The effects of prenatal maternal stress and early life maternal stress on adolescent hippocampal morphology: Project Ice Storm

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April 2018

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science (M.Sc. Science)

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Abstract

Background: Prenatal maternal stress (PNMS) is associated with altered hippocampal (HC) structure in animals, and HC-associated psychopathologies in humans. The objective of this study was to determine the extent to which PNMS experienced by women pregnant during the 1998 Quebec ice storm affects HC morphology (volume, surface area and shape) in their children; and to determine the extent to which the effects of maternal stress exposure differ between prenatally exposed children and a matched comparison group of early life exposed children, born 1-year before the storm.

Methods: Using a longitudinal design, stress measures (objective hardship, subjective distress and cognitive appraisal) were collected from mothers following the storm, and high-resolution T1-weighted structural magnetic resonance images (MRI) were collected from the children at the age of 11½. Automated neuroimaging techniques were used to derive HC morphology measures.

Results: Results show that PNMS exposure, but not early life maternal stress (ELMS) exposure, lead to altered bilateral hippocampal volumes, as well as specific volumetric changes in subfields CA1, subiculum and stratum radiatum/lacunosum-moleculare. The direction of the effects depends on the aspect of the stress assessed. Overall, maternal cognitive appraisal was found to be the strongest predictor of adolescent hippocampal volumes, such that a negative appraisal of the storms consequences predicted smaller hippocampal volumes. A trend was observed for higher objective hardship and subjective distress levels predicting larger HC volumes. Hippocampal surface area and shape appear to be unaffected by either PNMS or ELMS.

Discussion: These findings lend support to the idea that PNMS contributes to fetal programming and can exert long-lasting effects on children's brain structure.

Résumé

Contexte: Le stress maternel prénatal (SMPN) est associé à une altération de la structure de l'hippocampe (HC) chez les animaux et à des psychopathologies associées aux HC chez les humains. L'objectif de cette étude était de déterminer dans quelle mesure les SMPN chez les femmes enceintes durant la tempête de verglas de 1998 affectent la morphologie des HC (volume, surface et forme) chez leurs enfants; et de déterminer dans quelle mesure les effets de l'exposition au stress maternel diffèrent entre les enfants exposés avant la naissance et un groupe de comparaison apparié d'enfants exposés au début de la vie, nés un an avant la tempête.

Méthodes: À l'aide d'un plan longitudinal, des mesures de stress (difficultés objectives, détresse subjective et évaluation cognitive) ont été recueillies auprès des mères après la tempête, et des images par résonance magnétique structurale (IRM) à haute résolution ont été recueillies auprès des enfants âge 11½. Des techniques automatisées de neuro-imagerie ont été utilisées pour dériver des mesures de morphologie de HC.

Résultats: Les résultats montrent que l'exposition au SMPN, mais pas l'exposition précoce au stress maternel (EPSM), entraîne une altération des volumes bilatéraux de l'hippocampe, ainsi que des changements volumétriques spécifiques dans les sous-domaines CA1, subiculum et stratum radiatum /lacunosum-moleculare. La direction des effets dépend de l'aspect du stress évalué. Dans l'ensemble, l'évaluation cognitive maternelle s'est avérée être le prédicteur le plus fort des volumes d'hippocampe chez les adolescents, de sorte qu'une évaluation négative des conséquences des tempêtes a prédit de plus petits volumes d'hippocampe.

La surface et la forme de l'hippocampe ne semblent pas affectées par le SMPN ou l' EPSM.

Discussion: Ces découvertes soutiennent l'idée que le SMPN contribue à la programmation fœtale et peut exercer des effets durables sur la structure cérébrale des enfants.

Acknowledgements

I would first like to thank my thesis advisor, Dr. Suzanne King, for welcoming me into her lab and for her guidance and support throughout my M.Sc. study and research. Dr. King's expertise and enthusiasm has been invaluable at every stage of this thesis. I would also like to extend a sincere thank you to my co-supervisor, Dr. Mallar Chakravarty and his team, particularly Gabriel A. Devenyi, Raihaan Patel and Jürgen Germann, for always being available with advice and assistance as well as fostering an atmosphere rich with scientific curiosity.

I would like to thank the rest of my thesis committee: Dr. Jens Pruessner, Dr. Jamie Near, Dr. Gillian O Driscoll, and my student mentor Dr. Lalit Srivastava, for their difficult questions and discerning comments.

I thank my labmates, especially Dr. David P. Laplante and Isabelle Bouchard for their advice and all of the early work they have done over the years, making this research possible. I extend a special thank you to Guillaume Elgbeili for his friendship and generous guidance with statistics. I would also like to thank my officemates Dr. Sherri Jones and Dr. Lei Cao for their friendship and extensive encouragement beyond their many insightful suggestions. I also thank every other member of the King lab who has contributed to making Project Ice Storm what it has become over the past 20-years.

Last but not least, I thank my parents and brother – Monica, Bob, and Jesse – for being the family that we are and for their unwavering support.

Contribution of Authors

This thesis is ultimately built on the collaborative work of the dozens of researchers and students that have contributed to Project Ice Storm over the years.

Prior to my joining the King lab, the MRI scanning protocol was designed by Arnaud Charil. Additionally, Rowena Lung, Karine Ferron, Gila Foomani, Weirquan Zeng, Marjolaine Massé, Maria Papastergiou, André Cyr and Carollyne Hurst were all involved in the MRI data collection process.

The MRI preprocessing and automatic segmentation process was done by myself with support from Gabriel A. Devenyi, Raihaan Patel and Jürgen Germann.

I was primarily responsible for all major areas of concept formation, and manuscript composition. Statistical analyses and data interpretation were performed by myself, with guidance from Guillaume Elgbeili.

My supervisor, Suzanne King, and co-supervisor, Mallar Chakravarty were involved throughout the project and contributed to manuscript edits.

List of Abbreviations

11-HSD2	11-Hydroxysteroid Dehydrogenase Type 2
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BEaST	Brain Extraction based on nonlocal Segmentation Technique
CA	Cornu Ammonis
CONSEQ	Cognitive appraisal questionnaire
DG	Dentate Gyrus
DICOM	Digital Imaging and Communications in Medicine
DOHaD	Developmental Origins of Health and Disease
ELMS	Early Life Maternal Stress
FDR	False Discovery Rate
GR	Glucocorticoid Receptor
GW	Gestational Week
HC	Hippocampus
HPA	Hypothalamic Pictuitary Adrenal Axis
IES-R	Impact of Events Scale - Revised
MAGeTbrain	Multiple Automatically Generated Templates brain segmentation
Meff	Effective number
MINC2	Medical Image NetCDF
MP-RAGE	Magnetization-prepared gradient-eco image
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
PNMS	Prenatal Maternal Stress
PTSD	Post Traumatic Stress Disorder
SES	Socioeconomic Status
SR-SL-SM	Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare
Storm24	Objective hardship questionnaire (partial version)
Storm32	Objective hardship questionnaire (full version)
TE	Echo Time
TI	Inversion Time
TIC	Total Intracranial Volume
TR	Repitition Time
WBV	Whole Brain Volume

I. Introduction

Stressful experiences trigger an array of physiological changes in the human body including activation of the endocrine system, and dysregulated production of stress hormones such as glucocorticoids (Sapolsky, 1996). When a pregnant woman experiences stress – a phenomenon referred to as prenatal maternal stress (PNMS), stress hormones are also passed through the placenta to the developing fetus (Welberg & Seckl, 2001). Although glucocorticoids are necessary for normal fetal development, research suggests that excessive glucocorticoid levels, a consequence of PNMS, is harmful to the fetus and has been associated with maladaptive cognitive, behavioral and physical development later in life (Cole et al., 1995; Welberg & Seckl, 2001). Abnormal glucocorticoid levels impair brain development via delays in neuronal maturation, altering myelination, glia, vasculature, and synapse formation (Lupien et al., 2009), evidenced in vivo as morphological changes, visualized for example with magnetic resonance imaging (MRI).

Much that is known about the health consequences of PNMS comes from animal research where experimental conditions such as the type, duration, and timing of the stress experience can be carefully controlled. Studying PNMS in humans is restricted by ethical constraints and is often limited to retrospective studies where it can be difficult to disentangle the effects of the stress from other environmental and maternal factors. Studying PNMS in animal models helps overcome many of these constraints but introduces other limitations such as an inability to study the effects of the subjective and cognitive appraisal components of stress; as well as the usual difficulties associated with translating research from animal models directly to humans. Unique approaches to studying the impact of PNMS on offspring are necessary. One such methodology employs the study of mothers who were pregnant through the course of a natural disaster.

One such disaster is the North American Ice Storm of 1998, one of the worst natural disaster Canada had ever experienced. Freezing rain from five separate weather events fell between January 4-10th, 1998. The weight of the accumulating ice caused unprecedented damage to trees and infrastructure, essentially shutting down major cities as roadways were blocked, homes and businesses were damaged, and the power grid was destroyed. In Quebec alone, an estimated 3 million people were left without power, some for as long as 45-days, during the coldest months of the year. Consequently, this natural disaster acted as a 'natural experiment' as a large number of pregnant women were quasi-randomly exposed to known, sudden-onset stressor, independent of maternal characteristics, during various stages of fetal development. Recognizing this rare opportunity Dr. Suzanne King began Project Ice Storm, recruiting women from the hardest hit region in Quebec, with the aim of prospectively studying the physiological and psychological effects of PNMS on their children.

Many maternal stress-related health outcomes are thought to be mediated by structural brain changes in the offspring, particularly changes to the hippocampus, thus making advanced computational neuroimaging techniques a powerful tool in elucidating the role that PNMS plays in child/adolescent development (Johnson et al., 2013; Khashan et al., 2008; Kinney & Miller, 2008; Li et al., 2010; Nelson et al., 1998; Plessen et al., 2006; Sparks et al., 2002). Effects of PNMS may differ for males and females given differences in the way that placentas manage stress hormones depending on fetal sex (Clifton, 2010). Starting at age 11½, high-resolution structural magnetic resonance (MR) images were acquired from a subset of adolescent Project Ice Storm participants along with the recruitment of a matched infancy-exposed group born 1-year prior to the storm, to assess individual and group differences in brain structure associated with prenatal and early life maternal stress (ELMS). Thus, the goas of the project were to: (i)

determine the extent to which PNMS and ELMS exposure can predict three measures of adolescent hippocampal morphology (shape, volume and surface area), and (ii) to determine the extent to which the sex of the child moderates the relationship between maternal stress and hippocampal morphology.

II. Literature Review

Maternal Stress, Fetal Programming & Developmental Origins of Health and Disease

We now appreciate that human development is shaped by both genes and environment. Interestingly, susceptibility to environmental influence begins much earlier than the day one is born. During pregnancy, nutrition and maternal hormones pass from the mother via the placenta to the developing fetus, imparting information about the state of the outside world. This exchange of information allows the fetus the opportunity to 'program' its phenotype to better cope with predicted environmental challenges. Although prenatal phenotypic plasticity can be a powerful evolutionary tool, problems arise when there is a mismatch between the predicted environment and the actual environment a child is born into. For example, if a pregnant woman is living in a food-scarce environment, the fetus responds by developing metabolically prepared to grow up with inconsistent access to food, likely involving insulin and leptin resistance (Vickers, 2001). However, if conditions change, and food becomes plentiful, a child primed for food scarcity my now have a higher susceptibility for developing metabolic conditions such as obesity, and type II diabetes (Barker, 1995; Hales & Barker., 2013).

The idea that conditions during early development play a role in adult health and disease, known as the fetal programming hypothesis, and more recently referred to as the Developmental Origins of Health and Disease (DOHaD), is not limited to fetal malnutrition. The fetal environment is similarly susceptible to fluctuations in maternal glucocorticoids, steroid

hormones produced primarily by the adrenal glands. Cortisol, the most important human glucocorticoid, is necessary for many cardiovascular, metabolic, and immunologic functions, as well as numerous physiological responses in the brain including acting as an essential mediator of the stress response (Turkay et al., 2012). Although it is true that normal fetal development requires exposure to maternal glucocorticoids, so much so that the glucocorticoid receptor (GR)-deficient mice die hours after birth (Cole et al., 1995), there is a growing body of evidence suggesting that overexposure (and underexposure) to glucocorticoids during early development is also detrimental to health. In human and animal models, elevated maternal glucocorticoids have been associated with reduced birth weight, dysregulated-activation of the fetal hypothalamic pituitary adrenal axis (HPA), and increased risk of cardiovascular, psychological, cognitive, and neurodevelopmental problems later in life (Benediktsson et al., 1993, 1997; Buss et al., 2010; Laplante et al., 2004, 2008; Stewart et al., 1995; van Os and Selten, 1998; Ward et al., 2004).

Stress, a multidimensional perspective

Stress is not a universally homogeneous experience. What one person finds stressful, another might find benign, or exhilarating. This has been demonstrated physiologically by exposing groups of people to common stressors and then assessing individual differences in their cortisol response. These studies consistently report considerable variance in individual cortisol reactivity (Lopez-Duran et al., 2009; Nicolson et al., 1997). This can be problematic given that one of the most popular methods for studying the impact of stress in humans is to identify a 'universal stressor', such as a natural or man-made disaster, and then prospectively, or retrospectively, assess the impacts of that event on a sample. Although a disaster model offers researchers an opportunity to study the effects of a truly independent, sudden-onset, objectively-

defined stressor that has been randomly distributed across the population, on its own this approach fails to account for individual differences in how a so-called universal stressor is interpreted and reacted to. With animal models, researchers can easily overcome individual differences in the stress response by artificially manipulating endogenous glucocorticoid levels using synthetic glucocorticoids, or via inhibition of the placental glucocorticoid regulatory enzyme 11-hydroxysteroid dehydrogenase type 2 (11-HSD2). However, in humans, especially pregnant women, artificial manipulation of glucocorticoids would be unethical. Human research therefore calls for a multidimensional perspective of stress that accounts for variations in personal experience.

Lazarus and Folkman (1984) proposed that stress is a relationship between the person and the environment, with stress occurring when the demands of a situation exceed the individual's ability to cope. For a complete assessment of the stress experience, it is therefore necessary to consider (i) the objective characteristics of the event, (ii) the person's subjective reaction, and (iii) their overall appraisal of the event, i.e., whether they believe they have sufficient material and/or cognitive resources to adequately overcome the challenges associated with the event. Consequently, it had been shown that one can more accurately predict an individual's cortisol response to a potentially stressful event when you consider their subjective assessment of situational demands, and available resources (Harvey et al., 2010).

Although research is beginning to make the connection that stressful events experienced by pregnant women can have long-lasting impacts on their child's development; and it is believed that PNMS impacts fetal development via fluctuations in the level of maternal stress hormones the fetus is exposed to (Lazinski et al., 2008), to date, it is still not understood how the various aspects of the stress experience get transduced by the placenta into a signal that programs

the fetus.

The hippocampus: stages of structural development

The human hippocampus (HC) experiences its most dramatic periods of structural development prenatally, followed by rapid volumetric increases throughout the first 2-years of life. The hippocampus becomes distinguishable from surrounding neuroanatomy between the 6th and 7th gestational week (GW) (Humphrey, 1964). Between the 13th and 20th GW the basic anatomy of the hippocampus starts to take shape (Kier et al., 1997). During the 15th and 16th GW the dentate gyrus (DG) and cornu ammonis (CA) begin to fold into the temporal lobe as the CA1, CA2 and CA3 fields start to arrange linearly. Between the 15th and 19th GW, the hippocampal fissure forms and the subicular, ammonic and dentate subfields become discernable (Arnold & Trojanowski, 1996). By the 25th GW, the morphology of the hippocampus, including the cytoarchitecture of all its subdivisions, is similar to that of an adult (Arnold and Trojanowski, 1996; Humphrey, 1964). The remainder of the prenatal period is marked predominantly by hippocampal growth.

By the time of birth, even though the basic architecture of the hippocampus resembles that of an adult, its size does not. The hippocampus grows at a rapid pace throughout the first two-years of life, followed by protracted growth until early-adolescence, with a right greater than left hemisphere asymmetry in peak hippocampal volume (Giedd et al., 1996; Uematsu et al., 2012; Utsunomiya et al., 1999). In terms of sex differences, males and females have been shown to share similar temporal growth curves, however peak volume in males is significantly larger than in females (Uematsu et al., 2012; Utsunomiya et al., 1999). Following the onset of puberty, a period marked by significant synaptic pruning, hippocampal volume begins to decrease until stabilizing in adulthood (Blanton et al., 2012; Neufang et al., 2009; Paus et al., 2008;

Satterthwaite et al., 2014).

Prenatal maternal stress: causes and consequences

Prenatal maternal stress refers generally to any stress that a woman experiences during her pregnancy. Chronic PNMS is associated with ongoing life events such as living in poverty, a difficult divorce, or domestic abuse. Chronic PNMS can also result from cumulative everyday stressors that are poorly managed or ignored. Acute PNMS is associated with sudden life changes such as an unexpected death of a spouse, or experiencing a natural disaster. Due to the strong correlation between maternal and fetal hormonal profiles, both prolonged exposure (chronic stressors) and/or short periods of exposure to moderately stressful situations (acute stressors) can have detrimental impacts on fetal/child development (Kramer et al., 2009; Lou et al., 2008).

Research with rodents and non-human primates has linked acute PNMS exposures and synthetic corticosteroid administrations to an array of offspring neurodevelopmental changes including volume reductions in the hippocampus, amygdala, frontal cortex, cerebellum, hypothalamus, and corpus callosum (Charil et al., 2010). Human PNMS research is however often limited to birth outcomes (e.g., reduced birth weight, reduced head circumference, preterm labor and delivery), and mental health complications throughout life (e.g., anxiety, temperament, externalizing problems, intellectual deficits, and psychopathology) (Beydoun & Saftlas, 2008). Human studies aimed at measuring PNMS related morphological changes in the brain are needed if we hope to understand the mechanisms that lay between PNMS and disease.

Early Life Maternal Stress: causes and consequences

Less understood are the effects of maternal stress in infancy. Research proposes two primary mechanistic hypotheses for how a mother's physiological reactivity in response to a

stressful event may influence infant development. The first is through direct transmission of stress-related hormones via breast milk from stressed mothers. Animal studies have demonstrated a relationship between maternal glucocorticoid levels and corticosterone levels in breastfed offspring (Catalani et al., 2000, 2002; Domenici et al., 1996). In terms of neurodevelopmental effects, male rats exposed to the milk of mothers drinking corticosterone had an increased number of glucocorticoid receptors in the hippocampus at both 1- and 15-months of age (Catalani et al., 2000); for breastfed females, however, glucocorticoid receptors in the HC appear to be unaffected by maternal glucocorticoids (Catalani et al., 2002). For both sexes, exposure between postnatal days 30 to 45 have been linked with reductions in HC CA1 synaptic plasticity (Domenici et al., 1996). Together, these studies suggest that the glucocorticoids ingested via breastmilk are associated with neurodevelopment, and that these effects are largely sex- and time-dependent.

Understanding the role breastfeeding plays in infant development is far from straightforward. Any detrimental effects associated with maternal glucocorticoid transmission need to be considered within the context of the many protective factors related to breastfeeding. Even if we limit the discussion to stress reactivity, the cumulative effects of breastfeeding are not clear. It has been shown that breastfed children (age 10-years) are more resilient to the psychological stress associated with parental divorce/separation compared with children that were bottle-fed (Montgomery et al., 2006). In fact, the act of breastfeeding is believed to have beneficial effects for mothers too. Sibolboro Mezzacappa (2004) reports that breastfeeding is associated with a decreased neuroendocrine response to stressors and fewer maternal depressive symptoms.

Breast milk is not the only way that an infant can be impacted by ELMS. Another

mechanism that has been proposed views stress as a form of contagion. Waters et al., (2014) studied mother-infant pairs in a series of experiments in which mothers and infants were separated, the mother was exposed to a stressful task (or a non-stressful control task), and then reunited with her infant. Intriguingly, within minutes of being reunited with their stressed mothers the 12- to 14-month old infants' physiological reactivity mirrored that of their mothers (sympathetic nervous system activation inferred from heart rate and electrocardiograph activity). Moreover, the stronger the mothers' physiological response to the stressor, the stronger the infant response. This would suggest that stress experienced by the mother (and potentially the father) can not only be understood by the infant, but can translate into a corresponding physiological change that could presumably lead to similar developmental outcomes associated with direct prenatal and early life exposures to maternal glucocorticoids.

Prenatal maternal stress and child neurodevelopment

The expression of 11β-HSD2 enzyme in the placenta and neonate brain helps protect the fetus from abnormally high levels of cortisol by converting it to the inactive metabolite cortisone. If, however, a pregnant woman experiences severe or prolonged periods of stress, the enzyme can become saturated. Importantly, because fetal cortisol levels are so much lower than maternal levels, it only takes a 10-20% increase in maternal levels to double fetal concentrations (Gitau et al., 2001).

We know from early work with animal models that glucocorticoids play important roles in normal development of the central nervous system. Meyer (1983), suggests that glucocorticoids help regulate neurogenesis, and myelin deposition. Consequently, prenatal overexposure to glucocorticoids has been shown to reduce brain weight at birth in sheep, likely due to maturational delays in neurons, myelin, glia and cerebral vasculature (Huang et al., 1999;

2001). Similarly, in rhesus monkeys, prenatal exposure to synthetic glucocorticoids during prenatal day 132 is associated with hippocampal degeneration: fewer pyramidal neurons in CA regions, fewer granular neurons in the dentate gyrus and significant degeneration of axodendritic synaptic terminals of the mossy fibers in CA3. Degeneration was present when observed at 162 days (near term) and found to be more severe with higher glucocorticoid concentrations, and results showed that multiple lower doses were more damaging compared with a single high dose (Uno et al., 1990). Taken together, this suggests that brain regions that express high concentrations of glucocorticoid receptors, such as the hippocampus, are especially vulnerable to prenatal exposure to exogenous glucocorticoids. A follow-up experiment showed ~30% reduction in hippocampal volume in 20-month old monkeys prenatally exposed to synthetic glucocorticoids compared with controls (Uno et al., 1994).

