3.11)	13.08 (2.39)	11.25 (2.05)	5.00 (0.00)	29.33 (3.80)
1	Low	No	20	24.89 (3.83)	22.71 (2.11)	3.35 (3.31)	31.25 (2.29)	13.75 (2.77)	11.15 (1.18)	5.05 (0.22)	29.95 (3.35)
1	High	Yes	12	24.10 (4.54)	24.10 (2.76)	3.17 (2.08)	21.92 (6.30)	22.33 (7.97)	14.67 (5.55)	5.50 (1.17)	42.50 (12.80)
1	High	No	20	24.41 (4.78)	22.49 (2.41)	3.35 (3.45)	24.05 (5.17)	22.45 (7.40)	16.30 (6.14)	6.25 (2.79)	45.05 (12.84)
2	Low	Yes	15	23.65 (2.82)	23.15 (2.44)	3.93 (3.43)	33.00 (2.17)	13.20 (2.68)	10.87 (0.99)	5.00 (0.00)	29.07 (2.87)
2	Low	No	14	24.56 (3.76)	22.27 (2.29)	4.07 (3.93)	31.42 (2.77)	13.00 (2.99)	10.86 (1.10)	5.07 (0.27)	28.93 (3.45)
2	High	Yes	17	24.73 (3.77)	22.99 (2.53)	6.71 (5.69)	16.29 (7.66)	33.50 (9.04)	19.19 (5.97)	6.38 (3.16)	57.88 (15.50)
2	High	No	18	24.76 (4.26)	23.12 (1.75)	9.06 (5.86)	18.50 (6.84)	29.17 (8.59)	18.61 (6.87)	5.89 (1.64)	53.67 (14.45)

Means and standard deviations for ELA and demographic variables for Studies 1 and 2. Mean and standard deviation reported as a M (SD). CTQ=Childhood Trauma Questionnaire, ELA=Early life adversity, PBI=Parental Bonding Instrument, PHQ-9=Patient Health Questionnaire.

Effects of death thoughts on cortisol and subjective stress *before* the psychosocial stressor

Figure 4.2 shows cortisol and subjective stress over time. To see if cortisol or standardized subjective stress changed after death thoughts (before the stress task), we performed a mixed design ANOVA on Box-Cox transformed cortisol with death thoughts, ELA, and Study as between-subject factors, and time (sample before vs. sample after death thought manipulation) as the within-subject factor (see Figure 4.1 for sample times). There was no significant time by

death thought interaction, or time by death thought by ELA interaction (F[1,123]<0.15, p>0.701). The same analysis was performed with Box-Cox transformed subjective stress as the dependent variable. Like cortisol, there was no significant time by death thought, or time by death thought by ELA interaction (F[1,123]<0.16, p>0.689).

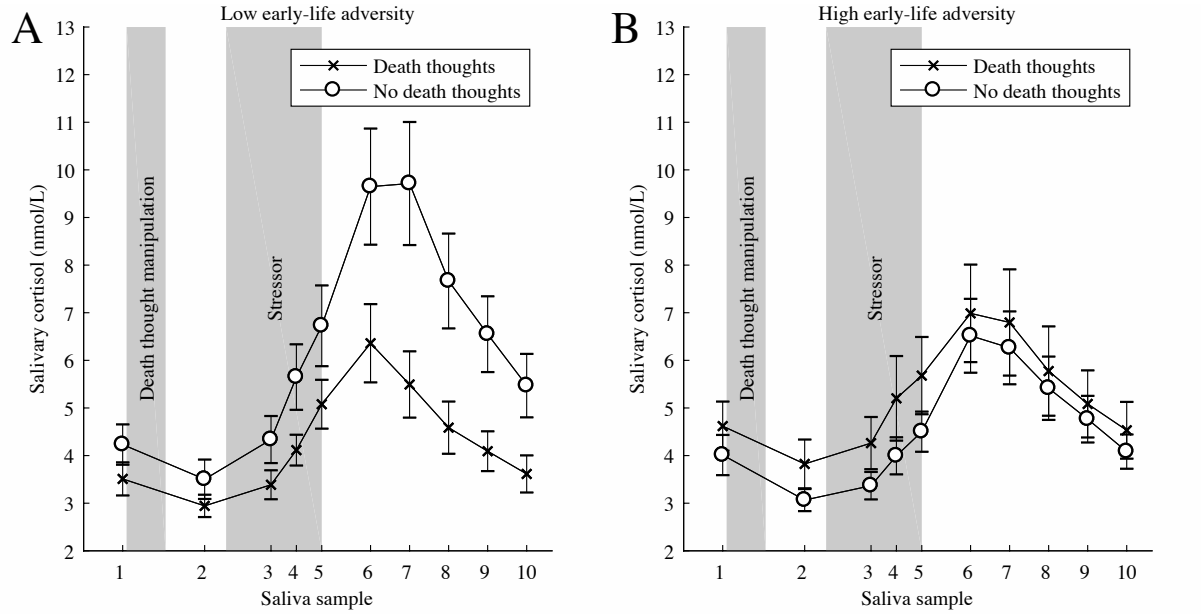

Figure 4.2 Change in cortisol levels over time. During the death thought manipulation, participants in the experimental condition ("X" markers) wrote about death, while those in the control condition (open markers) wrote about a non-death related topic. Shortly after the manipulation, participants performed a psychosocial stress task. See Figure 4.1 for sample times.