Sexual dimorphisms: placenta, brain and development

An interesting trend is beginning to emerge from the growing body of evidence linking PNMS and risk for developing neurodevelopmental disorders such as schizophrenia (Beversdorf et al., 2005; Kinney & Miller, 2008), attention deficit/hyperactivity disorder (ADHD) (Li et al., 2010), and autism spectrum disorders (ASD) (Khashan et al., 2008): namely, the male prominence of these disorders. Not only are men more likely to develop these conditions (schizophrenia 2:1 male prevalent; ADHD 3:1 male prevalent; ASD 4:1 male prevalent) average age of onset is earlier and symptom severity is typically worse in men (Hanamsagar & Bilbo, 2016). Researchers have started to consider whether males may be more susceptible to prenatal environmental insults, and whether this sensitivity might help explain the male-biased prevalence of these disorders.

The placenta develops from both embryonic-derived cells and maternal uterine tissue.

Due to the contribution of embryonic cells (either a male XY, or female XX embryo), the placenta expresses the genetic sex of the fetus, resulting in sex-specific responses to fluctuations in the uterine environment. Clifton (2010) reviewed the sexually dimorphic placental functions associated with fetal growth and survival, reporting that the female placenta tends to be more adaptive to fluctuations in the maternal stress response. The findings are suggestive of sex-specific responses to adverse maternal environments: the female placenta responds with changes in gene and protein expression resulting in slightly slowed fetal growth, possibly to conserve nutritional resources and oxygen, whereas the male placenta makes few adjustments in response to an adverse maternal environment in favor of continued growth, which may increase the risk of adverse pre/postnatal outcomes.

Another interesting commonality among the male-biased neurodevelopmental disorders associated with prenatal stress is abnormal hippocampal anatomy. Hippocampal atrophy is frequently observed in patients with schizophrenia (Nelson et al., 1998), as well as significant diffuse bilateral inward and outward deformations of the hippocampal surface in both childhood onset schizophrenic patients and healthy siblings (Johnson et al., 2013). Hippocampal enlargement has been reported in ADHD and ASD (Plessen et al., 2006; Sparks et al., 2002), though volumetric abnormalities in these conditions are inconsistent between studies. One study which failed to find any volumetric differences in the hippocampi of children with ASD did however report significant shape differences compared with normally developing children, especially with respect to inward deformations of the subiculum (Dager et al., 2007). It appears likely that the hippocampus is one of the vulnerable targets affected by prenatal insults such as PNMS, and that these hippocampal perturbations are, at least in part, acting to mediate the relationship between PNMS and risk of developing mental health complications later in life.

III. Rationale: Problem Statement, Objectives & Research Questions:

Research with rodents and non-human primates has linked acute PNMS exposure and synthetic glucocorticoid administration (both prenatally and during infancy) to structural changes of the hippocampus, as well as alterations to hippocampal-dependent behaviors including memory and emotional regulation. Animal studies are invaluable for helping guide human research, translating findings from animal models to humans needs to be done with an abundance of caution. Important limitations that ought to be considered include: (i) corticosteroids are known to be teratogenic in animals but not in humans (Fraser & Sajoo, 1995; Brooks & Needs, 1985); (ii) key neurodevelopmental events during gestation and early life, as well as level of brain maturity at birth vary widely between species; (iii) gross species differences in the structure and organization of the central nervous system across all stages of development; and (iv) an inability to assess the effects of the subjective component of a stressor in animal models. Human studies are required to overcome these limitations.

There is a poverty of neuroimaging research to corroborate the effects of PNMS and ELMS on the structural development of the hippocampi in humans. There is, however, a growing body of evidence suggesting that PNMS increases a child's risk of developing mental health complications (e.g., anxiety, externalizing problems, intellectual deficits, PTSD, ASD and schizophrenia) that are known to be associated with altered hippocampal development.

The goal of this project was to determine the extent to which maternal stress (prenatal and early life exposure) in response to a sudden-onset, independent stressor impacts the structure of the hippocampi as observed during adolescence.

Specific research questions were as follows:

Prenatal maternal stress research question 1(a): In the prenatal stress cohort, what are the

individual and joint effects of maternal objective hardship, subjective distress and/or cognitive appraisal on *hippocampal volume* at age 11½?

Prenatal maternal stress research question 1(b): In the prenatal stress cohort, what are the individual and joint effects of maternal objective hardship, subjective distress and/or cognitive appraisal on *global hippocampal surface* area at age 11½?

Prenatal maternal stress research question 1(c): In the prenatal stress cohort, what are the individual and joint effects of maternal objective hardship, subjective distress and/or cognitive appraisal on *hippocampal shape* at age 11½?

Early life maternal stress research question 2(a): In the ELMS cohort, what are the individual and joint effects of maternal objective hardship, and/or cognitive appraisal on *hippocampal volume* at age 11½?

Early life maternal stress research question 2(b): In the ELMS cohort, what are the individual and joint effects of maternal objective hardship, and/or cognitive appraisal on *global hippocampal surface area* at age 11½?

Early life maternal stress research question 2(c): In the ELMS cohort, what are the individual and joint effects of maternal objective hardship, and/or cognitive appraisal on *hippocampal shape* at age 11½?

Prenatal vs. early life stress research question 3(a): To what extent do the effects of maternal stress on *hippocampal volume* differ between PNMS and ELMS stress cohorts?

Prenatal vs. early life stress research question 3(b): To what extent do the effects of maternal stress on *global hippocampal surface area* differ between PNMS and ELMS cohorts?

Prenatal vs. early life stress research question 3(c): To what extent do the effects of maternal stress on *hippocampal shape* differ between PNMS and ELMS cohorts?

Male vs. Female research question 4(a): To what extent do the effects of PNMS and ELMS on *hippocampal volume* differ between male and female offspring?

Male vs. Female research question 4(b): To what extent do the effects of PNMS and ELMS on *global hippocampal surface area* differ between male and female offspring?

Male vs. Female research question 4(c): To what extent do the effects of PNMS and ELMS stress on *hippocampal shape* differ between male and female offspring?

Taking into consideration that this was the first study to assess the effects of pre- and postnatal maternal stress on the morphology of the human hippocampi, the research questions were largely exploratory in nature. We did, however, maintain the following hypotheses: (1) higher PNMS or ELMS scores (objective and/or subjective), and/or a negative cognitive appraisal will be associated with smaller hippocampal volumes, reduced hippocampal surface area and/or greater shape differences (inward and outward deformations), (2) prenatal exposure to maternal stress will have a greater effect on hippocampal morphology compared to early life (postnatal) exposure, and (3) male offspring will be more sensitive to the effects of both PNMS and ELMS compared to females.

Inclusion of shape and surface area indices were important additions to the more traditional volumetric measurements of the hippocampus. After all, describing the size of an object alone fails to account for the complexity of a three-dimensional structure. Shape analysis in particular is gaining increased interest in neuroimaging research due to its potential to more precisely localize morphological changes in pathological structures. In fact, a growing number of studies are finding significant differences in the shape of brain structures without finding volumetric differences (Corbo et al., 2005, Schuetze etl al., 2016, Schroeder et al., 2017). Importantly, Lin et al., (2013) concluded that shape analysis can detect sub-regional differences

of the hippocampus, otherwise invisible to volumetric analysis.

IV. Methods:

Participants

Prenatal maternal stress cohort, born 1998

Beginning June 1998, Project Ice Storm recruited 178 women who were pregnant during Quebec's 1998 ice storm, or who became pregnant within 3-months of the storm, giving birth between January and December 1998. Women were identified with the help of obstetricians from four hospitals in the Montérégie, a region southeast of Montreal, the epicenter of the storm. Inclusion criteria: women were (i) either pregnant during, or became pregnant within 3-months of the storm, (ii) white French-Canadian, and (iii) 18 years of age, or older. Compared with the regional average, women in the final sample skewed toward a higher socioeconomic status (SES), with more years of education. Of the original 178 women recruited into Project Ice Storm, a subset of their children (n = 67; 34 male, 33 female; birthdates spread evenly between January and December 1998) underwent MRI as part of the age 11½-year assessments. Scans were completed between 2009 and 2010.

Early life maternal stress cohort, born in 1997

Matching for birth month, sex, and SES to the Project Ice Storm children, 60 control participants (30 male, 30 female), born the year before the ice storm, and their mothers were recruited. Children were recruited from the same schools attended by the prenatally exposed cohort. All adolescent (age 11½) MRIs and maternal stress questionnaires were completed between May 2008 and May 2009.

Exclusion criteria

For both cohorts, exclusion criteria included (i) cesarean-section birth, (ii) any

contraindications for MRI scanning (i.e., cerebral or cardiac clips, ocular implants), (iii) although not excluded at the time of recruitment, left-handed and mixed-handed children were excluded from the study prior to analyses. Child handedness was determined by asking mothers which hand their child uses for writing, drawing, colouring, throwing a ball, holding a toothbrush, and using utensils. Children were classified as mixed-handed if they were found to use either hand for any 2, or more, of these items. Additionally, any participant with a hippocampal segmentation that failed quality control procedures (see below), or was missing any maternal stress data was excluded.

Maternal Measures

Objective Ice Storm Hardship:

For the prenatal stress cohort, a custom-designed questionnaire was used to estimate the objective storm-related consequences experienced by the women. In keeping with previous disaster studies, the questionnaire assessed 4 distinct disaster-related stress dimensions: Threat (e.g., Were you injured?), Loss (e.g., Did your residence suffer damage as a result of the ice storm?), Scope (e.g., How many days were you without electricity), and Change (e.g., How often were you required to change residence during the ice storm?). All four dimensions were weighted equally, each with a maximum score of 8. Scores from each dimension were summed to produce a 32-point objective storm-related stress score (Storm32). The objective hardship questionnaire was sent out to participants June 1st, 1998.

Retesting women in the prenatal stress group with the Storm32 questionnaire at a 6-year follow up assessment found excellent test-retest reliability for Loss, Scope, and Change; however, poor retrospective reliability was found for the Threat component ($r = 0.34 - 0.46$). Although the Storm32 questionnaire was used to collect objective storm-related hardship

information in the early life stress cohort, recruited in 2009, their total objective stress score was calculated using the Scope, Loss, and Change dimensions only. This variant of the questionnaire, with the Threat component removed, is referred to as Storm24. For consistency, all group-wise comparisons with respect to objective hardship will use Storm24 scores.

Subjective Stress:

In the prenatal stress cohort, subjective storm-related distress was measured using the Impact of Events Scale–Revised (IES-R), which assesses post-traumatic stress disorder (PTSD) symptoms across three categories (avoidance, intrusion and hyperarousal) (Weiss and Marmar, 1997). IES-R is a 22-item scale where each item can be responded to on a five-point (0-4) Likert scale, from "not at all" (0), to "extremely" (4). A score above 23 is indicative of full, or partial, PTSD. For use in Project Ice Storm, the IES-R was translated to French and was assessed for internal validity (Brunet et al., 2003). The IES-R was distributed alongside the Storm32 questionnaire, June 1st, 1998.

Cognitive Appraisal:

Cognitive appraisal of the ice storm was assessed at the same time as the previously described questionnaires and was based on the mothers' responses to the following question: "If you think about all of the consequences of the ice storm on your household members, would you say they were…"; response options were on a five-point scale of "Very negative" (1), "negative" (2), "neutral" (3), "Positive" (4), and "Very positive" (5). This item was recoded into "negative" (0) or "neutral/positive" (1).

Magnetic Resonance Imaging (MRI)

MRI Acquisition

When the children were 11½-years of age we obtained whole brain structural MRIs from

both the prenatal stress and early life stress cohorts. Anatomical MRIs were acquired at the Unité de Neuroimagerie Fonctionnelle du Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal on a 3.0T Siemens MAGNETOM Trio TIM Syngo (Siemens, Erlangen, Germany), with a 12-channel head coil. The total MRI scanning session lasted approximately 1-hour during which the children were allowed to watch a movie (nature documentary) via a mirror mounted on the head coil. Ear plugs and MRI-safe headphones acted as a buffer against scanner noise while allowing participants to listen to the movie. Multiple head and abdominal sequences were acquired during the 1-hour scanning session, however only one sequence was used for the present study: a three-dimensional, high-resolution, whole brain, structural T1-weighted magnetization-prepared gradient-echo image (MP-RAGE) sequence TR = 2,300 ms, TE = 2.98 ms, TI = 900 ms; 256 mm field of view, 176 slices, voxel size 1 mm isometric, sagittal acquisition, time = 9 min.

MRI preprocessing

All MR images were converted from their standard Digital Imaging and Communications in Medicine (DICOM) format to MINC2 (Medical Image NetCDF). Images were then preprocessed using the minc-bpipe-library (https://github.com/CobraLab/minc-bpipe-library), a set of chainable MINC file processing functions. Preprocessing steps included: N4correction, clean and center, cutneckapplyautocrop, and BEaST (Brain Extraction based on nonlocal Segmentation Technique). *N4correction* applies an updated variation of the nonparametric nonuniform intensity normalization (N3; Sled et al., 1998) algorithm used for bias field correction, referred to as N4ITK (Tustison et al., 2010). *Clean and center* normalizes to unit orientation in each cardinal direction and sets the zero-point of the scan to the center of the image. *Cutneckapplyautocrop* crops off areas of non-interest from images, reducing file size and

reducing the computational resources needed during the segmentation process. *BEaST* is the brain extraction toolchain (Eskildsen et al., 2012) that produced head and brain masks used to derive total intracranial (TIC), and whole-brain volumes (WBV) for each participant using a patch-based segmentation procedure. Total intracranial volume is defined as the combined volumes of the brains grey and white matter, blood vessels, ventricles, spinal fluid and brainstem. Whole brain volume defined as the sum of all grey and white matter, brainstem, and blood vessel volume, excluding ventricle and spinal fluid volumes.

Automatic Segmentation with MAGeTbrain

Hippocampal Volume:

For all subjects, bilateral hippocampal volumes, including subfields ((*i*) cornu ammonis (CA) 1, (*ii*) CA2/CA3, (*iii*) CA4/dentate gyrus (DG), (*iv*) stratum radiatum/ stratum lacunosum/ stratum moleculare (SR-SL-SM), and (*v*) subiculum) were automatically segmented using the Multiple Automatically Generated Templates brain segmentation (MAGeTbrain) algorithm (Pipitone et al., 2014). Segmentations were derived from digital atlases developed by Winterburn et al. (2013), based on five high-resolution (0.3 mm isotropic) T1-weighted images (2 males and 3 females, ages 29–57, avg. 37). The MAGeTbrain pipeline optimizes segmentation accuracy by performing nonlinear image registrations between each of the five manually delineated input atlases and a template library consisting of a representative subset of target images (in the present study, the template library consisted of 21 target images, sampling equally from males and females, prenatally and early life stressed participants). The labels created during this process are then propagated to the entire set of target images followed by a majority voting procedure to fuse the large number of resulting labels into a single segmentation per subject. Quality of the final segmentations were manually inspected prior to analyses. All

nonlinear registrations were performed using the Advanced normalization tools (ANTs) toolkit (Avants et al., 2009).

Hippocampal shape & global surface area:

Hippocampal shape and global surface area delineation was carried out using an adapted surface-based methodology (Lerch et al., 2008; Raznahan et al., 2014). Using the nonlinear deformation fields produced during the volumetric segmentation process described previously (Pipitone et al., 2014), indices of hippocampal shape (vertex-wise inward and outward displacements relative to the surface normal) were derived based on the dot product between the nonlinear deformation vector at each vertex, and the surface normal at each vertex. Group differences in hippocampal shape were assessed with respect to a common hippocampal model created by averaging the five manually segmented input atlases (Pipitone et al., 2014; Winterburn et al., 2013). Global hippocampal surface area was derived based on methods described by Raznahan et al., 2014. Briefly, global left and right hippocampal surface area was calculated based on the sum of all vertex specific surface area values (~1,000 vertices/hemisphere).

Statistical Analyses:

Descriptive statistics (mean, range, standard deviation) were performed for all outcome and predictor variables. Pearson's correlations were computed between prenatal and early life maternal stress predictor variables and morphological outcome variables. To correct for multiple testing, a false discovery rate (FDR) correction was applied which adjusts correlated tests based on an 'effective number' of independent tests derived using the eigenvalues of a correlation matrix between outcome variables (Li & Ji., 2005). The false discovery rate adjusted p-value (or q-value) threshold was set at 0.05. A 0.05 threshold asserts that 5% of significant results will be

false positives.

To test research questions 1(a), 1(b), 2(a) and 2(b), two multiple linear regression models (equations 1 and 2; see below) were tested separately for all bilateral hippocampal volume variables, including subfields CA1, CA2/CA3, CA4/DG, SR-SL-SM, subiculum, and bilateral global hippocampal surface area. To maintain consistency between cohorts two separate statistical models were used because the ELMS cohort lacks Storm32 and IES-R data. Next, to determine the individual contributions of objective hardship, subjective distress, cognitive appraisal and Sex on hippocampal morphology, results that survived 5% FDR ($q < .05$) were further explored using hierarchical regression analyses (equations 3 and 4; see below). Similarly, to test research questions 1(c) and 2(c), two separate vertex-wise general linear models were used based on the same multiple linear regression equations (1) and (2) presented below. Although results normalized to WBV are of primary interest, to explore the impact of the normalization procedures used, all analyses were repeated using raw hippocampal volumes and again with volumes normalized to TIC. For the following models: dependent variable (DV), objective hardship (Storm32), objective hardship excluding the threat component (Storm24), subjective distress (IESR), and cognitive appraisal (CONSEQ) represent the variables in the linear relationship, and epsilon (ε) the regression's error term.

Multiple Linear Regression & Vertex-Wise General Linear Equations

$$\mathrm{DV}_{Model\,1} = \beta_1(\mathrm{Storm32}) + \beta_2(\mathrm{IESR}) + \beta_3(\mathrm{CONSEQ}) + \beta_4(\mathrm{Sex}) + \varepsilon \quad (1)$$

$$\mathrm{DV}_{Model\,2} = \beta_1(\mathrm{Storm24}) + \beta_3(\mathrm{CONSEQ}) + \beta_4(\mathrm{Sex}) + \varepsilon \quad (2)$$

Hierarchical Regression Equations

Model 1 (3)

$$\text{Step 1: } \mathrm{DV} = \beta_1(\mathrm{Storm32}) + \varepsilon$$

$$\text{Step 2: } \mathrm{DV} = \beta_1(\mathrm{Storm32}) + \beta_2(\mathrm{IESR}) + \varepsilon$$

$$\text{Step 3: } \mathrm{DV} = \beta_1(\mathrm{Storm32}) + \beta_2(\mathrm{IESR}) + \beta_3(\mathrm{CONSEQ}) + \varepsilon$$

$$\text{Step 4: } DV = \beta_1(\text{Storm32}) + \beta_2(\text{IESR}) + \beta_3(\text{CONSEQ}) + \beta_4(\text{Sex}) + \varepsilon$$

Model 2 (4)

$$\text{Step 1: } DV = \beta_1(\text{Storm24}) + \varepsilon$$

$$\text{Step 2: } DV = \beta_1(\text{Storm24}) + \beta_2(\text{CONSEQ}) + \varepsilon$$

$$\text{Step 3: } DV = \beta_1(\text{Storm24}) + \beta_2(\text{CONSEQ}) + \beta_3(\text{Sex}) + \varepsilon$$

To test exploratory research questions 3(a) and 3(b), a multiple linear regression (equation 2) including a maternal stress by cohort moderation effect was performed separately for each stress variable on hippocampal morphological outcomes. Moderation analyses were performed using the PROCESS macro for SPSS. Table 1 (see appendix) contains a complete list of hippocampal volume outcome variables, maternal stress predictor variables and moderators.

To test exploratory research question 3(c), a vertex-wise general linear model (equation 2) was used. The model included Maternal Stress x Group as the interaction term. All vertex-wise general linear models were tested using the R language for statistical computing (R Core Team, 2013).

To test exploratory research questions 4(a) and 4(b) a multiple linear regression (equation 2) including a Maternal Stress by Sex moderation effect was performed separately for each stress variable on hippocampal subfield volume outcomes.

To test exploratory research question 4(c), a vertex-wise general linear model (equation 2) was used. The model included Maternal Stress x Sex as the interaction term.

V. Results:

Descriptive statistics for maternal stress predictors and hippocampal morphological outcomes are presented for PNMS and ELMS cohorts separately in Tables 3-4. Similarly, Pearson's correlation coefficients between predictor and outcome variables are presented in Tables 5-6.

Prenatal maternal stress research question 1(a): *What are the individual and joint effects of maternal objective hardship, maternal subjective distress and/or maternal cognitive appraisal on hippocampal volume at age 11½ in the prenatal stress cohort.*

Model 1: PNMS cohort (using Storm32 and IES-R)

A multiple linear regression was calculated to predict hippocampal volumes based on maternal objective hardship (Storm32), maternal subjective distress, maternal cognitive appraisal and sex of the child. A complete summary of Model 1 results from the multiple regression analyses are presented in Table 7. With respect to volumes normalized to whole brain volume, PNMS, in particular, maternal cognitive appraisal, was found to predict significant ($q < .05$) variance in adolescent bilateral total HC volumes, as well as bilateral subfields CA1, subiculum, and left SR-SL-SM. Using raw volumes, there is a nearly identical pattern of results, except the regression equation falls to marginal significance ($q = 0.091$) for left SR-SL-SM. In comparison to WBV and raw volumes, PNMS variables were found to be less predictive of hippocampal volumes normalized to TIC, predicting significant variance in bilateral total HC and subiculum volumes, as well as right CA1 volumes.

Negative Cognitive Appraisal Predicts Smaller Total Left HC

Results from the hierarchical regression analysis for total left hippocampal volume normalized to whole brain volume (HC/WBV) in the PNMS cohort are presented in Table 8. In Steps 1 and 2, neither the main effect of maternal objective hardship (Storm32) nor maternal subjective distress significantly contributed to the variance explained. In Step 3, the addition of maternal cognitive appraisal was significantly associated with left HC/WBV ratios, explaining 15.2% of the variance ($p < .01$). The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 25.9% of the variance in total left HC/WBV

ratios. After 5% FDR correction only maternal cognitive appraisal was found to be a significant predictor of left HC/WBV ratios in prenatally exposed children. Although their contribution to the final model did not survive FDR corrections, maternal subjective distress scores predicted HC/WBV ratios at a strong trend level ($p = .06$) in Step 2, and significantly contributed to the variance explained in Steps 3 and 4: higher maternal subjective distress scores predictive of larger HC/WBV ratios. Similarly, maternal objective hardship predicted HC/WBV ratios at a trend level ($p < .10$) in Steps 3 and 4: the higher objective hardship scores, the larger HC/WBV ratios.

Complete results from the hierarchical regression analysis for raw total left hippocampal volume in the PNMS cohort are presented in Table 9; and are largely in agreement with the results using WBV ratios. The final model explained 20.7% of the variance in raw total left hippocampal volume, compared with 25.9% of the variance in total left HC/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Total Right HC

Results from the hierarchical regression analysis for total right hippocampal volume normalized to WBV (right HC/WBV) in the PNMS cohort are presented in Table 10. In Steps 1 and 2, neither the main effect of maternal objective hardship nor maternal subjective distress significantly contributed to the variance explained. In Step 3, the addition of maternal cognitive appraisal was significantly ($p < .01$) associated with right HC/WBV ratios, explaining 14.4% of the variance after controlling for objective hardship and subjective distress: negative cognitive appraisal associated with smaller right HC/WBV ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 19.1% of the variance in right HC/WBV ratios. Higher maternal objective hardship scores predicted larger right HC/WBV ratios at a trend level ($p < .10$) in Steps 3 and 4. After 5% FDR correction only

maternal cognitive appraisal was found to be a significant predictor of right HC/WBV in prenatally exposed children.

Complete results from the hierarchical regression analysis for raw total right hippocampal volume in the PNMS cohort are presented in Table 11; and are in agreement with the results using WBV ratios. However, the previously described trend between maternal objective hardship and right HC/WBV ratios were not observed when using raw volumes. The final model explained 13.8% of the variance in raw total right hippocampal volume, compared with 19.1% of the variance in total right HC/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Left CA1

Results from the hierarchical regression analysis for left CA1 volume normalized to WBV (CA1/WBV) in the PNMS cohort are presented in Table 12. In Step 1, the main effect of maternal objective hardship was not significantly associated with CA1/WBV ratios. In Step 2, the addition of maternal subjective distress significantly ($p < .05$) explained 8.9% of the variance in CA1/WBV ratios: the higher the subjective distress scores, the larger the CA1/WBV ratios. In Step 3, the addition of maternal cognitive appraisal significantly ($p < .01$) explained an additional 17.5% of the variance in CA1/WBV ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 31% of the variance in CA1/WBV ratios. After 5% FDR correction only maternal cognitive appraisal was found to be a significant predictor of CA1/WBV ratios in prenatally exposed children.

Complete results from the hierarchical regression analysis for raw left CA1 volume in the PNMS cohort are presented in Table 13; and are largely in agreement with the results using WBV ratios. The final model explained 25.5% of the variance in raw left CA1 volume, compared with 31% of the variance in left CA1/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Right CA1

Results from the hierarchical regression analysis for right CA1 volume normalized to WBV (CA1/WBV) in the PNMS cohort are presented in Table 14. In Steps 1 and 2, neither the main effect of maternal objective hardship nor maternal subjective distress significantly contributed to the variance explained. In Step 3, the addition of maternal cognitive appraisal was significantly ($p < .01$) associated with right CA1/WBV ratios, explaining 20.5% of the variance after controlling for objective hardship and subjective distress: negative cognitive appraisal, smaller right CA1/WBV ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 24% of the variance in right CA1/WBV ratios. Maternal objective hardship scores contributed to the amount of variance explained in right CA1/WBV ratios in Steps 3 and 4 at a trend level ($p < .10$): higher objective hardship scores, larger right CA1/WBV ratios. After 5% FDR correction only maternal cognitive appraisal was found to be a significant predictor of right CA1/WBV ratios in prenatally exposed children.

Complete results from the hierarchical regression analyses for raw right CA1 volume and right CA1/TIC ratios in the PNMS cohort are presented in Tables 15 and 16, respectively, and are generally in agreement with the results using WBV ratios. However, the previously described trend between maternal objective hardship and right CA1/WBV ratios were not observed when using raw volumes, or when using TIC ratios. The final model explained 13.2% of the variance in right CA1/TIC ratios, compared with 20.2% of the variance in raw total right hippocampal volume, and 24% of the variance in total right CA1/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Left Subiculum

Results from the hierarchical regression analysis for left subiculum volume normalized to

WBV (subiculum/WBV) in the PNMS cohort are presented in Table 17. In Steps 1 and 2, neither the main effect of maternal objective hardship nor maternal subjective distress significantly contributed to the variance explained. In Step 3, the addition of maternal cognitive appraisal was significantly ($p < .01$) associated with left subiculum/WBV ratios, explaining 16.3% of the variance after controlling for objective hardship and subjective distress: negative cognitive appraisal associated with smaller left subiculum/WBV ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 26.1% of the variance in left subiculum/WBV ratios at 11½ years of age. After 5% FDR correction only maternal cognitive appraisal was found to be a significant predictor of left subiculum/WBV ratios in prenatally exposed children. Although the effect of objective hardship did not survive FDR in the final model, objective hardship levels contributed to the variance in left subiculum/WBV ratios in steps 3 and 4 ($p < .05$): higher objective hardship scores, larger left subiculum/WBV ratios. Additionally, higher maternal subjective distress levels were also associated with larger left subiculum/WBV ratios at a strong trend level in Step 3 ($p = .055$), and Step 4 ($p = .052$): higher subjective distress, larger left subiculum/WBV ratios.

Complete results from the hierarchical regression analyses for raw left subiculum volume and left subiculum/TIC ratios in the PNMS cohort are presented in Tables 18 and 19, respectively. Relationships between maternal cognitive appraisal and left subiculum are in agreement between all 3 sets of analyses. However, the previously described trends for maternal objective hardship and maternal subjective distress with respect to left subiculum/WBV ratios were not observed when using raw volumes, or when using TIC ratios. The final model explained 18.3% of the variance in raw left subiculum volume and left subiculum/TIC ratios, compared with 26.1% of the variance in left subiculum/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Right Subiculum

Results from the hierarchical regression analysis for right subiculum volume normalized to WBV (subiculum/WBV) in the PNMS cohort are presented in Table 20. In Steps 1 and 2, neither the main effect of maternal objective hardship nor maternal subjective distress significantly contributed to the variance explained. In Step 3, the addition of maternal cognitive appraisal was significantly ($p < .01$) associated with right subiculum/WBV ratios, explaining 17.2% of the variance after controlling for objective hardship and subjective distress: negative cognitive appraisal predicting smaller right subiculum/WBV ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 26.1% of the variance in right subiculum/WBV. After 5% FDR correction only maternal cognitive appraisal was found to be significant predictor of right subiculum/WBV ratios in prenatally exposed children. Although the effect of objective hardship did not survive FDR in the final model, maternal objective hardship scores contributed to the amount of explained variance in right subiculum/WBV ratios in steps 3 and 4 ($p < .05$): higher objective hardship levels associated with larger right subiculum/WBV ratios. Similarly, in Steps 3 and 4, higher subjective distress scores were associated with larger right subiculum/WBV ratios at a trend level ($p < .10$).

Complete results from the hierarchical regression analyses for raw right subiculum volume and right subiculum/TIC ratios in the PNMS cohort are presented in Tables 21 and 22, respectively, and are largely in agreement with the results using WBV ratios. The final model explained 25% of the variance in raw right subiculum volume, compared with 26.6% of the variance in right subiculum/TIC ratios and 26.1% of the variance in right subiculum/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Left SR-SL-SM

Results from the hierarchical regression analysis for left SR-SL-SM volume normalized to WBV (SR-SL-SM/WBV) in the PNMS cohort are presented in Table 23. In Step 1, the main effect of maternal objective hardship was not significantly associated with SR-SL-SM/WBV ratios. In Steps 2 and 3, maternal subjective distress ($p < .05$) and maternal cognitive appraisal ($p < .05$) significantly explained 8.6% and 11.1% of the variance, respectively, in SR-SL-SM/WBV. Higher subjective distress levels predicted larger ratios. Negative cognitive appraisal predicted smaller ratios. The addition of sex in Step 4 did not significantly contribute to the variance explained. The final model explained 22.5% of the variance in left SR-SL-SM/WBV. After 5% FDR correction only cognitive appraisal was found to be a significant predictor of left SR-SL-SM/WBV in prenatally exposed children.

Model 1: Overview

After FDR corrections, of the 3 components of PNMS tested in this model, maternal cognitive appraisal of the ice storm in June 1998 was found to be the strongest predictor of hippocampal volumes, in their 11½ year-old prenatally exposed children. An overall negative cognitive appraisal of the ice storm, compared with a positive/neutral appraisal, was predictive of smaller bilateral total HC volumes, as well as bilateral subfields CA1, subiculum, and left SR-SL-SM. Figures 1, 2 and 3 illustrate the relationships between cognitive appraisal and mean bilateral total hippocampal volume (raw, WBV and TIC ratios), CA1 volume (raw, WBV and TIC ratios) and subiculum volume (raw, WBV and TIC ratios). Additionally, results show the presence of non-significant trends ($p < .10$) associating higher objective hardship levels with larger bilateral total HC and subiculum volumes, as well as right CA1 volume. Non-significant trends were also found associating higher subjective distress levels with a larger left total HC, left CA1, left SR-SL-SM and bilateral subiculum volumes. After controlling for objective

hardship, subjective distress and cognitive appraisal, the addition of sex to the model did not significantly contribute to any of the explained variance in children's hippocampal volumes.

Research Question 1(a)

Model 2: PNMS cohort (using Storm24, excluding IES-R)

Multiple linear regressions were tested to predict hippocampal volumes based on maternal objective hardship (Storm24), maternal cognitive appraisal and sex of the child, without the inclusion of IES-R, in order to parallel analyses conducted with the early life comparison group. A complete summary of Model 2 results from the multiple regression analyses are presented in Table 24. With respect to volumes normalized to whole brain volume, PNMS, in particular, maternal cognitive appraisal, was found to significantly predict ($q < .05$) variance in in total right HC, right CA1, and bilateral subiculum volumes. Using raw volumes, a similar pattern of results is seen, however, the regression equation did not significantly predict variance in raw total right HC volume. In agreement with Model 1 results, PNMS variables were found to be poor predictors of hippocampal volumes normalized to TIC, only predicting significant variance in right subiculum volumes.

Negative Cognitive Appraisal Predicts Smaller Total Right HC

Results from the hierarchical regression analysis for total right hippocampal volume normalized to WBV (HC/WBV) in the PNMS cohort are presented in Table 25. In Step 1, the main effect of maternal objective hardship was marginally significant ($p = .08$), explaining 6.3% of the variance in total right HC/WBV ratios: higher objective hardship levels, larger ratios. In Step 2, the addition of maternal cognitive appraisal explained an additional 11.9% of the variance in total right HC/WBV ratios ($p < .05$): negative cognitive appraisal, smaller ratios. The addition of sex in Step 3 did not significantly contribute to the variance explained. The final

model explained 18.4% of the variance in total right HC/WBV. After 5% FDR correction only maternal cognitive appraisal was found to be a significant predictor of total right HC/WBV ratios in prenatally exposed children. The role of objective hardship in the final model becomes significant at a more liberal 10% FDR level.

Negative Cognitive Appraisal Predicts Smaller Right CA1

Results from the hierarchical regression analysis for right CA1 volume normalized to WBV (CA1/WBV) in the PNMS cohort are presented in Table 26. In Step 1, higher maternal objective hardship levels were associated with larger right CA1/WBV ratios at the trend level ($p = .066$), explaining 6.9% of the variance. In Step 2, the addition of maternal cognitive appraisal was significantly associated with right CA1/WBV ratios, explaining an additional 18% of the variance ($p < .01$). The addition of sex in Step 3 did not significantly contribute to the variance explained. The final model explained 25.2% of the variance in total right CA1/WBV ratios. After 5% FDR correction only cognitive appraisal was found to be a significant predictor of total right CA1/WBV ratios in prenatally exposed children. The role of maternal objective hardship in the final model becomes significant at a more liberal 10% FDR level.

Complete results from the hierarchical regression analyses for raw right CA1 volumes are presented in Table 27, and are in line results using WBV ratios. However, the previously described trends with respect to the relationship between maternal objective hardship (Storm24) and right CA1/WBV ratios are much weaker when using raw volumes. The final model explained 22.5% of the variance in raw right CA1 volume, compared with 25.2% of the variance in right CA1/WBV ratios.

Objective Hardship & Cognitive Appraisal Predict Left Subiculum

Results from the hierarchical regression analysis for left subiculum volume normalized to

WBV (subiculum/WBV) in the PNMS cohort are presented in Table 28. In Steps 1, the main effect of maternal objective hardship significantly ($p < .05$) explained 11.5% of the variance in left subiculum/WBV ratios: higher objective hardship levels, larger subiculum/WBV ratios. In Step 2, the addition of maternal cognitive appraisal explained an additional 12.6% of unique variance ($p < .01$): negative cognitive appraisal predicting smaller subiculum/WBV ratios. The addition of sex in Step 3 did not significantly contribute to the variance explained. The final model explained 24.1% of the variance in left subiculum/WBV. After 5% FDR correction, maternal objective hardship (Storm24) and maternal cognitive appraisal were found to be significant predictors of left subiculum/WBV in prenatally exposed children.

Complete results from the hierarchical regression analyses for raw left subiculum volumes are presented in Table 29, and are in line with results using WBV ratios. The final model explained 19.6% of the variance in raw left subiculum volume, compared with 24.1% of the variance in left subiculum/WBV ratios.

Negative Cognitive Appraisal Predicts Smaller Right Subiculum

Results from the hierarchical regression analysis for right subiculum volume normalized to WBV (subiculum/WBV) in the PNMS cohort are presented in Table 30. In Step 1, the main effect of maternal objective hardship (Storm24) significantly ($p < .05$) explained 7.9% of the variance in right subiculum/WBV ratios: higher objective hardship levels, larger ratios. In Step 2, the addition of maternal cognitive appraisal explained an additional 12.8% of unique variance ($p < .01$): negative cognitive appraisal associated with smaller ratios. The addition of sex in Step 3 did not significantly contribute to the variance explained. The final model explained 21.1% of the variance in right subiculum/WBV ratios. After 5% FDR correction only cognitive appraisal was found to be a significant predictor of right subiculum/WBV ratios in prenatally exposed

children. The role of maternal objective hardship in the final model becomes significant at a more liberal 10% FDR level.

Complete results from the hierarchical regression analyses for raw right subiculum volumes, and right subiculum/TIC ratios are presented in Tables 31 and 32, respectively, and are in line with results using WBV ratios. The final model explained 22.9% of the variance in raw right subiculum volume, compared with 21.8% of the variance in right subiculum/TIC ratios, and 21.1% of the variance in left subiculum/WBV ratios.

Model 2: Overview

After FDR corrections, of the 2 components of PNMS tested in this model, maternal cognitive appraisal was found to be the strongest predictor of hippocampal volumes in 11½ year-old prenatally exposed children. With respect to volumes normalized to WBV, an overall negative maternal cognitive appraisal of the ice storm, compared with a positive/neutral appraisal, was predictive of smaller total right HC, right CA1, and bilateral subiculum volumes. Overall, the use of Storm24 in Model 2 was a more sensitive predictor of adolescent hippocampal volumes compared with Storm32 in Model 1. Higher Storm24 levels in Model 2 were significantly associated with larger left subiculum volumes ($q < .05$). Additionally, at a more liberal 10% FDR level, higher maternal objective hardship (Storm24) levels were also associated with larger total right HC, right CA1 and right subiculum volumes. As with Model 1, after controlling for objective hardship and cognitive appraisal, the addition of sex to the model did not significantly contribute to any of the variance explained in children's hippocampal volumes.

Prenatal maternal stress research question 1(b): *What are the individual and joint effects of*

maternal objective hardship, maternal subjective distress and/or maternal cognitive appraisal on global right and left hippocampal surface area at age 11½ in the prenatal stress cohort?

Model 1 results, which use Storm32 and include IES-R, are presented in Table 33. After 5% FDR correction, the data indicates no significant main effect of maternal objective hardship (Storm32), maternal subjective distress, maternal cognitive appraisal or sex associated with global hippocampal surface area. Model 2 results, using Storm24 and excluding IES-R, are presented in Table 34. After 5% FDR correction, we report no significant main effect of maternal objective hardship (Storm24), or maternal cognitive appraisal associated with global hippocampal surface area.

Prenatal maternal stress research question 1(c): *What are the individual and joint effects of maternal objective hardship, maternal subjective distress and/or maternal cognitive appraisal on hippocampal shape at age 11½ in the prenatal stress cohort?*

To address research question 1(c) two separate vertex-wise general linear models were tested (data not shown). Model 1 included maternal objective hardship (Storm32), maternal cognitive appraisal, maternal subjective distress and Sex. Model 2 included maternal objective hardship (Storm24), maternal cognitive appraisal and Sex. Neither model yielded any significant relationships between maternal stress measures and adolescent hippocampal shape at the 5% FDR level.

Early life maternal stress research question 2(a): *What are the individual and joint effects of maternal objective hardship, and maternal cognitive appraisal on hippocampal volume at age 11½ in the early life maternal stress cohort.*

Complete results from the multiple regression with the early life stress cohort are presented in Table 35. After 5% FDR correction, there were no significant main effects of maternal objective hardship (Storm32), maternal cognitive appraisal or Sex associated with hippocampal volumes in the comparison group of early life exposed 11½ year olds.

Early life maternal stress research Question 2(b): *What are the individual and joint effects of maternal objective hardship, and maternal cognitive appraisal on hippocampal surface area at age 11½ in the early life maternal stress cohort.*

Complete results from the multiple regression analyses are presented in Table 36. After 5% FDR, the regression model significantly predicted variance in left HC surface area normalized to total intracranial volume (HC-SA/TIC).

Results from the hierarchical regression analysis for global left HC-SA/TIC in the early life stress cohort are presented in Table 37. In Step 1, the main effect of maternal objective hardship (Storm24) significantly explained 13.4% of the variance ($p < .05$): higher objective hardship scores, larger left HC-SA/TIC ratios. In Step 2, the addition of maternal cognitive appraisal contributed an additional 9% of unique variance: negative cognitive appraisal associated with smaller left HC-SA/TIC ratios. The addition of Sex in Step 3 did not significantly contribute to the variance explained. The final model explained 22.7% of the variance in left HC-SA/TIC at 11½ years of age. After 5% FDR correction only maternal objective hardship was found to be a significant predictor of left HC-SA/TIC in early life exposed children.

Early life maternal stress research question 2(c): *What are the individual and joint effects of*

maternal objective hardship, and maternal cognitive appraisal on hippocampal shape at age 11½ in the early life maternal stress cohort?

To address research question 2(c) a vertex-wise general linear model was tested including maternal objective hardship (Storm24), maternal cognitive appraisal, and Sex (data not shown). No significant relationships were found between ELMS measures and adolescent hippocampal shape at the 5% FDR level.

Prenatal vs. early life stress research question 3(a): *To what extent do the effects of maternal stress on hippocampal volume at age 11½ differ between prenatal and early life maternal stress cohort?*

A multiple linear regression including a maternal stress by cohort moderation effect was performed separately for each stress variable on hippocampal subfield volume outcomes. After a 5% FDR correction, linear regression models showed no significant moderating effects of cohort between any of the mothers' stress measures and adolescent hippocampal volumes.

Comparing results from the multiple regression analyses performed independently in both cohorts (Tables 24 and 35), does however suggest that the prenatally exposed cohort was more sensitive to the effects of maternal stress. In the parentally exposed group (Model 2), a mother's negative cognitive appraisal was significantly ($q < .05$) associated with a smaller total right HC, right CA1 and bilateral subiculum. Higher objective hardship (Storm24) levels were significantly associated with a larger left subiculum. Comparatively, in the ELMS cohort, no significant associations were found between maternal stress variables and adolescent hippocampal volumes.

Post-hoc t-tests were used to compare hippocampal volumes between PNMS and ELMS cohorts irrespective of exposure severity. Results presented in Table 38 show statistically

significant differences ($p < .05$) between PNMS exposed and ELMS exposed children in bilateral CA1/WBV ratios. As well as trend level differences ($p < .10$) in, total right HC/WBC and bilateral SR-SL-SM/WBV ratios. In all cases, volumes and normalized ratios are found to be larger in prenatally exposed children compared with children exposed in the first year of life.

Prenatal vs. early life stress research question 3(b): *To what extent do the effects of maternal stress on global hippocampal surface area at age 11½ differ between prenatal and early life maternal stress cohorts?*

A multiple linear regression including a maternal stress by cohort moderation effect was performed separately for each maternal stress variable on left and right global hippocampal surface area outcomes. After a 5% FDR correction, linear regression models showed no significant moderating effect of cohort between any of the mothers' stress measures and adolescent hippocampal surface area measures.