Effects of psychosocial stress on cortisol and subjective stress

To see if cortisol and subjective stress changed after the psychosocial stressor, we performed a mixed ANOVA on Box-Cox transformed cortisol with death thoughts (yes vs. no), ELA (low vs. high), and Study (1 vs. 2) as between-subject factors, and time (sample before vs. sample after psychosocial stressor) as the within-subject factor (see Figure 4.1 for sample times). Another mixed design ANOVA was performed with Box-Cox transformed standardized subjective stress as the dependent variable. There was a significant main effect of time with both cortisol and

subjective stress levels being significantly higher after the psychosocial stressor compared to before the stressor ($F[1,123]=18.80$, $p< 0.001$; $F[1,121]=6.31$, $p=0.013$, respectively).

Effects of death thoughts and ELA on cortisol responsivity

For our primary hypothesis, we made a GLM regressing cortisol AUC_G onto the formula: ELA*Death thoughts + ELA + Death thoughts + Study + Intercept. Participants in Study 1 showed significantly greater cortisol AUC_G ($F[1,123]=4.43$, $p= 0.037$, partial $\eta^2 = 0.035$). We further observed a significant ELA by death thought interaction ($F[1,123]=5.90$, $p=0.017$, partial $\eta^2 = 0.046$), depicted in Figure 4.3. As hypothesized, post-hoc LSD t-tests showed that, without prior exposure to death thoughts, high ELA participants exhibited significantly blunted cortisol AUC_G compared to low ELA participants ($\Delta[123]$(standardized difference)$=2.31$, $p=0.023$). Furthermore, the difference between high and low ELA participants diminished if participants were primed with death thoughts ($\Delta[123]=1.23$, $p=0.223$). Death thoughts, relative to the control condition, had no significant effect on high ELA participants ($\Delta[123]=1.09$, $p=0.279$). In contrast, among low ELA participants, death thoughts significantly attenuated cortisol AUC_G ($\Delta[123]=2.28$, $p=0.024$).

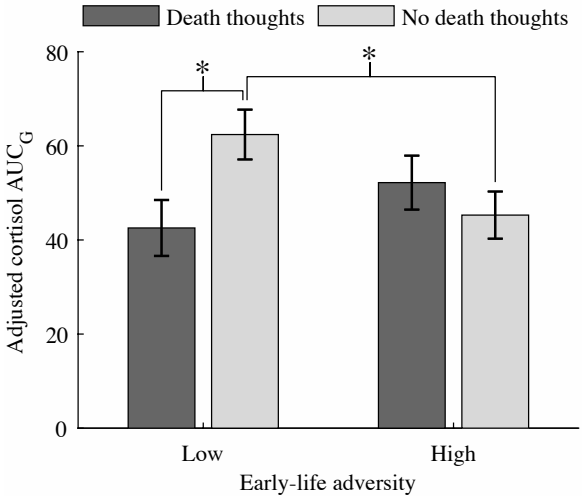

Figure 4.3 Group differences in cortisol responsivity to psychosocial stress. Average cortisol responsivity (AUC_G) for each group is adjusted to control for differences between Studies 1 and 2. Participants in the

experimental condition (dark bars) wrote about death, while those in the control condition (light bars) wrote about a non-death related topic. Without death thoughts, low ELA participants released significantly more cortisol after the stressor compared to high ELA participants. Inducing death thoughts did not significantly change cortisol responsivity in high ELA participants but significantly blunted responsivity in low ELA participants. *=$p<0.05$. Error bars are standard error.

Discussion

This study investigated whether inducing thoughts of one's own death momentarily moderates effects of ELA on HPA axis responsivity to psychosocial stressors. Cortisol and subjective stress did not increase up to 20 minutes after death thoughts. These results are in line with other studies reporting no change in stress markers (e.g. heart rate, negative affect) after death thoughts (Rosenblatt et al., 1989). However, both subjective stress and cortisol increased significantly after exposure to acute psychosocial stress. While death thoughts did not evoke a significant stress response by themselves, they changed how low ELA participants responded to the psychosocial stressor. As hypothesized, inducing death thoughts shortly before a psychosocial stressor significantly reduced HPA axis responsivity for participants reared in supportive conditions, but did not significantly affect responsivity in high ELA participants. This finding suggests that even subtle non-stressful death reminders presented before a psychosocial stressor can momentarily modulate HPA axis responsivity to stress, depending on the individual's exposure to ELA.

We believe that the interacting effects of death thoughts and ELA on cortisol responsivity are relevant to researchers studying the HPA axis and may partly explain why effects of ELA on cortisol responsivity vary across studies. If briefly contemplating their own death reduces the cortisol stress response in low ELA participants by more than 50%, any study examining HPA axis responsivity should account for potential death reminders that may be inadvertently present in the testing environment. For example, many questionnaires routinely used in behavioral studies ask about suicidal ideation to assess depression, or inquire into familial death to assess significant life events. If these assessments induce death thoughts, they could potentially blunt cortisol responsivity in low ELA participants, and may consequently contribute to inconsistent

findings across studies. Given the current results, we recommend that future investigations administer death-related assessments either after stress testing, or during a separate testing session.

Extensive research shows that cortisol responsivity differs between individuals high and low on ELA. This is the first evidence we know of to show that this difference may be temporarily affected by conditions participants experience immediately before testing. This finding extends past research (Engert, Efanov, et al., 2010) which found that repeated exposure to the TSST blunted cortisol responsivity over time, but only in adults without ELA. Cortisol responsivity in high ELA participants remained blunted across repeated TSST exposures. This resembles what we observed here, only instead of exposing participants to repeated stress, we induced death thoughts before the stressor. One possible explanation is that death contemplation may induce internal processes that are similar to those evoked by recurring stress, but without directly activating strong cortisol or subjective stress responses. In other words, inducing death thoughts may partially resemble a stressor without provoking an acute stress response.