Post-hoc t-tests were performed to further explore possible group differences in global hippocampal surface area. Results presented in Table 39 show statistically significant differences ($p < .05$) between PNMS-exposed and ELMS exposed children in global left and right hippocampal surface area (normalized to WBV and TIC). Results show that prenatally stressed children had larger bilateral hippocampal surface areas compared to ELMS, irrespective of severity of exposure.

Prenatal vs. early life stress research question 3(c): *To what extent do the effects of maternal stress on hippocampal shape at age 11½ differ between prenatal and early life maternal stress cohorts?*

Controlling for sex, a vertex-wise general linear model using a maternal stress-by-group interaction term was assessed and yielded no significant relationships (all $q > .05$) between maternal stress measures and local left and/or right adolescent hippocampal shape metrics (data not shown).

Male vs. Female research question 4(a): *To what extent do the effects of PNMS and ELMS on hippocampal volume at age 11½ differ between male and female offspring?*

A multiple linear regression including a maternal stress by sex moderation effect was performed separately for each stress variable on left and right hippocampal subfield volume outcomes. Linear regression models showed no significant moderating effect of sex between any of the mothers' stress measures and adolescent hippocampal volumes in either the PNMS or ELMS cohorts.

To further explore possible sex specific effects of pre- and post-natal maternal stress exposure on adolescent hippocampal measures post-hoc Pearson's correlation analyses were performed separately for boys and girls. Tables 40 and 41 present results for prenatally exposed boys and girls. Tables 42 and 43 present results for early life exposed boys and girls.

For boys in the PNMS cohort, Pearson's correlations showed significant ($p < .05$) associations between higher maternal subjective distress levels and smaller right CA2-CA3 (WBV and TIC ratios); and smaller left SR-SL-SM/WBV ratios. For girls in the PNMS cohort, significant associations were found between a mother's negative cognitive appraisal and smaller right CA1 (raw volume, TIC and WBV ratios), right subiculum (raw volume and WBV ratios) and bilateral raw total hippocampal volumes, and raw left CA4/DG volumes.

Thus, overall in the PNMS cohort, maternal stress measures significantly correlated with

a greater number of hippocampal subfields in girls compared with boys. Additionally, boys were found to be more sensitive to the subjective component of the mother's stress experience; more subjective distress correlated with smaller volumes. On the other hand, girls were found to be more sensitive to the objective and cognitive appraisal components of the stress experience, where more objective hardship (Storm24) correlated with larger volumes, and a mothers' negative cognitive appraisal correlated with smaller volumes.

For boys in the ELMS cohort, Pearson's correlations showed significant ($p < .05$) associations between a mother's negative cognitive appraisal and smaller raw total right hippocampal volume, as well as smaller right raw CA1 and CA4/DG volumes. For girls in the ELMS cohort it was the mothers' objective hardship (Storm24) levels that correlated with hippocampal volumes such that higher objective hardship levels were associated with larger total left HC/TIC ratios, left CA1/TIC ratios and left subiculum (raw volumes, TIC and WBV ratios).

Thus, overall in the ELMS cohort, maternal stress measures were associated with volumetric changes in the right hippocampus in boys, and the left hippocampus in girls. Interestingly, negative maternal cognitive appraisal was associated with smaller right CA1, CA4/DG and whole hippocampal volumes in boys. Whereas higher maternal objective hardship (Storm24) levels correlated with larger total left HC/TIC ratios, left CA1/TIC ratios and left subiculum (raw volumes, TIC and WBV ratios) in girls.

Male vs. Female research question 4(b): *To what extent do the effects of PNMS and ELMS on global hippocampal surface area at age 11½ differ between male and female offspring?*

A multiple linear regression including a maternal stress by sex moderation effect was performed separately for each stress variable on global left and right hippocampal surface area

measures. Linear regression models showed no significant moderating effect of sex between any of the mothers' stress measures and adolescent hippocampal surface area in either the PNMS or ELMS cohorts.

Additionally, post-hoc Pearson's correlations analyses performed separately for boys and girls (Tables 40-43) did not show any significant relationships between maternal stress measures and hippocampal surface area outcomes.

Male vs. Female research question 4(c): *To what extent do the effects of PNMS and ELMS on hippocampal shape at age 11½ differ between male and female offspring?*

A vertex-wise general linear model using a maternal stress-by-sex interaction term controlling for cohort was assessed and yielded no significant relationships ($q < .05$) between maternal stress measures and adolescent hippocampal shape metrics.

VI. Discussion:

The principle goal of the study was to determine the degree to which varying levels of stress from an independent sudden-onset stressor, the 1998 Quebec ice storm, experienced by mothers prenatally or during the first year of their child's life, explains variance in hippocampal morphology in their offspring at 11½ years of age. Importantly, using a natural disaster model of stress, along with a prospective design, made it possible to assess which dimension(s) of the stress experience best predict adolescent hippocampal morphology: the objective characteristics of the event (i.e., maternal objective hardship), the mother's subjective reaction to the event (i.e., subjective distress), and/or the mothers' overall appraisal of the event (i.e., cognitive appraisal).

PNMS and Hippocampal Volume

The present results are consistent with the hypothesis that higher PNMS scores and/or a

negative cognitive appraisal in response to a prenatal environmental stressor is associated with altered hippocampal volume in prenatally exposed offspring. Of the three measures of PNMS considered in this study, maternal cognitive appraisal was found to be the element of the stress experience most strongly associated with hippocampal volumes. The data suggest that a mother's overall negative cognitive appraisal of the disaster (compared with a neutral or positive appraisal) is predictive of smaller bilateral whole hippocampal volumes as well as specific volume reductions in hippocampal CA1 and subicular subfield volumes, in prenatally exposed offspring. Interestingly, while a negative cognitive appraisal corresponds with smaller hippocampal volumes, more severe objective and subjective exposure to the disaster trends toward larger volumes. At the trend level, higher objective hardship (Storm32 and Storm24) levels were found to predict larger bilateral subicula, as well as an overall larger right hippocampus and right CA1 when normalizing for whole brain volume. Similar trends were observed with respect to higher subjective distress levels, where more severe storm related subjective distress in the mother predicts larger bilateral total hippocampal and subicular volumes, as well as larger right CA1. Consequently, although a mothers' cognitive appraisal was found to have the greatest effect on prenatally exposed 11½ year old hippocampal volumes, particularly the CA1 and subicular subregions, her levels of objective and subjective exposure appear to have an opposite effect on hippocampal volumes.

The opposing volumetric effects for cognitive appraisal and subjective/objective PNMS were not originally predicted, however, this finding is not altogether surprising within the context of existing Project Ice Storm publications, which often report effects specific to a single stress dimension. For example, higher subjective ice storm related distress, but not objective hardship, correlate with greater dermatoglyphic asymmetry (a proposed marker for altered brain

development) in prenatally exposed children (King et al., 2009). Also, both cognitive appraisal (Cao-Lei et al., 2015) and objective hardship levels (Cao-Lei et al., 2014), but not subjective distress (Cao-Lei et al., 2014), correlate with genome-wide DNA methylation. The effects of objective stress (Cao-Lei et al., 2015) and cognitive appraisal (Cao-Lei et al., 2016) on the children's body mass index are mediated by their effects on the methylation of genes related to metabolism at the age of 13. Importantly, in the current subsample, a mother's cognitive appraisal of the event does not correlate with her level of subjective distress ($r = -214$, $p > .05$); and only weakly correlates with her level of objective storm related hardship (Storm32: $r = -.321$, $p < .05$; Storm24: $r = -212$, $p > .05$). Unpublished analyses in the King Lab suggest that scores on cognitive appraisal by Project Ice Storm mothers are completely uncorrelated with demographics, and with their personality as measured by the NEO Personality Inventory (NEO PI) which assesses the Big-Five personality traits: Neuroticism, Extraversion, Introversion, Agreeableness and Conscientiousness. As such, given the significant associations found between this cognitive appraisal item and child outcomes in DNA methylation and hippocampal development, and the inability to find correlates to explain the sources of women's ratings, more extensive evaluation of the construct is needed.

The age of our subjects may have influenced the direction of the results. The hippocampus is a brain region that undergoes protracted development until the onset of puberty, followed by a period of significant synaptic pruning before anatomically stabilizing in early adulthood. The literature on puberty onset is contentious, however, it is generally believed that girls begin puberty between 10-11 years of age. On average boys enter puberty a year later, between ages 11-12 (Ritzén, et al., 2003). As other groups have suggested, volumetric changes associated with PNMS exposure could therefore reflect a dysregulation of the hippocampi's

developmental time course. Although we do not have data concerning pubertal status of our participants, it would be reasonable to speculate that given their age at scanning (11½ years), most are either still prepubescent, or have only recently begun puberty; suggesting that the observed volume reductions associated with negative cognitive appraisal could be characteristic of a slowed hippocampal growth phase rather than an accelerated post-pubertal pruning phase. Higher objective/subjective PNMS may differentially impact this developmental window, interfering more with the pruning phase, leading to larger hippocampal volumes. Alternatively, results from existing histological studies suggest that volumetric reductions associated with PNMS are related to a number of cellular events such as reduced neurogenesis, reduced dendritic arborization, loss of glial cells and/or a general loss of synaptic density throughout the hippocampus (Barros et al., 2006; Uno et al., 1990).

Keeping in mind that comparative human literature is scarce on the topic of PNMS related structural brain effects, our volumetric findings do not appear to be immediately consistent with the only other human PNMS study of hippocampal volume known to this author. Qiu et al. (2013), reported that higher levels of maternal anxiety during pregnancy is predictive of slowed hippocampal growth at 6 months of age. Our closest proxy for maternal anxiety, maternal subjective distress, suggests a trend toward larger hippocampal volumes in the children born to women that reported high levels of disaster-related subjective distress. However, this disparity could be explained by the participants' age difference. Without the benefit of longitudinal or cross-sectional data, there is no reason to believe that the effect of PNMS on hippocampal volume at 6-months of age will be predictive of hippocampal volume at 11½ years of age. Nor can we assume the observed stress-related hippocampal changes at age 11½ will predict adult hippocampal volumes in our sample. In fact, Andersen et al., 2004, looking at early

maternal separation in rats, found delayed effects of early stress exposure, where alterations to the structure of the hippocampus only became apparent in adulthood. This finding also lends support to the theory that early stress related hippocampal changes arise due to disruption of the hippocampus' synaptic pruning process that occurs between the onset of puberty and early adulthood.

Animals are, of course, unable to report on the level of subjective stress they experience, or communicate their overall cognitive appraisal of a stressor. Rather, it is the level objective exposure that is measured in animal PNMS studies. A trend was observed predicting larger hippocampal volumes (whole HC, CA1 and subiculum volume) in children whose mothers reported higher levels of prenatal objective hardship, however, this is contrary to what would be expected based on the animal literature. Findings with rhesus macaques (Coe et al., 2003) and rats (Barros et al., 2006; Schmitz et al., 2002) consistently report whole hippocampal and subfield-specific volume reductions in adult offspring born to mothers exposed to various stressors during pregnancy (e.g., restraint stress, and acoustic startle), compared with controls. Again, the disparity between the literature and the present findings could very well reflect the age of our participants. Furthermore, without the benefit of a matched control group completely unexposed to the 1998 ice storm, it is only possible to speculate about the overall effect of PNMS exposure.

With respect to cognitive appraisal, overall it was found to be the strongest predictor of hippocampal volumes, and while the direction of the volumetric findings (negative cognitive appraisal predictive of smaller bilateral CA1, subiculum and total hippocampal volumes) corresponds with existing PNMS studies, cognitive appraisal as a measure of PNMS is qualitatively unlike other commonly used metrics of PNMS. To the best of our knowledge, no

other study has measured the effect of maternal cognitive appraisal during pregnancy on offspring brain structure. Therefore, it becomes difficult to discuss these findings within the context of existing literature. Irrespective of the direction of the effect, or the mechanism(s) ultimately responsible for the observed volumetric effects, our findings are interesting because of the hippocampal subregions in which these effects were observed, and the important functions these regions play in regulating the stress response, via moderation of the HPA axis.

It is well established that the hippocampus plays a critical role in negative feedback regulation of the HPA axis' response to stress (Herman et al., 1989; Jacobson & Sapolsky, 1991) In humans, self-reported maternal anxiety between the 12th and 22nd weeks of pregnancy has been linked with alterations to the circadian cortisol profile of 15-year-old children, and correlates with depressive symptoms in girls (Van den Bergh et al., 2008). Notably, this window of vulnerability to maternal anxiety coincides with the morphological and cytoarchitectural development of the hippocampal subfields, occurring between the 13th and 20th week of pregnancy (Kier et al., 1997). Furthermore, evidence from both human and animal models strongly suggests that stress-related dysfunction of the HPA axis is associated with anxiety-related behaviours as well as disorders associated with abnormal hippocampal anatomy such as schizophrenia, ADHD and ASD (Cottrell & Seckl, 2009; Johnson et al., 2013; Nelson et al., 1998; Philips et al., 2006; Plessen et al., 2006; Sparks et al., 2002; Weinstock et al., 2008). Importantly, hippocampal inhibition of the HPA axis is primarily moderated by a small group of neurons found in the ventral subicula (Herman, et al., 1995). In fact, the principle outflow from the hippocampus to the hypothalamus originates in the ventral CA1 and subicular subregions. Interestingly, our data indicate that PNMS exposure appears to have the greatest effect on the hippocampal subregions suspected of being responsible for the proper regulation of the stress

response via moderation of the HPA axis, namely hippocampal CA1 and subicular subfields. Further analyses are warranted to investigate potential relationships between the observed hippocampal volume changes and relevant cognitive/behavioral outcomes in our sample.

ELMS and Hippocampal Volume

No significant relationships were found between maternal stress measures and hippocampal volume in the ELMS cohort. Taking into account the previously discussed volumetric findings associated with PNMS, this would indicate that the prenatal period represents a sensitive period, while first year postpartum does not. Post-hoc analyses comparing hippocampal volumes between PNMS and ELMS cohorts show that, in general, volumes are larger in prenatally exposed children. Again, without a completely unexposed control group it is difficult to draw conclusions in regard to what these group differences might mean in terms of health outcomes later in life. It is generally reported, that for adults, smaller hippocampal volumes are commonly associated with worse psychopathological outcomes, such as PTSD and depression (Gilbertson et al., 2002; Velakoulis et al., 1999). If this trend holds true for adolescents, finding smaller volumes in early life exposed children could be interpreted in a number of ways: (i) disaster-related maternal stress exposure in early life, regardless of the severity of the exposure, is a powerful enough stressor to depress hippocampal volumes and mask possible dose-response relationships, (ii) prenatally exposed children are in fact more susceptible to maternal stress and the overall effect is toward larger hippocampal volumes; that as a function of the fetal programming hypothesis, larger volumes may develop as a protective mechanism to buffer the individual from growing up in a stress prone environment; or (iii) both scenarios are true and maternal stress exposure differentially impacts prenatally exposed and early life exposed individuals; with potentially protective volume increases in the former and

volume loss in the latter.

Maternal Stress, Global Hippocampal Surface Area, and Shape

Surprisingly, contrary to initial prediction that surface based measurements of the hippocampi would be more sensitive to the morphological changes associated with ice storm-related maternal stress, no significant associations were found between maternal stress measures and hippocampal shape and/or global hippocampal surface area in either cohort. Similar to our volumetric findings, post-hoc analyses show that bilateral global hippocampal surface area is significantly larger in the prenatally exposed children compared with children exposed in early life. All of the same stipulations for interpreting the volumetric group differences apply here as well. Ultimately, additional analyses and recruitment of a non-ice-storm exposed group will be needed to discern the meaning of these differences.

Group Differences

The hypothesis that prenatal exposure to maternal stress would have a greater effect on hippocampal morphology compared with early life (post-natal) exposure was partially supported by our results. Although moderation analyses did not detect a significant interaction between PNMS and group, the results from the regression analyses carried out in each cohort independently do suggest that hippocampal morphology is more sensitive to prenatal as opposed to postnatal exposure. Beyond the previously discussed issues, failure to detect moderation by group, or any significant morphological changes associated with severity of exposure in the early life exposed cohort, may be due to a lack of precision with respect to the postnatal stress measures used. Severity of maternal stress exposure in early life was inferred based on the assumption that a mother's negative cognitive appraisal of the disaster, and/or higher scores on the maternal objective stress measure, would correlate with a stronger stress response in the

infant – potentially via direct glucocorticoid exposures via breastmilk, or through the indirect stress contagion model proposed by Waters et al., (2014). It is therefore a possibility that this approach failed to accurately detect the relationship between the severity of the mother's stress and its subsequent effect on the infant stress response.

Sex Differences

Finally, results did not support our hypothesis that male offspring would be more sensitive to the effects of PNMS and ELMS compared to female offspring. Moderation analyses failed to detect any significant interaction between PNMS and sex in either the pre- or postnatal exposure cohorts. Failure to detect any sex differences in the effects of PNMS was unexpected given the current animal literature which consistently reports stress-related sex differences in hippocampal development (Coe et al., 2003; Schmitz et al., 2002; Szuran et al., 2000; Weinstock et al., 2011). Furthermore, males appear to be disproportionately vulnerable to most relevant intellectual, cognitive and behavioural problems that have so far been linked with abnormal hippocampal development and exposure to prenatal, and postnatal stressors.

Sex-specific post-hoc Pearson's correlations were employed to further explore possible sex effects related to maternal stress' influence on hippocampal structure. Overall, PNMS measures significantly correlated with a greater number of hippocampal subfields in girls, compared with boys. Moreover, boys appear to be more sensitive to the subjective component of the stress experience, while girls appear to be more sensitive to the objective and cognitive appraisal components. For the ELMS cohort, post-hoc Pearson's correlations suggest that maternal stress measures are associated with volumetric changes in the right hippocampus of boys, and the left hippocampus in girls. Ultimately, the failure to detect potential sex differences in PNMS effects may be due in part to the modest sample size and/or the age of the participants.

At age 11½ the hippocampus is still undergoing normal age-related developmental changes that may be masking the sex-specific effects associated with stress exposure. It is conceivable that stress-related sex differences in the hippocampus may become apparent later in life.

Limitations

Limitations of the present study include the lack of an unexposed control group preventing direct comparisons between exposed and unexposed children. A second limitation is the relatively modest sample size, restricting our ability to conduct analyses aimed at addressing how the precise timing of the stress exposure during pregnancy (or early life) influences the observed effects on hippocampal morphology. Thirdly, the generalizability of our results are limited by the demographic homogeneity of our sample – skewed toward the socio-economically advantaged, Caucasian, and recruited from a single geographic region in the southwest part of Quebec. It is however worth noting that while the sample may skew toward a higher than average SES, access to additional material resources both during the disaster and throughout child development likely had a buffering rather than a sensitizing effect on the observed neuroanatomical differences; it is probable that even stronger effects would be observed in a more socioeconomically diverse sample. Additionally, at the time of scanning some of our participants may have already began puberty, an important developmental period for the hippocampus that coincides with synaptic pruning and volume loss. Data with respect to pubertal status was not collected during the year 11½ assessments, and it was therefore not possible to account for the confounding effects of puberty on hippocampal morphology. This is potentially more problematic for the girls in our sample given that puberty tends to begin earlier in girls.

Strengths

Remaining cognizant of the limitations, results from this study contribute to the PNMS and ELMS literature. To our knowledge, this is the first attempt to measure the morphological effects on the human hippocampus associated with prenatal and early life maternal exposure to an independent stressor. The major strengths of this study include the independent nature of the ice storm and the longitudinal/prospective design of the study. All the women in our sample were exposed randomly to varying degrees of adversity from the same sudden onset stressor (natural disaster). This allowed us to breakdown the overall stress experience into three distinct stress measurements (objective hardship, subjective distress and/or cognitive appraisal). Lastly, it is important to mention that imaging data collection is ongoing in both the PNMS and ELMS cohorts. Analyses conducted in this study will soon be extended to the structural MRIs collected during the year 16 and 18 assessments, further increasing our understanding of how PNMS impacts hippocampal morphology from adolescence through early adulthood.

Future Directions

Results show that prenatal exposure to maternal negative cognitive appraisal during pregnancy, but not exposure in the first year of infancy, predicts hippocampal volume reductions at age 11½. It will be important that future work pair our imaging data with the extensive cognitive and behavioural data that have been collected over the 19-year history of Project Ice Storm to assess whether the observed hippocampal changes are associated with relevant cognitive and/or behavioural outcomes. To clarify the role that puberty plays in modulating the effect of PNMS on hippocampal morphology, future studies will want to include pubertal measures at all ages. Ultimately, additional human longitudinal studies with larger sample sizes and with more diverse geographical, socioeconomic and ethnic backgrounds will ultimately be required to validate and generalize our findings.

VII. Conclusion

In conclusion, this work provides evidence that PNMS exposure may lead to altered hippocampal volumes including specific changes in hippocampal CA1 and subiculum during adolescence, and the direction of the effects depend on the aspect of stress assessed: more severe objective exposure and subjective distress in mothers tend to predict larger volumes while a negative cognitive appraisal predicts smaller volumes. Regardless of the mechanism, this finding is interesting because of the role these subfields are believed to play in regulating the HPA-axis' response to stress and the associations made in the broader literature between hippocampal volume reductions, dysregulation of the HPA-axis and increased prevalence of cognitive and behavioural problems later in life. It is yet unclear whether the observed effects correlate with cognitive/behavioural outcomes in our sample, or whether these effects will persist into adulthood. We hope to address these questions as we begin to examine the relationships between our longitudinal structural MRI data (scans acquired at ages 11½, 16½ and 18½) and our rich collection psychometric and behavioural data.

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Appendix

Table 1

List of hippocampal subfield volume outcome variables, maternal stress predictor variables and moderators.

Outcome		Predictor	Moderator
Left HC	**Right HC**	Objective Hardship	Group
Total	Total	Subjective Distress	Sex
Subiculum	Subiculum	Cognitive Appraisal	
CA1	CA1		
CA2-3	CA2-3		
CA4-DG	CA4-DG		
SR-SL-SM	SR-SL-SM		
Left/TIC	**Right/TIC**		
Total	Total		
Subiculum	Subiculum		
CA1	CA1		
CA2-3	CA2-3		
CA4-DG	CA4-DG		
SR-SL-SM	SR-SL-SM		
Left/WBV	**Right/WBV**		
Total	Total		
Subiculum	Subiculum		
CA1	CA1		
CA2-3	CA2-3		
CA4-DG	CA4-DG		
SR-SL-SM	SR-SL-SM		

Note. HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR-SL-SM: Stratum Radiatum-Stratum Lacunosum-Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain

Table 2

List of global hippocampal surface area variables, maternal stress predictor variables and moderators.

Outcome	Predictor	Moderator
Left HC	Objective Hardship	Group
Total surface area (mm^2)	Subjective Distress	Sex
Right HC	Cognitive Appraisal	
Total surface area (mm^2)		

Note. HC: Hippocampus

Table 3

Descriptive statistics for the prenatal maternal stress (PNMS) cohort

Variables		N	Minimum	Maximum	Mean	Std. Deviation
Maternal measures	Objective hardship (Storm32)	51	5	24	11.53	4.42
	Objective hardship (Storm24)	51	3	20	9.80	3.83
	Subjective distress (IES-R)	51	0	55	10.90	11.86
	Subjective distress (IES-R log)	51	0	4.03	1.94	1.13
	Cognitive appraisal	50	0	1	0.64	0.49
Head/ brain masks (mm^3)	Total Intracranial Volume (TIC)	51	1177800	1652248	1413821.39	96438.06
	Whole Brain Volume (WBV)	51	1064773	1522738	1294429.31	93210.69
Surface area (mm^2)	Left HC Surface Area	51	1424.23	1845.16	1675.59	95.94
	Right HC Surface Area	51	1393.01	1954.96	1734.15	110.01
	Left HC Surface Area / TIC	51	0.11	0.14	0.12	0.01
	Right HC Surface Area / TIC	51	0.10	0.14	0.12	0.01
	Left HC Surface Area / WBV	51	0.11	0.16	0.13	0.01
	Right HC Surface Area / WBV	51	0.11	0.16	0.13	0.01
Raw volume (mm^3)	Total Left HC	51	1816	2831	2419.86	234.55
	Left CA1	51	555	922	743.12	78.67
	Left CA2 CA3	51	95	192	154.18	22.56
	Left CA4 & DG	51	466	729	630.84	69.03
	Left Subiculum	51	229	447	320.47	42.28
	Left SR SL SM	51	389	722	571.26	66.83
	Total Right HC	51	1935	2839	2471.59	229.98
	Right CA1	51	555	856	724.65	77.87
	Right CA2 & CA3	51	96	206	150.63	25.83
	Right CA4 & DG	51	512	771	655.16	71.15
	Right Subiculum	51	244	473	337.28	49.35
	Right SR SL SM	51	445	719	603.88	66.25
Volume normalized to TIC	Total Left HC / TIC	51	0.14	0.20	0.17	0.02
	Left CA1 / TIC	51	0.04	0.06	0.05	0.01
	Left CA2 CA3 / TIC	51	0.01	0.02	0.01	0.002
	Left CA4 & DG / TIC	51	0.04	0.06	0.05	0.01
	Left Subiculum / TIC	51	0.02	0.03	0.02	0.003
	Left SR SL SM / TIC	51	0.03	0.05	0.04	0.01
	Total Right HC / TIC	51	0.14	0.22	0.18	0.02
	Right CA1 / TIC	51	0.04	0.06	0.05	0.01
	Right CA2 & CA3 / TIC	51	0.01	0.02	0.01	0.002
	Right CA4 & DG / TIC	51	0.04	0.06	0.05	0.01
	Right Subiculum / TIC	51	0.02	0.03	0.02	0.003
	Right SR SL SM / TIC	51	0.03	0.06	0.04	0.01
Volume normalized to WBV	Total Left HC / WBV	51	0.15	0.23	0.19	0.02
	Left CA1 / WBV	51	0.04	0.07	0.06	0.01
	Left CA2 CA3 / WBV	51	0.01	0.02	0.01	0.002
	Left CA4 & DG / WBV	51	0.04	0.07	0.05	0.01
	Left Subiculum / WBV	51	0.02	0.03	0.03	0.003
	Left SR SL SM / WBV	51	0.03	0.06	0.04	0.01
	Total Right HC / WBV	51	0.15	0.24	0.19	0.02
	Right CA1 / WBV	51	0.04	0.07	0.06	0.01
	Right CA2 & CA3 / WBV	51	0.01	0.02	0.01	0.002
	Right CA4 & DG / WBV	51	0.04	0.07	0.05	0.01
	Right Subiculum / WBV	51	0.02	0.04	0.03	0.004
	Right SR SL SM / WBV	51	0.04	0.06	0.05	0.01

Note. Storm32: Objective Hardship questionnaire (full); Storm24: Objective Hardship questionnaire (partial); IES-R: Impact of Event Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 4

Descriptive statistics for the early life maternal stress (ELMS) cohort

Variables		N	Minimum	Maximum	Mean	Std. Deviation
Maternal measures	Objective hardship (Storm24)	47	0	17	7.57	4.78
	Cognitive appraisal	47	0	1	0.70	0.46
Head/ brain masks (mm^3)	Total Intracranial Volume (TIC)	47	1237163	1626246	1422943.72	92972.69
	Whole Brain Volume (WBV)	47	1140827	1528630	1316511.74	94597.90
Surface area (mm^2)	Left HC Surface Area	47	1437.10	1867.61	1653.63	103.96
	Right HC Surface Area	47	1482.57	1947.86	1697.12	98.66
	Left HC Surface Area / TIC	47	0.10	0.13	0.12	0.01
	Right HC Surface Area / TIC	47	0.11	0.14	0.12	0.01
	Left HC Surface Area / WBV	47	0.11	0.14	0.13	0.01
	Right HC Surface Area / WBV	47	0.12	0.15	0.13	0.01
Raw volume (mm^3)	Total Left HC	47	1861	2839	2394.83	237.49
	Left CA1	47	524	843	724.17	77.58
	Left CA2 CA3	47	98	200	153.92	22.81
	Left CA4 & DG	47	489	786	639.87	69.43
	Left Subiculum	47	234	460	317.67	46.70
	Left SR SL SM	47	377	710	559.19	69.13
	Total Right HC	47	1964	2876	2443.56	254.11
	Right CA1	47	561	883	704.29	82.99
	Right CA2 & CA3	47	77	210	145.43	31.19
	Right CA4 & DG	47	499	844	659.60	72.64
	Right Subiculum	47	247	479	341.55	51.09
	Right SR SL SM	47	465	738	592.69	75.65
Volume normalized to TIC	Total Left HC / TIC	47	0.14	0.20	0.17	0.01
	Left CA1 / TIC	47	0.04	0.06	0.05	0.004
	Left CA2 CA3 / TIC	47	0.01	0.01	0.01	0.001
	Left CA4 & DG / TIC	47	0.04	0.05	0.05	0.004
	Left Subiculum / TIC	47	0.02	0.03	0.02	0.003
	Left SR SL SM / TIC	47	0.03	0.05	0.04	0.004
	Total Right HC / TIC	47	0.14	0.20	0.17	0.01
	Right CA1 / TIC	47	0.04	0.06	0.05	0.004
	Right CA2 & CA3 / TIC	47	0.01	0.02	0.01	0.002
	Right CA4 & DG / TIC	47	0.04	0.06	0.05	0.004
	Right Subiculum / TIC	47	0.02	0.03	0.02	0.004
	Right SR SL SM / TIC	47	0.03	0.05	0.04	0.004
Volume normalized to WBV	Total Left HC / WBV	47	0.15	0.22	0.18	0.01
	Left CA1 / WBV	47	0.04	0.06	0.06	0.01
	Left CA2 CA3 / WBV	47	0.01	0.02	0.01	0.001
	Left CA4 & DG / WBV	47	0.04	0.06	0.05	0.004
	Left Subiculum / WBV	47	0.02	0.03	0.02	0.003
	Left SR SL SM / WBV	47	0.03	0.05	0.04	0.004
	Total Right HC / WBV	47	0.15	0.21	0.19	0.01
	Right CA1 / WBV	47	0.04	0.06	0.05	0.01
	Right CA2 & CA3 / WBV	47	0.01	0.02	0.01	0.002
	Right CA4 & DG / WBV	47	0.04	0.06	0.05	0.004
	Right Subiculum / WBV	47	0.02	0.04	0.03	0.004
	Right SR SL SM / WBV	47	0.03	0.05	0.05	0.01

Note. Storm32: Objective Hardship questionnaire (full); Storm24: Objective Hardship questionnaire (partial); IES-R: Impact of Event Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 5

Pearson's correlation coefficients between predictors and hippocampal measures in the prenatal maternal stress cohort

Variables		Storm32	Storm24	IESR_log	CONSEQ	Sex
Storm32	Pearson Correlation	1	.937**	.285*	-.321*	-0.007
	Sig. (2-tailed)	-	5.67E-24	.042	.023	0.962
	N	51	51	51	50	51
Storm24	Pearson Correlation	.937**	1	.212	-.202	0.011
	Sig. (2-tailed)	5.66E-24	-	.135	.159	0.937
	N	51	51	51	50	51
IESR_log	Pearson Correlation	.285*	.212	1	-.214	-0.117
	Sig. (2-tailed)	.042	.135	-	.136	0.415
	N	51	51	51	50	51
CONSEQ	Pearson Correlation	-.321*	-.202	-.214	1	-0.137
	Sig. (2-tailed)	.023	.159	.136	-	0.344
	N	50	50	50	50	50
Sex	Pearson Correlation	-0.007	0.011	-0.117	-0.137	1
	Sig. (2-tailed)	0.962	0.937	0.415	0.344	-
	N	51	51	51	50	51
Total Intracranial Volume (TIC)	Pearson Correlation	-.068	-.044	.043	.208	-.358**
	Sig. (2-tailed)	.638	.759	.765	.148	0.01
	N	51	51	51	50	51
Whole Brain Volume (WBV)	Pearson Correlation	-.156	-.133	-.030	.046	-0.23
	Sig. (2-tailed)	.274	.354	.832	.749	0.104
	N	51	51	51	50	51
Left HC Surface Area	Pearson Correlation	.047	.117	.102	.242	-0.257
	Sig. (2-tailed)	.741	.414	.476	.090	0.069
	N	51	51	51	50	51
Right HC Surface Area	Pearson Correlation	.074	.099	.178	.185	-0.151
	Sig. (2-tailed)	.607	.488	.211	.199	0.291
	N	51	51	51	50	51
Left HC Surface Area / TIC	Pearson Correlation	.137	.182	.053	.032	0.171
	Sig. (2-tailed)	.338	.200	.711	.824	0.231
	N	51	51	51	50	51
Right HC Surface Area / TIC	Pearson Correlation	.149	.150	.130	-.015	0.227
	Sig. (2-tailed)	.298	.293	.362	.920	0.109
	N	51	51	51	50	51
Left HC Surface Area / WBV	Pearson Correlation	.231	.269	.127	.191	0.019
	Sig. (2-tailed)	.102	.057	.374	.185	0.896
	N	51	51	51	50	51
Right HC Surface Area / WBV	Pearson Correlation	.231	.232	.186	.131	0.087
	Sig. (2-tailed)	.102	.102	.192	.363	0.542
	N	51	51	51	50	51
Total Left HC	Pearson Correlation	.059	.088	.232	.286*	-0.22
	Sig. (2-tailed)	.680	.537	.102	.044	0.121
	N	51	51	51	50	51
Left CA1	Pearson Correlation	.048	.093	.242	.290*	-.321*
	Sig. (2-tailed)	.740	.515	.088	.041	0.022
	N	51	51	51	50	51
Left CA2 CA3	Pearson Correlation	-.055	-.124	.036	.154	-0.061
	Sig. (2-tailed)	.701	.387	.804	.285	0.672
	N	51	51	51	50	51
Left CA4 & DG	Pearson Correlation	.041	.030	.120	.186	-0.041
	Sig. (2-tailed)	.773	.837	.400	.197	0.774
	N	51	51	51	50	51

Left Subiculum	Pearson Correlation	.137	.261	.197	.292*	-0.114
	Sig. (2-tailed)	.338	.064	.166	.040	0.427
	N	51	51	51	50	51
Left SR SL SM	Pearson Correlation	.041	.046	.267	.237	-0.259
	Sig. (2-tailed)	.778	.747	.058	.098	0.066
	N	51	51	51	50	51
Total Right HC	Pearson Correlation	.037	.140	.083	.307*	-0.145
	Sig. (2-tailed)	.797	.326	.565	.030	0.311
	N	51	51	51	50	51
Right CA1	Pearson Correlation	.036	.160	.058	.367**	-0.228
	Sig. (2-tailed)	.802	.264	.688	.009	0.107
	N	51	51	51	50	51
Right CA2 & CA3	Pearson Correlation	-.214	-.185	-.215	.060	-0.076
	Sig. (2-tailed)	.131	.194	.129	.678	0.598
	N	51	51	51	50	51
Right CA4 & DG	Pearson Correlation	.090	.122	.096	.120	0.022
	Sig. (2-tailed)	.528	.393	.502	.405	0.88
	N	51	51	51	50	51
Right Subiculum	Pearson Correlation	.169	.251	.219	.347*	-0.078
	Sig. (2-tailed)	.237	.076	.123	.014	0.587
	N	51	51	51	50	51
Right SR SL SM	Pearson Correlation	-.053	.053	.037	.226	-0.17
	Sig. (2-tailed)	.710	.710	.799	.115	0.234
	N	51	51	51	50	51
Total Left HC / TIC	Pearson Correlation	.116	.130	.213	.172	0.033
	Sig. (2-tailed)	.418	.365	.134	.232	0.82
	N	51	51	51	50	51
Left CA1 / TIC	Pearson Correlation	.103	.136	.245	.198	-0.101
	Sig. (2-tailed)	.471	.342	.084	.169	0.48
	N	51	51	51	50	51
Left CA2 CA3 / TIC	Pearson Correlation	-.017	-.086	.003	.067	0.117
	Sig. (2-tailed)	.906	.546	.984	.643	0.412
	N	51	51	51	50	51
Left CA4 & DG / TIC	Pearson Correlation	.088	.065	.092	.080	0.236
	Sig. (2-tailed)	.540	.653	.521	.579	0.095
	N	51	51	51	50	51
Left Subiculum / TIC	Pearson Correlation	.184	.299*	.210	.208	0.059
	Sig. (2-tailed)	.197	.033	.139	.147	0.682
	N	51	51	51	50	51
Left SR SL SM / TIC	Pearson Correlation	.091	.085	.252	.141	-0.051
	Sig. (2-tailed)	.527	.552	.075	.329	0.723
	N	51	51	51	50	51
Total Right HC / TIC	Pearson Correlation	.093	.181	.055	.188	0.116
	Sig. (2-tailed)	.515	.203	.699	.191	0.418
	N	51	51	51	50	51
Right CA1 / TIC	Pearson Correlation	.089	.203	.038	.278	-0.009
	Sig. (2-tailed)	.535	.153	.790	.050	0.949
	N	51	51	51	50	51
Right CA2 & CA3 / TIC	Pearson Correlation	-.185	-.162	-.246	-.005	0.072
	Sig. (2-tailed)	.193	.256	.082	.973	0.615
	N	51	51	51	50	51
Right CA4 & DG / TIC	Pearson Correlation	.136	.153	.071	.021	0.174
	Sig. (2-tailed)	.342	.283	.621	.883	0.223
	N	51	51	51	50	51

Right Subiculum / TIC	Pearson Correlation	.213	.287*	.229	.276	0.092
	Sig. (2-tailed)	.133	.041	.105	.052	0.522
	N	51	51	51	50	51
Right SR SL SM / TIC	Pearson Correlation	-.010	.083	.004	.120	0.049
	Sig. (2-tailed)	.947	.561	.977	.406	0.731
	N	51	51	51	50	51
Total Left HC / WBV	Pearson Correlation	.186	.198	.256	.270	-0.052
	Sig. (2-tailed)	.191	.163	.070	.058	0.715
	N	51	51	51	50	51
Left CA1 / WBV	Pearson Correlation	.173	.204	.285*	.296*	-0.181
	Sig. (2-tailed)	.225	.151	.043	.037	0.204
	N	51	51	51	50	51
Left CA2 CA3 / WBV	Pearson Correlation	.032	-.035	.032	.124	0.057
	Sig. (2-tailed)	.825	.808	.824	.390	0.692
	N	51	51	51	50	51
Left CA4 & DG / WBV	Pearson Correlation	.150	.127	.132	.170	0.112
	Sig. (2-tailed)	.294	.373	.354	.238	0.433
	N	51	51	51	50	51
Left Subiculum / WBV	Pearson Correlation	.232	.339*	.240	.279	-0.013
	Sig. (2-tailed)	.101	.015	.089	.050	0.928
	N	51	51	51	50	51
Left SR SL SM / WBV	Pearson Correlation	.151	.144	.284*	.224	-0.122
	Sig. (2-tailed)	.292	.314	.043	.117	0.393
	N	51	51	51	50	51
Total Right HC / WBV	Pearson Correlation	.163	.246	.105	.288*	0.025
	Sig. (2-tailed)	.252	.081	.465	.043	0.861
	N	51	51	51	50	51
Right CA1 / WBV	Pearson Correlation	.151	.258	.084	.362**	-0.091
	Sig. (2-tailed)	.292	.068	.557	.010	0.526
	N	51	51	51	50	51
Right CA2 & CA3 / WBV	Pearson Correlation	-.163	-.136	-.233	.049	0.048
	Sig. (2-tailed)	.253	.342	.100	.733	0.739
	N	51	51	51	50	51
Right CA4 & DG / WBV	Pearson Correlation	.199	.218	.114	.110	0.178
	Sig. (2-tailed)	.162	.124	.428	.447	0.212
	N	51	51	51	50	51
Right Subiculum / WBV	Pearson Correlation	.227	.282*	.226	.294*	0.006
	Sig. (2-tailed)	.109	.045	.111	.038	0.965
	N	51	51	51	50	51
Right SR SL SM / WBV	Pearson Correlation	.052	.146	.046	.214	-0.024
	Sig. (2-tailed)	.719	.306	.746	.136	0.867
	N	51	51	51	50	51

*p < .05; **p < .01

Note. Storm32: Objective Hardship questionnaire (full); Storm24: Objective Hardship questionnaire (partial); IES-R: Impact of Event Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 6

Pearson's correlation coefficients between predictors and hippocampal measures in the early life maternal stress cohort

Variables		Storm24	CONSEQ	Sex
Storm24	Pearson Correlation	1	-0.226	-0.038
	Sig. (2-tailed)	-	0.127	0.8
	N	47	47	47
CONSEQ	Pearson Correlation	-0.226	1	-0.014
	Sig. (2-tailed)	0.127	-	0.926
	N	47	47	47
Sex	Pearson Correlation	-0.038	-0.014	1
	Sig. (2-tailed)	0.8	0.926	-
	N	47	47	47
Total Intracranial Volume (TIC)	Pearson Correlation	-0.214	0.054	-0.212
	Sig. (2-tailed)	0.148	0.721	0.152
	N	47	47	47
Whole Brain Volume (WBV)	Pearson Correlation	-0.135	0.138	-0.278
	Sig. (2-tailed)	0.365	0.356	0.058
	N	47	47	47
Left HC Surface Area	Pearson Correlation	0.034	0.199	-0.197
	Sig. (2-tailed)	0.819	0.181	0.185
	N	47	47	47
Right HC Surface Area	Pearson Correlation	-0.004	0.1	0.022
	Sig. (2-tailed)	0.978	0.505	0.884
	N	47	47	47
Left HC Surface Area / TIC	Pearson Correlation	.366*	0.209	0.038
	Sig. (2-tailed)	0.012	0.159	0.799
	N	47	47	47
Right HC Surface Area / TIC	Pearson Correlation	0.269	0.047	.307*
	Sig. (2-tailed)	0.067	0.756	0.036
	N	47	47	47
Left HC Surface Area / WBV	Pearson Correlation	0.256	0.05	0.174
	Sig. (2-tailed)	0.082	0.741	0.243
	N	47	47	47
Right HC Surface Area / WBV	Pearson Correlation	0.168	-0.078	.385**
	Sig. (2-tailed)	0.258	0.601	0.008
	N	47	47	47
Total Left HC	Pearson Correlation	0.083	0.046	-0.115
	Sig. (2-tailed)	0.579	0.759	0.441
	N	47	47	47
Left CA1	Pearson Correlation	0.115	-0.093	-0.096
	Sig. (2-tailed)	0.443	0.533	0.521
	N	47	47	47
Left CA2 CA3	Pearson Correlation	0.047	0.026	0.06
	Sig. (2-tailed)	0.756	0.86	0.687