The question arises what psychological and physiological processes are initiated by death thoughts. Numerous experiments demonstrate robust effects of death thoughts on risk taking and reproductive preferences (Burke et al., 2010). Participants primed with death thoughts desired more offspring (Fritsche et al., 2007; Mathews and Sear, 2008; Wisman and Goldenberg, 2005), were more willing to engage in casual or risky sex (Gillath et al., 2011; Hirschberger et al., 2002a; Lam et al., 2009; Silveira et al., 2013; Taubman Ben-Ari, 2004), and other risky behaviors (Hart et al., 2010; Hirschberger et al., 2002b; Kelley and Schmeichel, 2015; Routledge et al., 2004). Interestingly, momentary effects of death thoughts on risk taking and reproductive

tendencies are similar to some of the chronic effects of ELA on risk taking and reproduction as reviewed in the General Introduction (Kogan et al., 2015; Lovallo, 2013; Simpson et al., 2012).

Life history theory offers a potential explanation for why ELA and death thoughts exert similar effects. If inducing death thoughts momentarily shifts life history strategy to the fast end, then this may momentarily alter the HPA axis. Across species, blunted HPA axis activity during stress facilitates faster life history strategy, while high responsivity facilitates slow life history strategy (Carere et al., 2010; Réale et al., 2010). According to the adaptive calibration model (Del Giudice et al., 2011), HPA axis responsivity changes to adapt life history strategy to levels of premature mortality the individual detects in their environment.

Results from previous studies suggest that humans avoid thinking about their own death (Hayes et al., 2010). Since death thoughts typically occur in situations with increased mortality (Abdel-Khalek, 2003; Alaimo et al., 2002; Cox et al., 2012; Robertson et al., 2006; Shakil and Yousaf, 2015), acute death thoughts induced experimentally may also signal increased premature mortality and therefore elicit temporary adaptive changes in HPA axis responsivity and subsequently life history strategy. Our study supported this hypothesis in two key aspects. First, without death thoughts, participants showed greater cortisol responsivity if they were reared in supportive conditions, and blunted responsivity if they experienced high ELA. This is consistent with life history theory as it claims that high ELA chronically signals increased risk of premature mortality (Chisholm, 1993, 1996; Del Giudice, Ellis, et al., 2011; Ellis et al., 2009; Nettle et al., 2013). Second, low ELA participants also showed blunted HPA axis responsivity but only when they were primed with death thoughts. Here, death thoughts could have *temporarily* shifted low ELA participants from high HPA axis responders to low responders perhaps to facilitate faster life history strategy. The interpretation would be that the risk of premature mortality in an

individual's environment can change acutely as well as chronically. Death thoughts may therefore have similar biobehavioral effects as ELA since both death thoughts and ELA signal higher premature morality; however, we expect the effects of death thoughts would occur on a much shorter time scale than effects of ELA.

In addition to life history theory, terror management theory could also provide some insight into our findings. Terror management theory (Greenberg et al., 1997; Solomon et al., 1991) argues that when individuals are confronted with the thought of their own death, they employ various cognitive defense strategies (terror management processes) such as worldview defense or self-esteem striving to avoid existential terror. Terror management processes vary between individuals as a function of attachment style and other individual characteristics (Mikulincer and Florian, 2000). It is possible that death thoughts trigger different terror management processes in low and high ELA participants and different terror management processes may differentially impact cortisol responsivity. This claim should be investigated empirically and may provide a proximal cognitive mechanism mediating the effect of death thoughts on life history strategy.

In summary, the current study shows that thinking about death for ten minutes lowered cortisol responsivity of low ELA participants to the level of those reporting high ELA. Therefore, future studies examining ELA and HPA axis responsivity should control for situational factors that might induce acute death thoughts. Previous studies from terror management theory provide examples of the vast array of stimuli that can cause these thoughts, e.g., images of natural disaster, reading about death, etc. (Hayes et al., 2010).

Limitations

Several limitations should be considered regarding the results of this study. First, as mentioned in Chapter 2, participants were healthy young men. Given potential sex differences in life history strategy (Del Giudice, Ellis, et al., 2011), our findings may not generalize to women. It is also unclear whether our findings generalize to older or younger participants whose life history strategy may be calibrated or expressed differently. Future research should replicate these findings in a more diverse population.

Another limitation is that the current study only examined HPA axis responsivity as this, but not other neuroendocrine data was available for all the participants in this investigation. In addition to the HPA axis, life history strategy is also theoretically facilitated by hypothalamic-pituitary-gonadal (HPG) axis, the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) as proposed in the General Introduction and elsewhere (Réale et al., 2010). Future research should therefore include additional biomarkers, such as testosterone, alpha-amylase and heart rate variability to respectively index the HPG axis, SNS, and PSNS.

Furthermore, this study did not measure any psychological indicators of life history strategy (e.g. reproductive or risk taking preferences). While there is a validated questionnaire to examine trait levels of life history strategy (i.e. the Arizona Life History Battery (Figueredo et al., 2007)), there is currently no validated multi-trait based measure of assessing states related to life history strategy. Future research should establish a state measure of life history strategy and determine whether cortisol responsivity and other biomarkers (e.g. testosterone responsivity) mediate the effects of death thoughts on psychological states related to life history strategy. Alternatively, researchers could examine specific psychological states that reflect life history strategy (e.g. risk taking or reproductive preferences). Indeed, numerous studies have found that

priming death thoughts induces specific psychological characteristics of fast life history strategy (Fritsche et al., 2007; Gillath et al., 2011; Hart et al., 2010; Hirschberger et al., 2002a; Hirschberger et al., 2002b; Kelley and Schmeichel, 2015; Lam et al., 2009; Mathews and Sear, 2008; Routledge et al., 2004; Silveira et al., 2013; Taubman Ben-Ari, 2004; Taubman Ben-Ari et al., 1999; Wisman and Goldenberg, 2005). Using a specific state to index life history strategy (e.g. preference for risk) however may not be as accurate as a comprehensive measure based on multiple characteristics.