	N	47	47	47
Left CA4 & DG	Pearson Correlation	0.021	0.211	-0.089
	Sig. (2-tailed)	0.891	0.154	0.553
	N	47	47	47
Left Subiculum	Pearson Correlation	0.086	0.074	-0.189
	Sig. (2-tailed)	0.564	0.62	0.203
	N	47	47	47
Left SR SL SM	Pearson Correlation	0.062	-0.009	-0.09
	Sig. (2-tailed)	0.678	0.952	0.545
	N	47	47	47
Total Right HC	Pearson Correlation	0.047	0.23	-0.273
	Sig. (2-tailed)	0.756	0.119	0.063
	N	47	47	47
Right CA1	Pearson Correlation	0.056	0.226	-0.283
	Sig. (2-tailed)	0.709	0.127	0.054
	N	47	47	47
Right CA2 & CA3	Pearson Correlation	0.019	0.155	-0.097
	Sig. (2-tailed)	0.9	0.299	0.519
	N	47	47	47
Right CA4 & DG	Pearson Correlation	0.008	0.233	-0.252
	Sig. (2-tailed)	0.956	0.115	0.087
	N	47	47	47
Right Subiculum	Pearson Correlation	0.098	0.009	-0.107
	Sig. (2-tailed)	0.511	0.952	0.475
	N	47	47	47
Right SR SL SM	Pearson Correlation	0.013	0.232	-0.254
	Sig. (2-tailed)	0.93	0.117	0.085
	N	47	47	47
Total Left HC / TIC	Pearson Correlation	.299*	0.015	0.028
	Sig. (2-tailed)	0.041	0.919	0.852
	N	47	47	47
Left CA1 / TIC	Pearson Correlation	.303*	-0.156	0.036
	Sig. (2-tailed)	0.038	0.295	0.809
	N	47	47	47
Left CA2 CA3 / TIC	Pearson Correlation	0.16	0.016	0.162
	Sig. (2-tailed)	0.282	0.915	0.275
	N	47	47	47
Left CA4 & DG / TIC	Pearson Correlation	0.158	0.251	-0.159
	Sig. (2-tailed)	0.288	0.089	0.285
	N	47	47	47
Left Subiculum / TIC	Pearson Correlation	0.205	0.046	-0.081
	Sig. (2-tailed)	0.167	0.761	0.587
	N	47	47	47
Left SR SL SM / TIC	Pearson Correlation	0.207	-0.045	0.019
	Sig. (2-tailed)	0.163	0.763	0.9

	N	47	47	47
Total Right HC / TIC	Pearson Correlation	0.234	0.257	-0.183
	Sig. (2-tailed)	0.113	0.081	0.217
	N	47	47	47
Right CA1 / TIC	Pearson Correlation	0.233	0.25	-0.218
	Sig. (2-tailed)	0.115	0.09	0.142
	N	47	47	47
Right CA2 & CA3 / TIC	Pearson Correlation	0.085	0.155	-0.04
	Sig. (2-tailed)	0.57	0.298	0.789
	N	47	47	47
Right CA4 & DG / TIC	Pearson Correlation	0.201	0.255	0.041
	Sig. (2-tailed)	0.175	0.083	0.786
	N	47	47	47
Right Subiculum / TIC	Pearson Correlation	0.197	-0.019	-0.009
	Sig. (2-tailed)	0.185	0.901	0.954
	N	47	47	47
Right SR SL SM / TIC	Pearson Correlation	0.146	0.252	-0.176
	Sig. (2-tailed)	0.328	0.088	0.238
	N	47	47	47
Total Left HC / WBV	Pearson Correlation	0.242	-0.067	0.105
	Sig. (2-tailed)	0.101	0.655	0.483
	N	47	47	47
Left CA1 / WBV	Pearson Correlation	0.252	-0.221	0.101
	Sig. (2-tailed)	0.088	0.135	0.498
	N	47	47	47
Left CA2 CA3 / WBV	Pearson Correlation	0.12	-0.034	0.213
	Sig. (2-tailed)	0.421	0.822	0.151
	N	47	47	47
Left CA4 & DG / WBV	Pearson Correlation	0.146	0.177	0.116
	Sig. (2-tailed)	0.329	0.234	0.436
	N	47	47	47
Left Subiculum / WBV	Pearson Correlation	0.181	-0.001	-0.038
	Sig. (2-tailed)	0.223	0.993	0.8
	N	47	47	47
Left SR SL SM / WBV	Pearson Correlation	0.172	-0.101	0.072
	Sig. (2-tailed)	0.248	0.498	0.632
	N	47	47	47
Total Right HC / WBV	Pearson Correlation	0.19	0.183	-0.11
	Sig. (2-tailed)	0.201	0.219	0.46
	N	47	47	47
Right CA1 / WBV	Pearson Correlation	0.191	0.188	-0.156
	Sig. (2-tailed)	0.197	0.205	0.296
	N	47	47	47
Right CA2 & CA3 / WBV	Pearson Correlation	0.061	0.123	-0.007
	Sig. (2-tailed)	0.683	0.409	0.965

	N	47	47	47
Right CA4 & DG / WBV	Pearson Correlation	0.109	0.183	-0.09
	Sig. (2-tailed)	0.467	0.218	0.548
	N	47	47	47
Right Subiculum / WBV	Pearson Correlation	0.17	-0.061	0.029
	Sig. (2-tailed)	0.253	0.682	0.849
	N	47	47	47
Right SR SL SM / WBV	Pearson Correlation	0.116	0.194	-0.122
	Sig. (2-tailed)	0.438	0.19	0.413
	N	47	47	47

*p < .05; **p < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 7

Multiple regression summary table from the prenatal maternal stress (PNMS) cohort - Model 1

Hemisphere	Structure		Storm32			IESR_log			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	Whole HC	0.207	0.095	0.513	0.667	0.276	0.055§	0.155	0.355	0.017*	0.042*	-0.151	0.270	0.928
	Whole HC / TIC	0.154	0.134	0.375	0.636	0.309	0.039*	0.152	0.291	0.056§	0.095§	0.070	0.618	0.961
	Whole HC / WBV	0.259	0.236	0.098§	0.370	0.330	0.019*	0.123	0.418	0.004**	0.017*	0.010	0.937	0.985
	CA1	0.255	0.078	0.581	0.722	0.281	0.045*	0.155	0.340	0.018*	0.042*	-0.255	0.058§	0.576
	CA1 / TIC	0.186	0.115	0.436	0.653	0.338	0.022*	0.123	0.298	0.046*	0.090§	-0.064	0.640	0.961
	CA1 / WBV	0.310	0.217	0.113	0.370	0.357	0.009**	0.091§	0.426	0.003**	0.011*	-0.118	0.355	0.928
	CA2 CA3	0.028	-0.025	0.875	0.927	0.062	0.694	0.713	0.155	0.332	0.392	-0.028	0.853	0.985
	CA2 CA3 / TIC	0.021	0.002	0.989	0.989	0.055	0.728	0.728	0.097	0.547	0.582	0.125	0.408	0.939
	CA2 CA3 / WBV	0.031	0.070	0.663	0.761	0.070	0.655	0.691	0.173	0.281	0.343	0.080	0.594	0.961
	CA4 & DG	0.076	0.074	0.635	0.751	0.178	0.246	0.385	0.247	0.117	0.168	-0.005	0.974	0.985
	CA4 & DG / TIC	0.082	0.107	0.495	0.596	0.184	0.230	0.496	0.179	0.251	0.435	0.186	0.206	0.780
	CA4 & DG / WBV	0.136	0.198	0.195	0.510	0.213	0.154	0.324	0.299	0.052§	0.092§	0.146	0.306	0.928
	Subiculum	0.183	0.203	0.172	0.483	0.205	0.157	0.324	0.397	0.009**	0.027*	-0.031	0.822	0.985
	Subiculum / TIC	0.183	0.228	0.127	0.382	0.257	0.078§	0.192	0.352	0.02*	0.042*	0.119	0.388	0.939
	Subiculum / WBV	0.261	0.299	0.037*	0.295	0.271	0.052§	0.155	0.442	0.003**	0.011*	0.066	0.613	0.961
	SR SL SM	0.205	0.047	0.748	0.834	0.306	0.035*	0.152	0.291	0.049*	0.091§	-0.195	0.156	0.852
	SR SL SM / TIC	0.143	0.081	0.592	0.722	0.331	0.028*	0.138	0.236	0.120	0.168	-0.014	0.919	0.985
	SR SL SM / WBV	0.225	0.169	0.241	0.556	0.345	0.017*	0.123	0.344	0.019*	0.042*	-0.064	0.635	0.961
Right	Whole HC	0.138	0.118	0.437	0.653	0.122	0.411	0.517	0.359	0.020*	0.042*	-0.087	0.539	0.961
	Whole HC / TIC	0.100	0.157	0.311	0.596	0.144	0.343	0.478	0.289	0.065§	0.106	0.141	0.332	0.928
	Whole HC / WBV	0.191	0.258	0.084§	0.365	0.172	0.232	0.385	0.418	0.006**	0.021*	0.076	0.581	0.961
	CA1	0.202	0.141	0.336	0.596	0.100	0.483	0.555	0.410	0.006**	0.021*	-0.170	0.217	0.852
	CA1 / TIC	0.132	0.183	0.231	0.556	0.126	0.397	0.516	0.367	0.018*	0.042*	0.021	0.884	0.985
	CA1 / WBV	0.240	0.270	0.062§	0.352	0.152	0.275	0.397	0.477	0.001**	0.011*	-0.037	0.779	0.985
	CA2 & CA3	0.083	-0.177	0.258	0.562	-0.184	0.231	0.385	-0.050	0.746	0.766	-0.103	0.482	0.961
	CA2 & CA3 / TIC	0.072	-0.156	0.323	0.596	-0.193	0.211	0.385	-0.093	0.552	0.582	0.024	0.868	0.985
	CA2 & CA3 / WBV	0.056	-0.115	0.468	0.653	-0.183	0.240	0.385	-0.025	0.875	0.875	0.013	0.930	0.985
	CA4 & DG	0.049	0.119	0.453	0.653	0.124	0.424	0.517	0.192	0.227	0.295	0.052	0.728	0.985
	CA4 & DG / TIC	0.095	0.152	0.327	0.667	0.136	0.369	0.385	0.133	0.390	0.316	0.243	0.098	0.852
	CA4 & DG / WBV	0.139	0.243	0.112	0.370	0.168	0.259	0.388	0.252	0.098§	0.147	0.206	0.150	0.852
	Subiculum	0.250	0.255	0.076§	0.365	0.225	0.107	0.246	0.480	0.001**	0.011*	0.024	0.855	0.985
	Subiculum / TIC	0.266	0.281	0.049*	0.321	0.272	0.050*	0.155	0.449	0.002**	0.011*	0.175	0.185	0.852
	Subiculum / WBV	0.261	0.303	0.035*	0.295	0.249	0.073§	0.192	0.457	0.002**	0.011*	0.092	0.483	0.961
	SR SL SM	0.077	-0.003	0.982	0.989	0.078	0.611	0.662	0.223	0.156	0.210	-0.136	0.355	0.928
	SR SL SM / TIC	0.024	0.024	0.880	0.927	0.083	0.597	0.662	0.153	0.341	0.392	0.053	0.727	0.985
	SR SL SM / WBV	0.075	0.115	0.463	0.653	0.112	0.464	0.549	0.275	0.082§	0.128	0.003	0.985	0.985

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm32: Objective Hardship questionnaire (full); IESR: Impact of Events Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1 neutral or positive); Sex (0: male, 1: female); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 8

Summary of hierarchical regression analysis for variables predicting total left hippocampal volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.038	0.038
Objective Hardship (STORM32)	0.195	0.001	0.001	0.175	-		
Step 2						0.106	0.068
Objective Hardship (STORM32)	0.117	0.0005	0.001	0.418	-		
Subjective Distress (IESR_log)	0.273	0.005	0.002	0.064§	-		
Step 3						0.259	0.152
Objective Hardship (STORM32)	0.235	0.001	0.001	0.094§	-		
Subjective Distress (IESR_log)	0.328	0.005	0.002	0.018*	-		
Cognitive Appraisal (CONSEQ)	0.416	0.016	0.005	0.004**	-		
Step 4						0.259	0.000
Objective Hardship (STORM32)	0.236	0.001	0.001	0.098§	0.370		
Subjective Distress (IESR_log)	0.330	0.005	0.002	0.019*	0.123		
Cognitive Appraisal (CONSEQ)	0.418	0.016	0.005	0.004**	0.017*		
Sex	0.010	0.0003	0.005	0.937	0.985		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 9

Summary of hierarchical regression analysis for variables predicting total left hippocampal volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.003	0.003
Objective Hardship (STORM32)	0.059	3.144	7.663	0.683	-		
Step 2						0.057	0.054
Objective Hardship (STORM32)	-0.009	-0.502	7.853	0.949	-		
Subjective Distress (IESR_log)	0.242	52.071	31.735	0.108	-		
Step 3						0.185	0.128
Objective Hardship (STORM32)	0.098	5.236	7.684	0.499	-		
Subjective Distress (IESR_log)	0.293	63.006	30.104	0.042*	-		
Cognitive Appraisal (CONSEQ)	0.381	186.050	69.316	0.010*	-		
Step 4						0.207	0.022
Objective Hardship (STORM32)	0.095	5.058	7.665	0.513	0.667		
Subjective Distress (IESR_log)	0.276	59.378	30.199	0.055§	0.155		
Cognitive Appraisal (CONSEQ)	0.355	173.694	70.012	0.017*	0.042*		
Sex	-0.151	-70.714	63.349	0.270	0.928		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 10

Summary of hierarchical regression analysis for variables predicting total right hippocampal volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.030	0.030
Objective Hardship (STORM32)	0.172	0.001	0.001	0.232	-		
Step 2						0.041	0.011
Objective Hardship (STORM32)	0.141	0.001	0.001	0.348	-		
Subjective Distress (IESR_log)	0.109	0.002	0.002	0.467	-		
Step 3						0.185	0.144
Objective Hardship (STORM32)	0.256	0.001	0.001	0.083*	-		
Subjective Distress (IESR_log)	0.163	0.003	0.002	0.249	-		
Cognitive Appraisal (CONSEQ)	0.405	0.015	0.005	0.006**	-		
Step 4						0.191	0.006
Objective Hardship (STORM32)	0.258	0.001	0.001	0.084§	0.365		
Subjective Distress (IESR_log)	0.172	0.003	0.002	0.232	0.385		
Cognitive Appraisal (CONSEQ)	0.418	0.016	0.005	0.006**	0.021*		
Sex	0.076	0.003	0.005	0.581	0.961		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 11

Summary of hierarchical regression analysis for variables predicting total right hippocampal volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.001	0.001
Objective Hardship (STORM32)	0.037	1.922	7.522	0.799	-		
Step 2						0.007	0.006
Objective Hardship (STORM32)	0.014	0.720	7.901	0.928	-		
Subjective Distress (IESR_log)	0.081	17.167	31.931	0.593	-		
Step 3						0.130	0.123
Objective Hardship (STORM32)	0.120	6.242	7.783	0.427	-		
Subjective Distress (IESR_log)	0.131	27.689	30.492	0.369	-		
Cognitive Appraisal (CONSEQ)	0.374	179.025	70.208	0.014*	-		
Step 4						0.138	0.007
Objective Hardship (STORM32)	0.118	6.141	7.837	0.437	0.653		
Subjective Distress (IESR_log)	0.122	25.634	30.878	0.411	0.517		
Cognitive Appraisal (CONSEQ)	0.359	172.027	71.585	0.020*	0.042*		
Sex	-0.087	-40.051	64.772	0.539	0.961		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 12

Summary of hierarchical regression analysis for variables predicting left CA1 volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.033	0.033
Objective Hardship (STORM32)	0.182	0.0002	0.0001	0.207	-		
Step 2						0.122	0.089
Objective Hardship (STORM32)	0.094	0.0001	0.0002	0.514	-		
Subjective Distress (IESR_log)	0.311	0.002	0.001	0.034*	-		
Step 3						0.297	0.175
Objective Hardship (STORM32)	0.220	0.0003	0.0002	0.108	-		
Subjective Distress (IESR_log)	0.370	0.002	0.001	0.007**	-		
Cognitive Appraisal (CONSEQ)	0.446	0.005	0.002	0.001**	-		
Step 4						0.310	0.013
Objective Hardship (STORM32)	0.217	0.0003	0.0002	0.113	0.370		
Subjective Distress (IESR_log)	0.357	0.002	0.001	0.009**	0.090§		
Cognitive Appraisal (CONSEQ)	0.426	0.005	0.002	0.003**	0.011*		
Sex	-0.118	-0.001	0.001	0.355	0.928		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 13

Summary of hierarchical regression analysis for variables predicting left CA1 volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.002	0.002
Objective Hardship (STORM32)	0.048	0.853	2.572	0.742	-		
Step 2						0.064	0.061
Objective Hardship (STORM32)	-0.025	-0.450	2.625	0.865	-		
Subjective Distress (IESR_log)	0.258	18.609	10.609	0.086§	-		
Step 3						0.193	0.129
Objective Hardship (STORM32)	0.083	1.485	2.565	0.565	-		
Subjective Distress (IESR_log)	0.309	22.298	10.050	0.031*	-		
Cognitive Appraisal (CONSEQ)	0.383	62.751	23.141	0.009**	-		
Step 4						0.255	0.063
Objective Hardship (STORM32)	0.078	1.384	2.491	0.581	0.722		
Subjective Distress (IESR_log)	0.281	20.239	9.815	0.045*	0.155		
Cognitive Appraisal (CONSEQ)	0.340	55.740	22.753	0.018*	0.042*		
Sex	-0.255	-40.124	20.588	0.058§	0.576		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 14

Summary of hierarchical regression analysis for variables predicting right CA1 volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.025	0.025
Objective Hardship (STORM32)	0.160	0.0002	0.0002	0.268	-		
Step 2						0.033	0.008
Objective Hardship (STORM32)	0.134	0.0002	0.0002	0.376	-		
Subjective Distress (IESR_log)	0.092	0.0005	0.001	0.542	-		
Step 3						0.238	0.205
Objective Hardship (STORM32)	0.271	0.0004	0.0002	0.059§	-		
Subjective Distress (IESR_log)	0.156	0.001	0.001	0.254	-		
Cognitive Appraisal (CONSEQ)	0.483	0.006	0.002	0.001**	-		
Step 4						0.240	0.001
Objective Hardship (STORM32)	0.270	0.0004	0.0002	0.062§	0.352		
Subjective Distress (IESR_log)	0.152	0.001	0.001	0.275	0.397		
Cognitive Appraisal (CONSEQ)	0.477	0.006	0.002	0.001**	0.011*		
Sex	-0.0004	0.000	0.002	0.779	0.985		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 15

Summary of hierarchical regression analysis for variables predicting right CA1 volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.001	0.001
Objective Hardship (STORM32)	0.037	0.654	2.546	0.798	-		
Step 2						0.005	0.003
Objective Hardship (STORM32)	0.020	0.354	2.678	0.895	-		
Subjective Distress (IESR_log)	0.060	4.277	10.824	0.695	-		
Step 3						0.174	0.170
Objective Hardship (STORM32)	0.144	2.550	2.567	0.326	-		
Subjective Distress (IESR_log)	0.119	8.460	10.058	0.405	-		
Cognitive Appraisal (CONSEQ)	0.439	71.173	23.159	0.004**	-		
Step 4						0.202	0.028
Objective Hardship (STORM32)	0.141	2.483	2.552	0.336	0.596		
Subjective Distress (IESR_log)	0.100	7.104	10.055	0.483	0.555		
Cognitive Appraisal (CONSEQ)	0.410	66.556	23.310	0.006**	0.021*		
Sex	-0.170	-26.423	21.092	0.217	0.852		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 16

Summary of hierarchical regression analysis for variables predicting total right CA1 volume normalized to total intracranial volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.010	0.010
Objective Hardship (STORM32)	0.101	0.0001	0.0002	0.486	-		
Step 2						0.015	0.005
Objective Hardship (STORM32)	0.080	).00009	0.0002	0.600	-		
Subjective Distress (IESR_log)	0.075	0.0003	0.001	0.622	-		
Step 3						0.132	0.116
Objective Hardship (STORM32)	0.183	0.0002	0.0002	0.227	-		
Subjective Distress (IESR_log)	0.123	0.001	0.001	0.398	-		
Cognitive Appraisal (CONSEQ)	0.363	0.004	0.002	0.017*	-		
Step 4						0.132	0.0004
Objective Hardship (STORM32)	0.183	0.0002	0.0002	0.231	0.556		
Subjective Distress (IESR_log)	0.126	0.001	0.001	0.397	0.516		
Cognitive Appraisal (CONSEQ)	0.367	0.004	0.002	0.018*	0.042*		
Sex	0.021	0.000	0.001	0.884	0.985		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 17

Summary of hierarchical regression analysis for variables predicting left subiculum volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.055	0.055
Objective Hardship (STORM32)	0.234	0.0002	0.0001	0.102	-		
Step 2						0.094	0.039
Objective Hardship (STORM32)	0.175	0.0001	0.0001	0.232	-		
Subjective Distress (IESR_log)	0.206	0.0006	0.0004	0.161	-		
Step 3						0.257	0.163
Objective Hardship (STORM32)	0.297	0.0002	0.0001	0.036*	-		
Subjective Distress (IESR_log)	0.264	0.0008	0.0004	0.055§	-		
Cognitive Appraisal (CONSEQ)	0.431	0.003	0.001	0.003**	-		
Step 4						0.261	0.004
Objective Hardship (STORM32)	0.299	0.0002	0.0001	0.037*	0.295		
Subjective Distress (IESR_log)	0.271	0.001	0.0004	0.052§	0.155		
Cognitive Appraisal (CONSEQ)	0.442	0.003	0.001	0.003**	0.011*		
Sex	0.066	0.0004	0.001	0.613	0.961		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 18

Summary of hierarchical regression analysis for variables predicting left subiculum volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.018	0.018
Objective Hardship (STORM32)	0.133	1.275	1.366	0.355	-		
Step 2						0.040	0.022
Objective Hardship (STORM32)	0.090	0.856	1.423	0.550	-		
Subjective Distress (IESR_log)	0.155	5.978	5.750	0.304	-		
Step 3						0.182	0.142
Objective Hardship (STORM32)	0.204	1.943	1.382	0.166	-		
Subjective Distress (IESR_log)	0.209	8.049	5.415	0.144	-		
Cognitive Appraisal (CONSEQ)	0.402	35.249	12.468	0.007**	-		
Step 4						0.183	0.001
Objective Hardship (STORM32)	0.203	1.937	1.397	0.172	0.483		
Subjective Distress (IESR_log)	0.205	7.915	5.503	0.157	0.324		
Cognitive Appraisal (CONSEQ)	0.397	34.793	12.759	0.009**	0.027*		
Sex	-0.031	-2.612	11.545	0.822	0.985		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 19