Finally, another interesting direction for future research is to experiment with cues that signal low premature mortality. If cues like ELA or death thoughts induce blunted cortisol responsivity and faster life history strategy because these events signal high premature mortality, one might expect events predicting the opposite conditions (i.e. low premature mortality) to have the opposite effect on life history strategy and cortisol responsivity. This possibility should be researched in the future as it may help develop interventions to improve health and development outcomes in individuals exposed to ELA.

Conclusion

In conclusion, we showed how high ELA interacts with acute exposure to mortality cues in adulthood (death thoughts) to affect the stress response of the HPA axis, a neuroendocrine system believed to play a role in regulating life history strategy. Future studies should therefore control for the presence of mortality cues in their testing protocols to avoid contaminating associations between ELA and HPA axis function.

General Discussion

This thesis examined whether individual differences in life history strategy covary with the activity of the HPA axis, HPG axis and SNS in response to stress, and whether ecological factors theorized to program life history strategy are capable of altering stress responsive neuroendocrine systems chronically as well as acutely. More specifically, this thesis pursued four aims.

1. Replicate past research showing a relationship between ELA and faster life history strategy.
2. Determine if the association between life history strategy and activity of the HPA axis, HPG axis and SNS predicted by the pace of life model generalizes to humans during stress.
3. Determine if life history strategy covaries with HC volume, a neuroanatomical feature that influences and is influenced by the HPA axis, HPG axis and SNS activity.
4. Determine if exposure to mortality cues, a condition theorized to underlie the effects of ELA on life history strategy, can also account for temporary changes in the physiological systems that mediate life history strategy.

I will discuss how each aim relates to the findings reported throughout Chapters 1 through 4. For each aim, I will reiterate the rationale for this aim, the relevant analyses, and whether the corresponding results are consistent with our hypotheses, other findings from this thesis and results published elsewhere. I will then discuss implications for life history theory and research examining the effects of ELA on health and development. I then describe the limitations and make recommendations for future research.

Aim 1: Replicate relationship between ELA and faster life history strategy

Individuals exposed to various forms of ELA such as poverty or low parental care, show signs of faster life history strategy (e.g. early puberty, early sexual debut, impulsivity, aggression), as reviewed in the General Introduction and Chapter 1. Most studies associating life history strategy with ELA have focused on childhood socioeconomic deprivation or fragmented family structure without directly examining exposure to emotional, physical, sexual maltreatment which may be perpetrated by parents, other family members or other people. Furthermore, most studies have focused on specific life history strategy related characteristics (e.g. pubertal onset, age at first pregnancy). A narrow set of outcomes may not always indicate an individual's overall life history strategy since life history strategy is a latent general bias toward prioritizing one broad category of fitness (e.g. reproduction) over another (e.g. longevity). The risk of misrepresenting a person's life history strategy with a single outcome increases when the assessment relies exclusively on reproductive outcomes (e.g. early puberty, age at first pregnancy, number of children) since the relationship between reproductive outcomes and life history strategy in humans may be confounded by social and economic factors like access to birth control or parental leave (Figueredo et al., 2015), as well as difficulties in examining certain reproductive outcomes (e.g. pubertal timing, age at first pregnancy) in males. Research studying life history strategy in humans should therefore examine a broad range of indicators of life history strategy that do not exclusively rely on reproductive or sexual outcomes.

In Chapter 1, given the challenges and inconsistencies surrounding the quantification of ELA and life history strategy, we aimed to replicate the association between ELA and life history using a multi-trait measure of life history strategy, the Arizona Life History Battery (ALHB) (Figueredo et al., 2007) and the short form of the ALHB, the Mini-K, which both assess a broad range of psychological processes that mediate life history trade-offs (e.g. impulsivity,

attachment, altruism) and do not exclusively depend on reproductive outcomes. ELA was assessed by two routinely used retrospective questionnaires; the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), which assesses physical, emotional, sexual maltreatment, and the Parental Bonding Instrument (PBI) (Parker et al., 1979) which assesses maternal care received in childhood. We also aimed to examine the psychometric properties of the PBI, CTQ and ALHB. Specifically, we examined the association between PBI mother-care and the different CTQ subscales to see if they inter-correlated consistently with past research. We also tested convergent validity of the ALHB by examining its correlations with questionnaire measures of unrestricted sexuality and the tendency to experience and express hostile emotions, which theory and evidence suggest should be related to a valid measure of life history strategy.

Our measures of ELA and life history strategy showed evidence of convergent validity. Inter-correlations between PBI mother-care and CTQ subscales were consistent with past research (Herrenkohl & Herrenkohl, 2007). The ALHB showed high internal consistency (alpha=0.93). Matching past research findings (Dunkel & Decker, 2010; Giosan & Wyka, 2009; Kruger, 2017; Patch & Figueredo, 2017), ALHB total scores significantly negatively correlated with unrestricted sexuality and the tendency to express hostile emotions. Evidence of internal consistency and convergent validity reported in Chapter 1 may reduce the potential for measurement error to contaminate findings reported in Chapter 2-4.

Furthermore, as hypothesized, participants reporting high ELA exhibited a faster life history strategy as indicated by both the short and long forms of the ALHB. These findings replicate results from other studies that used different, often narrower, measures of life history strategy and different, often narrower, measures of ELA, as reviewed in Chapter 1. Our results in Chapter 1 therefore provide further empirical support that individuals exposed to ELA exhibit a

general pattern of traits consistent with a faster life history strategy—not just one specific characteristic of faster life history strategy.

Life history theorists (Belsky et al., 1991; Chisholm, 1993, 1996; Del Giudice, Ellis, et al., 2011; Ellis et al., 2009; Kuzawa & Bragg, 2012; Nettle et al., 2013) propose that humans evolved to detect conditions that over the course of evolution reliably predict high premature mortality and other ecological conditions that determine whether a faster or slower life history strategy is more optimal in terms of reproductive fitness. Harsh, unpredictable or uncontrollable rearing conditions, particularly in the form of adverse interpersonal relations, reliably covary with higher future premature mortality (Cabeza de Baca et al., 2016; Quinlan, 2007; Quinlan, 2010) and are therefore theorized to evoke a faster life history strategy. This is consistent with the association we observed between higher ELA and faster life history strategy in Chapter 1.

Chapter 1 along with the other studies examining ELA and life history strategy in humans, is correlational and therefore cannot establish whether higher ELA causes faster life history strategy. Since life history strategy is partly heritable (Figueredo, Vasquez, Brumbach, & Schneider, 2004), and parents with faster life history strategy tend to provide less parental care (Cabeza De Baca, Figueredo, & Ellis, 2012), the association between adverse rearing conditions and faster life history strategy may reflect genetic inheritance between parents and offspring rather than environmental programming of the offspring by parental behavior. Life history strategy has been associated with numerous genetic polymorphisms (Minkov & Bond, 2015), many of which could impact stress responsive neuroendocrine systems investigated in Chapter 2. For instance, production and sensitivity to testosterone, a hormone regulated by the HPG axis, is affected by the number of CAG repeats in the androgen receptor gene (Choong, Kemppainen, Zhou, & Wilson, 1996). CAG repeat polymorphism is associated with marital conflict and child

abandonment (Comings, Muhleman, Johnson, & MacMurray, 2002) and has been found to partially mediate the relationship between father absence and daughters' early menarche (Schlomer et al., 2019). It is unlikely however that genes completely explain the relationship between parental care and offspring's life history strategy. Cross-fostering experiments in animals (Cameron, Fish, & Meaney, 2008; Maestripieri, 2005b) show that care from non-biologically related parents impacts behavioral markers of life history strategy. Nonetheless, we can only assume these findings in animals apply to humans since we cannot randomly assign humans to adverse rearing conditions. Experiments that expose human participants to cues that convey similar ecological information compared to ELA (i.e. cues conveying high premature mortality) could provide causal evidence that life history strategy responds to mortality cues. This is explored in the fourth aim (Chapter 4).

In addition to the limitations inherent to correlational research, Chapter 1 is also limited by the use of retrospective self-report questionnaires to examine ELA and life history strategy. As stated in Chapter 1, while retrospective self-report questionnaires are susceptible to subjective bias and recall errors, retrospective self-report questionnaires, compared to alternative methods (e.g. behavioral observation), allowed us to inexpensively sample a broad range of phenomena over a long period time. To lessen the risks of subjective bias and recall errors, Chapter 1 suggests potential alternative methodology for future research.

Aim 2: Determine association between life history strategy and activity of the HPA axis, HPG axis and SNS

Chapter 1 replicated the observation that individuals with higher ELA show psychological signs of faster life history strategy as indicated by the ALHB and Mini-K. Life history strategy may therefore account for some of the psychological characteristics of ELA survivors (e.g.

impulsivity, insecure attachment), but can life history strategy account for physiological characteristics of ELA survivors? Since alterations of stress responsive neuroendocrine systems are believed to mediate some of the long-term consequences of ELA on health and development (see General Introduction), understanding the relationship between life history strategy and physiology may provide insight into the functional significance of the physiological changes in ELA survivors. Chapter 2 therefore aimed to investigate whether the effects of ELA on stress responsive neuroendocrine systems that have already been established by past research (see General Introduction) also accompany a faster life history strategy. The pace of life model (Réale et al., 2010) hypothesizes specific associations between life history strategy and the activity of the HPA axis, HPG axis and SNS. Specifically, individuals with a faster life history strategy are hypothesized to exhibit blunted HPA axis activity and enhanced HPG axis and SNS activity. As reviewed in Chapter 2, to date, most empirical support for the pace of life model comes from animal research. Research on the physiological correlates of life history strategy in humans typically examines only a narrow aspect of life history strategy (usually reproductive outcomes such as pubertal timing) and examines only one or two neuroendocrine systems (typically the HPG axis alone, or the HPG and HPA axes together), and often under baseline conditions. Chapter 2 therefore aimed to investigate whether stress induced activity of the HPA axis, HPG axis and SNS independently covary with scores on a broad, multi-trait measure of life history strategy (the ALHB). Stress was induced by a standardized psychosocial stress task, while salivary cortisol, testosterone and alpha-amylase were used as markers of HPA axis, HPG axis and SNS activity, respectively.

Chapter 2 found that cortisol, testosterone and alpha-amylase output during stress independently covary with life history strategy between individuals. As hypothesized by the pace

of life model (Réale et al., 2010), individuals with a faster life history strategy exhibited blunted cortisol output and increased testosterone output in response to stress. The relationship between life history strategy and alpha-amylase responsivity however was in the opposite direction to what was hypothesized by the pace of life model such that faster life history strategy was associated with a blunted (not greater) alpha-amylase stress response.