Summary of hierarchical regression analysis for variables predicting left subiculum volume normalized to total intracranial volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.035	0.035
Objective Hardship (STORM32)	0.187	0.0001	0.00009	0.193	-		
Step 2						0.072	0.037
Objective Hardship (STORM32)	0.131	).00008	0.00009	0.376	-		
Subjective Distress (IESR_log)	0.199	0.001	0.0004	0.180	-		
Step 3						0.169	0.097
Objective Hardship (STORM32)	0.225	0.0001	0.00009	0.130	-		
Subjective Distress (IESR_log)	0.244	0.001	0.0004	0.092§	-		
Cognitive Appraisal (CONSEQ)	0.332	0.002	0.001	0.025*	-		
Step 4						0.183	0.014
Objective Hardship (STORM32)	0.228	0.0001	0.00009	0.127	0.382		
Subjective Distress (IESR_log)	0.257	0.001	0.0004	0.078§	0.192		
Cognitive Appraisal (CONSEQ)	0.352	0.002	0.001	0.020*	0.042*		
Sex	0.119	0.001	0.001	0.388	0.939		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 20

Summary of hierarchical regression analysis for variables predicting right subiculum volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.051	0.051
Objective Hardship (STORM32)	0.227	0.0002	0.0001	0.114	-		
Step 2						0.081	0.030
Objective Hardship (STORM32)	0.176	0.0002	0.0001	0.234	-		
Subjective Distress (IESR_log)	0.179	0.001	0.001	0.225	-		
Step 3						0.252	0.172
Objective Hardship (STORM32)	0.301	0.0003	0.0001	0.035*	-		
Subjective Distress (IESR_log)	0.238	0.001	0.001	0.082§	-		
Cognitive Appraisal (CONSEQ)	0.441	0.004	0.001	0.002**	-		
Step 4						0.261	0.008
Objective Hardship (STORM32)	0.303	0.0003	0.0001	0.035*	0.295		
Subjective Distress (IESR_log)	0.249	0.001	0.001	0.073§	0.192		
Cognitive Appraisal (CONSEQ)	0.457	0.004	0.001	0.002**	0.011*		
Sex	0.092	0.001	0.001	0.483	0.961		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 21

Summary of hierarchical regression analysis for variables predicting right subiculum volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.027	0.027
Objective Hardship (STORM32)	0.164	1.819	1.579	0.255	-		
Step 2						0.050	0.023
Objective Hardship (STORM32)	0.119	1.321	1.644	0.426	-		
Subjective Distress (IESR_log)	0.159	7.105	6.644	0.290	-		
Step 3						0.250	0.200
Objective Hardship (STORM32)	0.254	2.818	1.538	0.073§	-		
Subjective Distress (IESR_log)	0.222	9.957	6.024	0.105	-		
Cognitive Appraisal (CONSEQ)	0.476	48.530	13.870	0.001**	-		
Step 4						0.250	0.001
Objective Hardship (STORM32)	0.255	2.824	1.554	0.076§	0.365		
Subjective Distress (IESR_log)	0.225	10.078	6.124	0.107	0.246		
Cognitive Appraisal (CONSEQ)	0.480	48.944	14.197	0.001**	0.011*		
Sex	0.024	2.368	12.846	0.855	0.985		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 22

Summary of hierarchical regression analysis for variables predicting right subiculum volume normalized to total intracranial volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.046	0.046
Objective Hardship (STORM32)	0.214	0.0002	0.0001	0.136	-		
Step 2						0.081	0.035
Objective Hardship (STORM32)	0.158	0.0001	0.0001	0.283	-		
Subjective Distress (IESR_log)	0.196	0.001	0.0004	0.184	-		
Step 3						0.236	0.155
Objective Hardship (STORM32)	0.277	0.0002	0.0001	0.053§	-		
Subjective Distress (IESR_log)	0.252	0.001	0.0004	0.069§	-		
Cognitive Appraisal (CONSEQ)	0.419	0.003	0.001	0.004**	-		
Step 4						0.266	0.030
Objective Hardship (STORM32)	0.281	0.0002	0.0001	0.049*	0.321		
Subjective Distress (IESR_log)	0.272	0.001	0.0004	0.050§	0.155		
Cognitive Appraisal (CONSEQ)	0.449	0.003	0.001	0.002**	0.011*		
Sex	0.175	0.001	0.001	0.185	0.852		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 23

Summary of hierarchical regression analysis for variables predicting left SR/SL/SM volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.024	0.024
Objective Hardship (STORM32)	0.156	0.0002	0.0002	0.278	-		
Step 2						0.110	0.086
Objective Hardship (STORM32)	0.070	).00008	0.0002	0.627	-		
Subjective Distress (IESR_log)	0.305	0.001	0.001	0.039*	-		
Step 3						0.221	0.111
Objective Hardship (STORM32)	0.171	0.0002	0.0002	0.233	-		
Subjective Distress (IESR_log)	0.352	0.002	0.001	0.013*	-		
Cognitive Appraisal (CONSEQ)	0.354	0.004	0.001	0.014*	-		
Step 4						0.225	0.004
Objective Hardship (STORM32)	0.169	0.0002	0.0002	0.241	0.556		
Subjective Distress (IESR_log)	0.345	0.002	0.001	0.017*	0.123		
Cognitive Appraisal (CONSEQ)	0.344	0.004	0.002	0.019*	0.042*		
Sex	-0.064	-0.001	0.001	0.635	0.961		

§p / q < .1; *p / q < .05; **p / q < .01

Note. SR/SL/SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

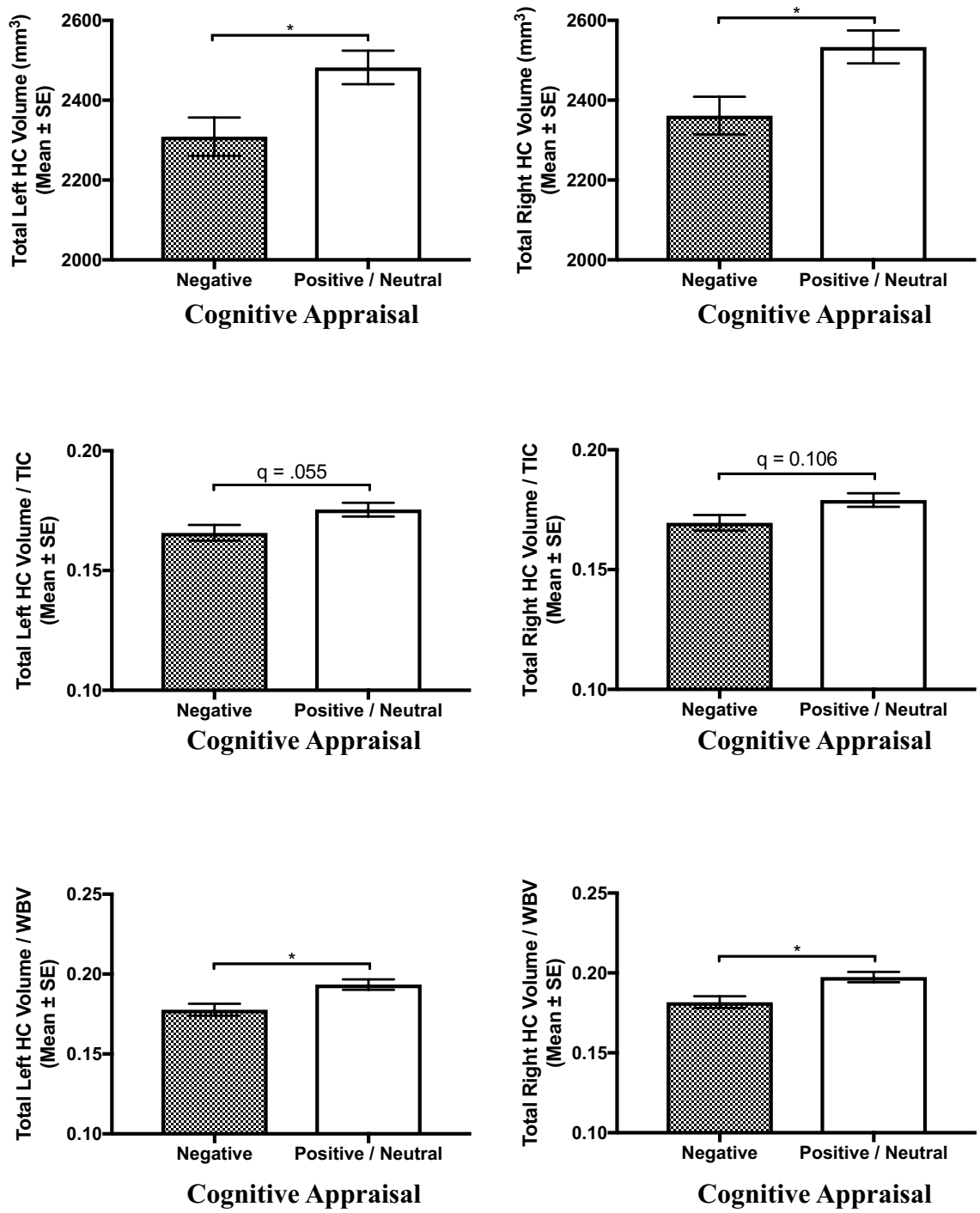

Figure 1. Relationship between cognitive appraisal and mean total hippocampal volume (± SE), mean HC/TIC ratios (± SE), and mean HC/WBV ratios (± SE), controlling for objective hardship (Storm32), subjective distress, and sex. *q < 0.05
Note. HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

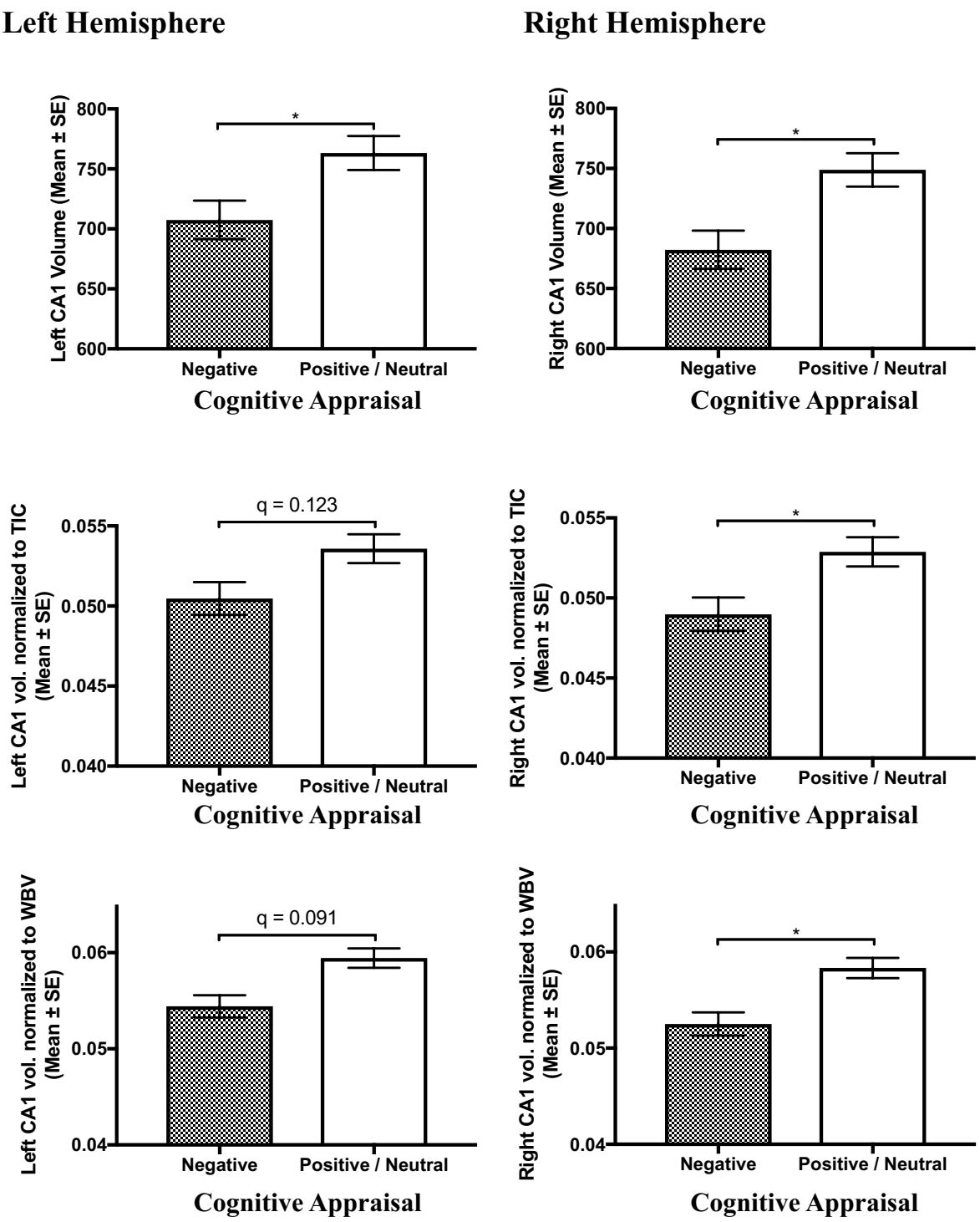

Figure 2. Relationship between cognitive appraisal and mean CA1 volume (± SE), mean CA1/TIC ratios (± SE) and mean CA1/WBV ratios (± SE), controlling for objective hardship (Storm32), subjective distress and sex. *$q < 0.05$

Note. HC: Hippocampus; CA: Cornu Ammonis; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

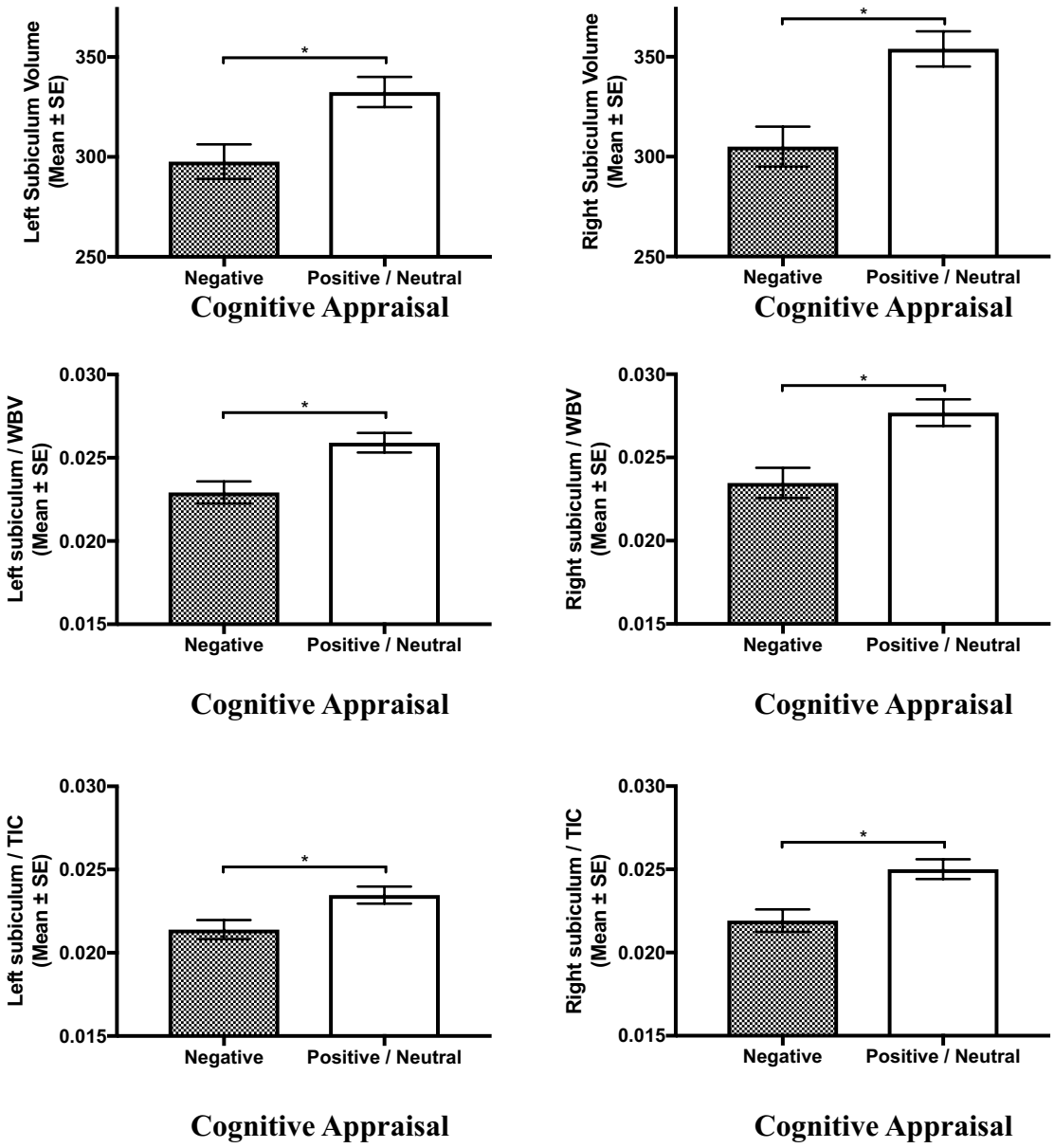

Figure 3. Relationship between cognitive appraisal and mean subiculum volume (± SE), mean subiculum/TIC ratios (± SE) and mean subiculum/WBV ratios (± SE), controlling for objective hardship (Storm32), subjective distress and sex. *$q < 0.05$

Note. HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 24

Multiple regression summary table from the prenatal maternal stress (PNMS) cohort - Model 2

Hemisphere	Structure		Storm24			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	Whole HC	0.138	0.150	0.290	0.405	0.292	0.045*	0.098§	-0.184	0.190	0.898
	Whole HC / TIC	0.060	0.176	0.234	0.373	0.212	0.157	0.235	0.032	0.828	0.923
	Whole HC / WBV	0.142	0.266	0.062§	0.174	0.319	0.028*	0.073§	-0.034	0.809	0.923
	CA1	0.189	0.154	0.262	0.379	0.282	0.045*	0.098§	-0.288	0.037*	0.370
	CA1 / TIC	0.084	0.186	0.203	0.373	0.221	0.136	0.217	-0.105	0.464	0.923
	CA1 / WBV	0.188	0.276	0.048*	0.157	0.329	0.020*	0.059§	-0.164	0.228	0.898
	CA2 CA3	0.034	-0.097	0.513	0.572	0.130	0.390	0.461	-0.035	0.811	0.923
	CA2 CA3 / TIC	0.024	-0.074	0.622	0.653	0.068	0.652	0.706	0.118	0.427	0.923
	CA2 CA3 / WBV	0.020	-0.009	0.953	0.953	0.132	0.385	0.461	0.069	0.643	0.923
	CA4 & DG	0.040	0.070	0.636	0.653	0.196	0.194	0.279	-0.027	0.852	0.923
	CA4 & DG / TIC	0.040	0.090	0.544	0.373	0.121	0.422	0.618	0.162	0.273	0.822
	CA4 & DG / WBV	0.070	0.174	0.236	0.373	0.221	0.139	0.217	0.115	0.426	0.923
	Subiculum	0.196	0.334	0.017*	0.068§	0.351	0.013*	0.047*	-0.058	0.665	0.923
	Subiculum / TIC	0.172	0.358	0.012*	0.059§	0.292	0.040*	0.098§	0.085	0.531	0.923
	Subiculum / WBV	0.241	0.413	0.003**	0.029*	0.366	0.008**	0.038*	0.028	0.827	0.923
	SR SL SM	0.117	0.094	0.508	0.572	0.224	0.123	0.215	-0.230	0.106	0.822
	SR SL SM / TIC	0.037	0.120	0.421	0.530	0.158	0.295	0.391	-0.054	0.714	0.923
	SR SL SM / WBV	0.100	0.197	0.174	0.340	0.249	0.0902§	0.168	-0.108	0.450	0.923
Right	Whole HC	0.147	0.209	0.139	0.302	0.335	0.021*	0.059§	-0.103	0.458	0.923
	Whole HC / TIC	0.102	0.236	0.105	0.242	0.252	0.086§	0.168	0.121	0.394	0.923
	Whole HC / WBV	0.184	0.322	0.022*	0.079§	0.360	0.012*	0.046*	0.050	0.713	0.923
	CA1	0.225	0.241	0.076§	0.187	0.391	0.005**	0.036*	-0.183	0.168	0.898
	CA1 / TIC	0.151	0.276	0.052§	0.158	0.335	0.021*	0.059§	0.002	0.986	0.986
	CA1 / WBV	0.252	0.349	0.010**	0.059§	0.425	0.002**	0.023*	-0.061	0.636	0.923
	CA2 & CA3	0.041	-0.181	0.225	0.373	0.013	0.931	0.931	-0.077	0.600	0.923
	CA2 & CA3 / TIC	0.030	-0.170	0.258	0.379	-0.032	0.830	0.875	0.051	0.731	0.923
	CA2 & CA3 / WBV	0.020	-0.131	0.385	0.501	0.028	0.853	0.875	0.037	0.804	0.923
	CA4 & DG	0.038	0.154	0.303	0.408	0.156	0.300	0.391	0.035	0.814	0.923
	CA4 & DG / TIC	0.077	0.173	0.239	0.589	0.087	0.555	0.484	0.224	0.125	0.923
	CA4 & DG / WBV	0.106	0.258	0.077§	0.187	0.187	0.200	0.279	0.180	0.208	0.898
	Subiculum	0.229	0.336	0.014*	0.063§	0.414	0.003**	0.026*	-0.008	0.954	0.979
	Subiculum / TIC	0.218	0.360	0.010**	0.059§	0.368	0.009**	0.038*	0.137	0.305	0.923
	Subiculum / WBV	0.211	0.357	0.011*	0.059§	0.374	0.008**	0.038*	0.056	0.675	0.923
	SR SL SM	0.081	0.101	0.487	0.572	0.227	0.126	0.215	-0.143	0.321	0.923
	SR SL SM / TIC	0.029	0.116	0.440	0.536	0.150	0.323	0.407	0.044	0.766	0.923
	SR SL SM / WBV	0.084	0.200	0.172	0.340	0.253	0.089§	0.168	-0.012	0.933	0.979