The relationship between faster life history strategy and greater testosterone output is consistent with the pace of life model and agrees with findings in human and animals that associated testosterone output with specific traits related to fast life history strategy (e.g. low parental investment, aggression, risk taking, unrestricted sexuality) (see General Introduction and Chapter 2). In humans, these traits and outcomes have also been observed in individuals with ELA (see General Introduction and Chapter 1 review). Increased testosterone output among individuals with faster life history strategy is consistent with research examining the effects of ELA on testosterone levels, which associate higher ELA with higher testosterone levels in adults (Zito et al., 2017).

The relationship between faster life history strategy and blunted cortisol output is also consistent with the pace of life model (Réale et al., 2010), and agrees with findings in human studies that associate cortisol output with specific characteristics of fast life history strategy (e.g. accelerated puberty, aggression, impulsivity, unrestricted sexuality) (see General Introduction and Chapter 2). In humans, these traits and outcomes have also been observed in individuals with ELA (see General Introduction and Chapter 1 review). Blunted cortisol responsivity to stress is consistent with research on the effects of ELA on the HPA axis, which, while findings vary between studies, tends to associate ELA with blunted cortisol responsivity (Bunea et al., 2017).

We also found that faster life history strategy accompanied greater SNS activity as indexed by greater alpha-amylase output. While this effect is opposite to what the pace of life model predicts (Réale et al., 2010), it is consistent with the Type I phenotype (sensitive type) predicted by the adaptive calibration model (ACM) (Del Giudice, Ellis, et al., 2011; Del Giudice, Hinnant, et al., 2011; Ellis, Oldehinkel, & Nederhof, 2017). The ACM predicts four patterns (types) of stress response system activity that develop in response to different levels of ELA and each type facilitates a different life history strategy. The sensitive type is predicted to develop in response to safe, supportive rearing conditions, exhibits a slow life history strategy and mounts a robust HPA axis and SNS response to stress. This matches our findings since participants with a slower life history strategy had low exposure to ELA (Chapter 1), and elevated HPA axis and SNS responsivity (Chapter 2). The relationship between ELA and SNS responsivity is more ambiguous than the relationships between ELA and HPA axis or HPG axis responsivity since there are relatively few studies examining the effects of ELA on SNS responsivity and among the few studies that do, findings vary considerably, with ELA survivors exhibiting SNS hyper-responsivity in some studies and hypo-responsivity in others (see General Introduction). Unfortunately, no meta-analysis or systematic literature review has been performed to determine which effect of ELA on SNS responsivity is more common. Future research should focus on the relationship between ELA, SNS and life history strategy since there is a paucity of this research compared to studies examining relations between ELA, life history strategy and the HPA and HPG axes. Chapter 2 suggests other directions for future research, such as testing other physiological systems (e.g. the parasympathetic nervous system) theorized to facilitate life history strategy trade-offs. Future research should also determine if HPG axis, HPG axis, and SNS responsivity mediate the effect of ELA on faster life history strategy. This could be done by

using structural equation modelling and ideally a longitudinal research design so that one can determine whether HPG axis, HPG axis, and SNS responsivity occur before or after changes in life history strategy.

Taken together, results from Chapter 2 show that individual differences in life history strategy covary with differences in activity of stress responsive neuroendocrine systems: the HPA axis, HPG axis and SNS. Since we used a broad multi-trait measure of life history strategy rather than focusing on specific life history strategy related outcomes (e.g. early puberty) our findings suggest that these neuroendocrine systems covary not only with specific traits or behaviors related to life history strategy, as suggested by past research in humans, but covary with an overall pattern of characteristics that reflect an individual's life history strategy.

Aim 3: Determine association between life history strategy and HC volume

Chapter 2 like other studies examining the relationship between life history strategy and stress responsive neuroendocrine systems focuses on the output of neuroendocrine systems (e.g. cortisol output, testosterone output). How life history strategy relates to the underlying neural regulation of the HPA axis, HPG axis and SNS has not been explicitly examined in humans or other animals. The activity of the HPA axis, HPG axis and SNS is regulated by multiple physiological mechanisms as reviewed in the General Introduction. Numerous brain regions play a critical role in coordinating the activity of the HPA axis, HPG axis and SNS in response to internal and external conditions (see General Introduction). Since life history strategy is assumed to be a stable trait, particularly in adulthood, then one would assume that the neuroanatomical correlates of HPA axis, HPG axis and SNS activity would covary with life history strategy.

The third aim of this thesis therefore was to examine whether life history strategy relates to volumetric differences in the hippocampus (HC), a key brain region that both influences and is

influenced by activity of the HPA axis, HPG axis and SNS, and whose structure and function has been found to covary with ELA in both humans and animals, as discussed in the General Introduction. Using structural MRI, Chapter 3 examined the relationship between life history strategy (as measured by the ALHB) and different measures of HC volume: voxel-based morphometry, manually segmented total HC volume and automated HC subfield segmentation.

Unexpectedly, we found no statistically significant association between life history strategy (ALHB scores) and left or right HC volume or HC subfield volume. The null association between life history strategy and HC volume was unexpected since in the same sample of participants, we had sufficient statistical power to detect a significant association between life history strategy and ELA, unrestricted sexuality and trait hostility (Chapter 1, Study 2) as well as statistically significant associations between life history strategy and HPA axis, HPG axis and SNS responsivity (Chapter 2). Since ALHB scores exhibited the expected association with other variables (with the exception of SNS responsivity), the non-significant association between life history strategy and HC volume is less likely to arise from the mismeasurement of life history strategy.

It is difficult to explain the null association between life history strategy and HC volume since this association has not been examined in either humans or animals prior to our investigation. Past neuroanatomical research focused on between-species differences in total brain size and life history strategy (see General Introduction and Chapter 3). Given the bias against publishing null findings, it is possible that past investigations also found no significant association between life history strategy and HC volume but never published this finding. It is important to publish null findings partly because it allows future researchers to refine their hypotheses or methods. Chapter 3 recommends methodological alterations (besides increasing

the sample size) that could be attempted in future studies examining the neuroanatomical correlates of life history strategy, such as studying different developmental periods, examining HC shape rather than volume, or studying other brain regions that also participate in the regulation the HPA axis, HPG axis or SNS (e.g. other parts of the limbic system).

One potential explanation for the non-significant association between HC volume and life history strategy is that the neuroendocrine profile in individuals with a faster life history strategy, at least during early adulthood, may have a combination of neurotoxic and neuroprotective effects on the HC that counter-balance each other. Chapter 2 found that individuals with a faster life history strategy released more gonadal sex steroids (testosterone) but reduced cortisol and SNS output during stress while individuals with a slower life history strategy did they opposite. Individuals with a slower life history strategy may be more susceptible to stress-induced HC damage since they exhibit increased cortisol and SNS responsivity to stress. High exposure to cortisol can induce HC neuron death (Reagan & McEwen, 1997). Likewise, heightened responsivity of the SNS can be disadvantageous particularly in the context of chronic stress since SNS activation acutely reduces HC glutamate transmission (Westhoff et al., 2011) while chronic SNS activation may interfere with blood flow to the HC leading to HC atrophy (Dhikav, Verma, & Anand, 2009). High cortisol and SNS responsivity to stress may render individuals with a slow life history strategy more susceptible to HC damage particularly under chronically stressful conditions. In contrast, blunted cortisol and SNS responsivity in individuals with a faster life history strategy may protect them from stress induced HC damage. On the other hand, blunted cortisol and SNS responsivity may have neurotoxic effects on the HC. Blunted glucocorticoid responsivity disinhibits corticotropin releasing hormone (CRH) secretion and CRH hyperactivity is known to inhibit HC dendritic arborization as well as exerting other neurotoxic effects on the

HC (Ivy et al., 2010). Furthermore, glucocorticoid and SNS activation play a critical role in inhibiting inflammation (see General Introduction), which is known to induce HC atrophy and suppress neurogenesis (Chiang et al., 2015). Blunted cortisol and SNS responsivity may therefore expose the HC of fast life history strategy individuals to potentially neurotoxic levels of CRH and inflammation thereby leading to HC atrophy. Individuals with fast life history strategy may however be protected from HC atrophy since these individuals also exhibit increased testosterone output (Chapter 2) and gonadal sex steroids are known to protect the CNS from inflammation (Larson, 2018), stimulate HC neurogenesis (Galea, 2008; Galea et al., 1999; Hamson et al., 2013) and promote regional blood flow to the HC (Maki & Resnick, 2000; Moffat & Resnick, 2007). High testosterone may therefore counter-balance the harmful effects of blunted glucocorticoid and SNS responsivity on HC integrity among individuals with faster life history strategies and this counter-balancing may potentially explain why we failed to observe a statistically significant difference in HC volume between healthy young men with slow vs. fast life history strategies. This potentially HC-protective neuroendocrine profile (i.e. low HPA axis and SNS responsivity, and elevated testosterone levels) seen in participants with a fast life history strategy may also explain why certain HC dependent cognitive abilities are actually enhanced by ELA particularly under stress (Oomen et al., 2010), given that ELA can induce a faster life history strategy (Chapter 1). Since we only tested healthy young men, it is possible that this HC-protective neuroendocrine profile may change over the course of development leading to age-related changes in the relationship between HC volume and life history strategy. For instance, gonadal sex steroid secretion declines steadily in adults as they age (Feldman et al., 2002; Zumoff, Strain, Miller, & Rosner, 1995). This could mean that individuals with faster life history strategies eventually exhibit HC atrophy later in adulthood as they are no longer

protected by elevated testosterone levels. It is therefore important for future research to study the relationship between life history strategy and HC integrity throughout development (ideally longitudinally) while simultaneously measuring markers of the SNS, HPA axis, HPG axis as well as inflammation. Given the relationship between ELA and fast life history strategy, developmental changes in the counter-balance between activity of the SNS, HPA axis, HPG axis and inflammation may also explain age related differences in the effects of ELA on the HC. Studies in humans and animals suggest that exposure to ELA may initially increase HC neurogenesis and volume but then lead to HC atrophy later in adulthood (Loi et al., 2014; Tupler & De Bellis, 2006). This is also consistent with the observation that certain ELA survivors do not show evidence of HC dependent cognitive dysfunction until later in adulthood (Brunson et al., 2005).

Life history strategy is likely associated with the structure of brain regions implicated in the regulation of stress responsive neuroendocrine systems particularly if ELA leads to gradual and enduring changes in stress responsive neuroendocrine systems which subsequently lead to changes in life history strategy (Del Giudice, et al., 2011). It is also possible that momentary changes in environment lead to momentary functional changes in brain regions that regulate the HPA axis, HPG axis and SNS, leading to acute changes in life history strategy.

Aim 4: Determine if death thoughts moderate effects of ELA on the HPA axis stress response

The theoretical explanation for why ELA survivors exhibit fast life history strategy characteristics (e.g. risk taking) and altered stress physiology is that humans evolved to detect ecological cues that signal higher premature mortality and other life history strategy relevant information and to optimize their life history strategies according to this information. This

theoretical process is believed to occur gradually, during specific developmental periods, particularly early in life (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012), and is consistent with the idea that ELA exerts an enduring impact on stress responsive neuroendocrine systems (Lupien et al., 2009). Nonetheless, in the General Introduction and Chapter 4, I reviewed evidence suggesting that life history strategy plasticity is not limited to slow changes early in life. Naturalistic research shows that key components of life history strategy (e.g. reproductive timing, risk taking) change acutely in adulthood following acute changes in mortality, while experimental evidence suggests that individuals exposed to cues that induce thoughts of their own death show signs of faster life history strategy (e.g. preference for more offspring, riskier behavior, a greater interest in casual sex). Since experimental induction of death thoughts momentarily induces certain *psychological* features of fast life history strategy (e.g. altered preferences for risk and reproduction), we predicted that priming death thoughts would also momentarily induce *physiological* features of fast life history strategy, specifically blunted HPA axis activity. Chapter 4 tested this hypothesis by exposing men with high and low ELA to either an experimental condition (death thoughts) or control condition (no death thoughts) prior to a psychosocial stressor. Salivary cortisol was sampled repeatedly to index HPA axis responsivity to stress.

As hypothesized, men exposed to either death thoughts or ELA showed evidence of blunted cortisol responsivity. As discussed in Chapter 4, the interaction between ELA and death thoughts may potentially contribute to heterogeneous research findings among studies examining the effects of ELA on stress responsive neuroendocrine systems. Studies that inadvertently induce death thoughts by for example administering questionnaires that ask about death may observe different relations between ELA and cortisol responsivity than studies that do prime

death thoughts. Furthermore, our findings are consistent with the idea that both acute mortality cues (death thoughts) and chronic mortality cues (ELA) may influence life history strategy at least temporarily, since Chapter 2 and other studies associate blunted cortisol responsivity with psychological signs of faster life history strategy. Chapter 4 therefore suggests that death thoughts not only affect *psychological* features of life history strategy (e.g. risk and reproductive preferences), as observed in past research, but also affect some of the *physiological* correlates of life history strategy, namely HPA axis responsivity to stress. While Chapter 4 provides experimental evidence that physiological correlates of life history strategy (i.e. cortisol responsivity) can be influenced mortality cues, it also challenges the putative notion that the plasticity of human life history strategy is limited to gradual changes early in life (Belsky et al., 1991; Del Giudice, Ellis, et al., 2011; Simpson et al., 2012). Indeed, it is possible that the effect of early experience on life history strategy may *appear* more enduring than it actually is because 1) studies relating ELA to human life history strategy are correlational and therefore limited in the types of rearing conditions participants experience, 2) the contextual factors that program life history strategy change over development (i.e. the events that program life history strategy in childhood may be different from those that program life history strategy in adulthood), or 3) as reviewed in Chapter 1, studies on ELA and life history strategy often focus on reproductive markers or other indicators of life history strategy (e.g. age at menarche or age at first offspring) which are by virtue of occurring once, immutable. It may therefore be important for future research examining relations between ELA, life history strategy and the physiological stress response systems to consider the current context as well as the early life context of the individual, and to choose broad multi-trait measures of life history strategy (not just reproductive outcomes) that are not based on events that occur only once.

Since Chapter 4 was an initial exploration, future research should attempt to replicate our findings in a larger more diverse sample including other ages and genders. Future research should also include markers of other physiological systems implicated in the regulation of life history strategy (e.g. the HPG axis; Chapter 2) and should also assess psychological states related to life history strategy (e.g. preference for risk) to see if HPA axis, HPG axis or SNS responsivity mediates the effects of death thoughts on psychological markers of life history strategy.

Conclusion

This thesis examined the environmental and neuroendocrine correlates of life history strategy to better understand why ELA affects stress responsive neuroendocrine systems and why effects of ELA on stress responsive neuroendocrine systems vary between studies. Consistent with past research using different measures of ELA and life history strategy, we found that men with high ELA showed psychological signs of faster life history strategy and that men with faster life history strategies showed altered functioning of the HPA axis and HPG axis that animal research predicts to correlate with fast life history strategy. SNS responsivity to stress was also significantly related to life history strategy but in the direction opposite to what the pace of life model predicts. Life history strategy was not significantly associated with HC volume or subfield volume suggesting that altered HC volume, at least in adulthood, is unlikely to drive the relationship we observed between faster life history strategy, ELA and altered stress physiology in the sample we tested. Future research should examine whether other neuroanatomical features implicated in the regulation of the HPA axis, HPG axis and SNS relate to life history strategy or examine whether the relationship between HC volume and life history strategy changes over development. Nonetheless, the association between ELA, faster life history strategy, and altered

stress responsive neuroendocrine function, while not providing insight into causation, is consistent with the theory that ELA alters the function of stress responsive neuroendocrine systems to optimize life history strategy for conditions with high premature mortality. While adverse events (e.g. ELA) and other conditions that signal premature mortality supposedly calibrate stress responsive neuroendocrine systems and subsequently life history strategy slowly during critical periods of development, this thesis contributes original knowledge by suggesting that certain physiological correlates of life history strategy (the cortisol stress response) may change acutely in adulthood in response to mortality cues (death thoughts), complementing research on the effects of death thoughts on psychological characteristics of life history strategy. The effect of death thoughts on cortisol responsivity and other characteristics of life history strategy may not be permanent and may involve different mechanisms than the effects of ELA on life history strategy. Nonetheless, the effects of death thoughts on psychological and physiological correlates of life history strategy have important implications for future research as any study examining stress physiology and ELA should control for death reminders (e.g. questionnaires asking about suicidality) which could otherwise confound relations between ELA and cortisol responsivity to stress and subsequently contribute to inconsistent findings within research examining the effects of ELA on stress physiology. While multiple factors likely contribute to inconsistent associations between ELA and stress physiology reported in the literature, identifying and controlling for the factors that moderate this association may provide a clearer picture of how ELA alters the physiological stress response which could subsequently improve therapeutic interventions for mental and physical problems experienced by ELA survivors.

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