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm24: Objective Hardship questionnaire (partial): CONSEQ: Cognitive Appraisal (0: negative, 1 neutral or positive); Sex (0: male, 1: female); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 25

Summary of hierarchical regression analysis for variables predicting total right hippocampal volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.063	0.063
Objective Hardship (STORM24)	0.250	0.001	0.001	0.080§	-		
Step 2						0.182	0.119
Objective Hardship (STORM24)	0.321	0.002	0.001	0.021*	-		
Cognitive Appraisal (CONSEQ)	0.353	0.013	0.005	0.012*	-		
Step 3						0.184	0.002
Objective Hardship (STORM24)	0.322	0.002	0.001	0.022*	0.079§		
Cognitive Appraisal (CONSEQ)	0.360	0.014	0.005	0.012*	0.046*		
Sex	0.050	0.002	0.005	0.713	0.923		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 26

Summary of hierarchical regression analysis for variables predicting right CA1 volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.069	0.069
Objective Hardship (STORM24)	0.262	0.0004	0.0002	0.066§	-		
Step 2						0.249	0.180
Objective Hardship (STORM24)	0.350	0.001	0.0002	0.009**	-		
Cognitive Appraisal (CONSEQ)	0.433	0.005	0.002	0.002**	-		
Step 3						0.252	0.004
Objective Hardship (STORM24)	0.349	0.001	0.0002	0.010*	0.059§		
Cognitive Appraisal (CONSEQ)	0.425	0.005	0.002	0.002**	0.023*		
Sex	-0.061	-0.001	0.002	0.636	0.923		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 27

Summary of hierarchical regression analysis for variables predicting right CA1 volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.026	0.026
Objective Hardship (STORM24)	0.160	3.245	2.895	0.268	-		
Step 2						0.192	0.166
Objective Hardship (STORM24)	0.244	4.956	2.721	0.075§	-		
Cognitive Appraisal (CONSEQ)	0.416	67.537	21.716	0.003**	-		
Step 3						0.225	0.033
Objective Hardship (STORM24)	0.241	4.898	2.694	0.076§	0.187		
Cognitive Appraisal (CONSEQ)	0.391	63.372	21.703	0.005**	0.036*		
Sex	-0.183	-28.592	20.422	0.168	0.898		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 28

Summary of hierarchical regression analysis for variables predicting left subiculum volume normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.115	0.115
Objective Hardship (STORM24)	0.339	).00028	0.00011	0.016*	-		
Step 2						0.241	0.126
Objective Hardship (STORM24)	0.412	0.0003	0.0001	0.003**	-		
Cognitive Appraisal (CONSEQ)	0.362	0.002	0.001	0.008**	-		
Step 3						0.241	0.001
Objective Hardship (STORM24)	0.413	0.0003	0.0001	0.003**	0.029*		
Cognitive Appraisal (CONSEQ)	0.366	0.002	0.001	0.008**	0.038*		
Sex	0.028	0.0001	0.001	0.827	0.923		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 29

Summary of hierarchical regression analysis for variables predicting left subiculum volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.069	0.069
Objective Hardship (STORM24)	0.262	2.878	1.531	0.066§	-		
Step 2						0.193	0.124
Objective Hardship (STORM24)	0.335	3.677	1.471	0.016*	-		
Cognitive Appraisal (CONSEQ)	0.359	31.538	11.741	0.010*	-		
Step 3						0.196	0.003
Objective Hardship (STORM24)	0.334	3.667	1.484	0.017*	0.068§		
Cognitive Appraisal (CONSEQ)	0.351	30.822	11.957	0.013*	0.047*		
Sex	-0.058	-4.911	11.251	0.665	0.922		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 30

Summary of hierarchical regression analysis for variables predicting total right subiculum normalized to whole brain volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.079	0.079
Objective Hardship (STORM24)	0.282	0.0003	0.0002	0.047*	-		
Step 2						0.208	0.128
Objective Hardship (STORM24)	0.356	0.0004	0.0002	0.010*	-		
Cognitive Appraisal (CONSEQ)	0.366	0.003	0.001	0.008**	-		
Step 3						0.211	0.003
Objective Hardship (STORM24)	0.357	0.0004	0.0002	0.011*	0.059§		
Cognitive Appraisal (CONSEQ)	0.374	0.003	0.001	0.008**	0.038*		
Sex	0.056	0.0005	0.001	0.675	0.923		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 31

Summary of hierarchical regression analysis for variables predicting right subiculum volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.064	0.064
Objective Hardship (STORM24)	0.252	3.219	1.783	0.077§	-		
Step 2						0.229	0.165
Objective Hardship (STORM24)	0.336	4.291	1.670	0.013*	-		
Cognitive Appraisal (CONSEQ)	0.415	42.299	13.329	0.003**	-		
Step 3						0.229	0.000
Objective Hardship (STORM24)	0.336	4.289	1.688	0.014*	0.063§		
Cognitive Appraisal (CONSEQ)	0.414	42.190	13.601	0.003**	0.026*		
Sex	-0.008	-0.746	12.798	0.954	0.979		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 32

Summary of hierarchical regression analysis for variables predicting total right subiculum normalized to total intracranial volume in the prenatal maternal stress sample. n = 50

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.083	0.083
Objective Hardship (STORM24)	0.288	0.00025	0.00012	0.043*	-		
Step 2						0.199	0.117
Objective Hardship (STORM24)	0.358	0.0003	0.0001	0.010*	-		
Cognitive Appraisal (CONSEQ)	0.349	0.002	0.001	0.012*	-		
Step 3						0.218	0.018
Objective Hardship (STORM24)	0.360	0.0003	0.0001	0.010*	0.059§		
Cognitive Appraisal (CONSEQ)	0.368	0.003	0.001	0.009**	0.038*		
Sex	0.137	0.001	0.001	0.305	0.923		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 33

Multiple regression summary table for hippocampal surface area outcomes in the prenatal maternal stress (PNMS) cohort - Model 1

Hemisphere	Structure		Storm32			IESR_log			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	HC Surface Area	0.126	0.103	0.498	0.536	0.091	0.541	0.541	0.267	0.082§	0.149	-0.2	0.160	0.399
	HC Surface Area / TIC	0.069	0.162	0.306	0.515	0.123	0.422	0.497	0.134	0.394	0.463	0.169	0.253	0.459
	HC Surface Area / WBV	0.163	0.301	0.048*	0.192	0.161	0.271	0.387	0.33	0.030*	0.121	0.057	0.681	0.681
Right	HC Surface Area	0.101	0.096	0.536	0.536	0.194	0.201	0.366	0.243	0.118	0.168	-0.099	0.494	0.581
	HC Surface Area /TIC	0.114	0.141	0.360	0.515	0.217	0.150	0.366	0.109	0.476	0.476	0.231	0.112	0.399
	HC Surface Area / WBV	0.168	0.267	0.077§	0.192	0.237	0.106	0.366	0.285	0.059§	0.147	0.123	0.377	0.539

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm32: Objective Hardship questionnaire (full); IESR: Impact of Events Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive) Sex (0: male, 1: female); HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 34

Multiple regression summary table for hippocampal surface area outcomes in the prenatal maternal stress (PNMS) cohort - Model 2

Hemisphere	Structure		Storm24			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	HC Surface Area	0.133	0.170	0.233	0.311	0.247	0.087§	0.218	-0.215	0.128	0.416
	HC Surface Area / TIC	0.064	0.207	0.162	0.294	0.095	0.522	0.615	0.151	0.299	0.543
	HC Surface Area / WBV	0.138	0.324	0.025*	0.099§	0.261	0.071§	0.218	0.031	0.825	0.825
Right	HC Surface Area	0.069	0.140	0.339	0.339	0.196	0.188	0.268	-0.123	0.395	0.564
	HC Surface Area /TIC	0.065	0.165	0.264	0.311	0.046	0.753	0.753	0.202	0.166	0.416
	HC Surface Area / WBV	0.097	0.275	0.061§	0.151	0.199	0.175	0.268	0.089	0.535	0.629

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive)
Sex (0: male, 1: female); HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 35

Multiple regression summary table for hippocampal volumetric outcomes in the early life maternal stress (ELMS) cohort

Hemisphere	Structure		Storm24			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	Whole HC	0.023	0.094	0.549	0.649	0.066	0.674	0.911	-0.111	0.468	0.847
	Whole HC / TIC	0.099	0.321	0.037*	0.275	0.088	0.555	0.834	0.041	0.777	0.905
	Whole HC / WBV	0.072	0.244	0.113	0.410	-0.010	0.947	0.991	0.114	0.443	0.847
	CA1	0.027	0.095	0.543	0.649	-0.073	0.638	0.911	-0.093	0.539	0.847
	CA1 / TIC	0.102	0.284	0.062§	0.322	-0.091	0.542	0.834	0.046	0.754	0.905
	CA1 / WBV	0.103	0.217	0.151	0.421	-0.171	0.255	0.499	0.107	0.462	0.847
	CA2 CA3	0.008	0.058	0.712	0.733	0.040	0.797	0.972	0.063	0.681	0.878
	CA2 CA3 / TIC	0.057	0.180	0.243	0.476	0.059	0.700	0.911	0.170	0.257	0.777
	CA2 CA3 / WBV	0.062	0.128	0.404	0.631	-0.002	0.991	0.991	0.218	0.148	0.650
	CA4 & DG	0.057	0.068	0.655	0.733	0.226	0.145	0.334	-0.083	0.579	0.847
	CA4 & DG / TIC	0.139	0.275	0.065§	0.421	0.318	0.034*	0.238	0.055	0.697	0.847
	CA4 & DG / WBV	0.084	0.201	0.187	0.421	0.224	0.142	0.334	0.127	0.390	0.847
	Subiculum	0.051	0.101	0.513	0.649	0.095	0.539	0.834	-0.184	0.222	0.777
	Subiculum / TIC	0.056	0.224	0.149	0.421	0.095	0.535	0.834	-0.071	0.632	0.851
	Subiculum / WBV	0.035	0.189	0.226	0.465	0.041	0.791	0.972	-0.030	0.841	0.905
	SR SL SM	0.012	0.059	0.705	0.733	0.003	0.984	0.991	-0.088	0.564	0.847
	SR SL SM / TIC	0.044	0.208	0.181	0.421	0.002	0.989	0.991	0.027	0.859	0.905
	SR SL SM / WBV	0.040	0.160	0.303	0.510	-0.064	0.678	0.911	0.077	0.610	0.850
Right	Whole HC	0.134	0.092	0.529	0.649	0.248	0.097§	0.333	-0.266	0.067§	0.521
	Whole HC / TIC	0.184	0.301	0.039*	0.275	0.323	0.027*	0.225	-0.168	0.231	0.777
	Whole HC / WBV	0.099	0.239	0.115	0.410	0.235	0.121	0.334	-0.098	0.503	0.847
	CA1	0.139	0.101	0.492	0.649	0.245	0.099§	0.333	-0.276	0.058	0.521
	CA1 / TIC	0.191	0.296	0.042*	0.275	0.314	0.031*	0.225	-0.202	0.149	0.650
	CA1 / WBV	0.114	0.240	0.111	0.410	0.240	0.110	0.333	-0.143	0.324	0.847
	CA2 & CA3	0.036	0.053	0.733	0.733	0.165	0.288	0.536	-0.092	0.542	0.847
	CA2 & CA3 / TIC	0.040	0.125	0.420	0.631	0.183	0.240	0.495	-0.033	0.827	0.905

CA2 & CA3 / WBV	0.024	0.094	0.548	0.649	0.144	0.356	0.633	-0.001	0.994	0.997
CA4 & DG	0.119	0.054	0.717	0.733	0.242	0.107	0.333	-0.247	0.092	0.521
CA4 & DG / TIC	0.133	0.220	0.139	0.322	0.299	0.047	0.225	-0.147	0.308	0.878
CA4 & DG / WBV	0.064	0.155	0.313	0.510	0.217	0.159	0.346	-0.081	0.586	0.847
Subiculum	0.021	0.101	0.517	0.649	0.030	0.845	0.981	-0.102	0.501	0.847
Subiculum / TIC	0.039	0.203	0.194	0.421	0.027	0.860	0.981	-0.001	0.997	0.997
Subiculum / WBV	0.031	0.166	0.288	0.510	-0.023	0.880	0.981	0.035	0.819	0.905
SR SL SM	0.120	0.058	0.693	0.733	0.242	0.107	0.333	-0.248	0.091§	0.521
SR SL SM / TIC	0.134	0.207	0.164	0.421	0.296	0.048*	0.238	-0.164	0.256	0.777
SR SL SM / WBV	0.077	0.163	0.284	0.510	0.230	0.134	0.334	-0.113	0.446	0.847

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1 neutral or positive); Sex (0: male, 1: female); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 36

Multiple regression summary table for hippocampal surface area outcomes in the early life maternal stress (ELMS) cohort

Hemisphere	Structure		Storm24			CONSEQ			Sex		
		R^2	β	p-value	q-value	β	p-value	q-value	β	p-value	q-value
Left	HC Surface Area	0.082	0.075	0.619	0.728	0.213	0.163	0.407	-0.191	0.199	0.288
	HC Surface Area / TIC	0.227	0.437	0.003**	0.011*	0.309	0.030*	0.121	0.059	0.662	0.779
	HC Surface Area / WBV	0.112	0.290	0.056§	0.102	0.118	0.430	0.595	0.186	0.202	0.288
Right	HC Surface Area	0.011	0.020	0.897	0.897	0.105	0.506	0.595	0.024	0.875	0.875
	HC Surface Area /TIC	0.187	0.309	0.034*	0.086§	0.121	0.398	0.595	0.320	0.025*	0.062§
	HC Surface Area / WBV	0.183	0.176	0.221	0.316	-0.033	0.816	0.816	0.391	0.007**	0.028*

§p / q < .1; *p / q < .05; **p / q < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive)
Sex (0: male, 1: female); HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 37

Summary of hierarchical regression analysis for variables predicting left hippocampal surface area normalized to total intracranial volume in the early life maternal stress sample. n = 47

Variable	β	B	SE	p	q	R^2	ΔR^2
Step 1						0.134	0.134
Objective Hardship (STORM24)	0.366	0.0003	0.0001	0.012*	-		
Step 2						0.223	0.090
Objective Hardship (STORM24)	0.435	0.0005	0.0001	0.003**	-		
Cognitive Appraisal (CONSEQ)	0.307	0.003	0.001	0.029*	-		
Step 3						0.227	0.003
Objective Hardship (STORM24)	0.437	0.0005	0.0001	0.003**	0.011*		
Cognitive Appraisal (CONSEQ)	0.309	0.003	0.001	0.030*	0.121		
Sex	0.059	0.001	0.001	0.662	0.779		

§p / q < .1; *p / q < .05; **p / q < .01

Note. Cognitive Appraisal (0: negative, 1: neutral or positive); Sex (0: male, 1: female)

Table 38

Results of t-tests for left and right hippocampal volume by group

	Structure	Group						95% CI for Mean Difference			
		Prenatal Maternal Stress			Early Life Maternal Stress						
		M	SD	n	M	SD	n	lower	upper	t	df
Raw volume (mm^3)	Total Left HC	2419.863	234.554	51	2394.826	237.490	47	-69.670	119.745	0.525	96
	Left CA1	743.118	78.669	51	724.174	77.579	47	-12.423	50.309	1.199	96
	Left CA2 CA3	154.176	22.555	51	153.915	22.812	47	-8.841	9.364	0.057	96
	Left CA4 & DG	630.843	69.029	51	639.872	69.428	47	-36.812	18.753	-0.645	96
	Left Subiculum	320.471	42.279	51	317.672	46.701	47	-15.043	20.640	0.311	96
	Left SR SL SM	571.255	66.829	51	559.191	69.128	47	-15.205	39.332	0.878	96
	Total Right HC	2471.588	229.975	51	2443.557	254.106	47	-69.034	125.096	0.573	96
	Right CA1	724.647	77.866	51	704.285	82.994	47	-11.893	52.617	1.253	96
	Right CA2 & CA3	150.627	25.826	51	145.434	31.193	47	-6.255	16.642	0.900	96
	Right CA4 & DG	655.157	71.150	51	659.596	72.641	47	-33.284	24.406	-0.305	96
	Right Subiculum	337.275	49.347	51	341.553	51.091	47	-24.423	15.866	-0.422	96
	Right SR SL SM	603.882	66.253	51	592.689	75.654	47	-17.269	39.655	0.781	96
Volume normalized to TIC	Total Left HC / TIC	0.171	0.016	51	0.168	0.013	47	-0.003	0.009	1.081	96
	Left CA1 / TIC	0.053	0.005	51	0.051	0.004	47	0.000	0.004	1.789§	96
	Left CA2 CA3 / TIC	0.011	0.002	51	0.011	0.001	47	0.000	0.001	0.434	96
	Left CA4 & DG / TIC	0.045	0.005	51	0.045	0.004	47	-0.002	0.002	-0.204	96
	Left Subiculum / TIC	0.023	0.003	51	0.022	0.003	47	-0.001	0.002	0.569	96
	Left SR SL SM / TIC	0.040	0.005	51	0.039	0.004	47	-0.001	0.003	1.351	96
	Total Right HC / TIC	0.175	0.016	51	0.172	0.014	47	-0.003	0.009	1.148	96
	Right CA1 / TIC	0.051	0.005	51	0.049	0.004	47	0.000	0.004	1.903*	96
	Right CA2 & CA3 / TIC	0.011	0.002	51	0.010	0.002	47	0.000	0.001	1.234	96
	Right CA4 & DG / TIC	0.046	0.005	51	0.046	0.004	47	-0.002	0.002	0.109	96
	Right Subiculum / TIC	0.024	0.003	51	0.024	0.004	47	-0.002	0.001	-0.228	96
	Right SR SL SM / TIC	0.043	0.005	51	0.042	0.004	47	-0.001	0.003	1.294	96
Volume normalized to WBV	Total Left HC / WBV	0.187	0.018	51	0.182	0.014	47	-.0011	.0120	1.6418	96
	Left CA1 / WBV	0.058	0.006	51	0.055	0.005	47	.0003	.0046	2.282*	96
	Left CA2 CA3 / WBV	0.012	0.002	51	0.012	0.001	47	-.0004	.0010	.7865	96
	Left CA4 & DG / WBV	0.049	0.006	51	0.049	0.004	47	-.0017	.0022	.2626	96
	Left Subiculum / WBV	0.025	0.003	51	0.024	0.003	47	-.0007	.0020	.9573	96
	Left SR SL SM / WBV	0.044	0.005	51	0.042	0.004	47	-.0002	.0037	1.795§	96
	Total Right HC / WBV	0.191	0.018	51	0.186	0.014	47	-.0008	.0124	1.751§	96

Right CA1 / WBV	0.056	0.006	51	0.053	0.005	47	.0005	.0048	2.444*	96
Right CA2 & CA3 / WBV	0.012	0.002	51	0.011	0.002	47	-.0002	.0014	1.4809	96
Right CA4 & DG / WBV	0.051	0.006	51	0.050	0.004	47	-.0014	.0026	.5873	96
Right Subiculum / WBV	0.026	0.004	51	0.026	0.004	47	-.0015	.0019	.2068	96
Right SR SL SM / WBV	0.047	0.005	51	0.045	0.005	47	-.0002	.0037	1.816§	96

§p < .1; *p < .05

Note. HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 39

Results of t-tests for global left and right hippocampal surface area by group

Hemisphere	Structure	Group						95% CI for Mean Difference			
		Prenatal Maternal Stress			Early Life Maternal Stress						
		M	SD	n	M	SD	n	lower	upper	t	df
Left	HC Surface Area (mm^2)	1675.591	95.938	51	1653.630	103.959	47	-18.120	62.042	1.088	96
	HC Surface Area / TIC	1734.148	110.011	51	1697.115	98.656	47	5.650E-05	0.005	2.032*	96
	HC Surface Area / WBV	0.119	0.007	51	0.116	0.005	47	0.001	0.007	2.749**	96
Right	HC Surface Area (mm^2)	0.123	0.008	51	0.119	0.006	47	-5.000	79.064	1.749§	96
	HC Surface Area /TIC	0.130	0.008	51	0.126	0.006	47	0.001	0.006	2.416*	96
	HC Surface Area / WBV	0.134	0.010	51	0.129	0.007	47	0.002	0.009	2.942**	96

§p < .1; *p < .05; **p < .01

Note. HC: Hippocampus; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 40

Pearson's correlation coefficients between predictors and hippocampal measures for boys in the prenatal maternal stress cohort.

Variables		Storm32	Storm24	IESR_log	CONSEQ
Storm32	Pearson Correlation	1	.940**	.270	-.511*
	Sig. (2-tailed)	-	3.24E-12	.192	.011
	N	25	25	25	24
Storm24	Pearson Correlation	.940**	1	.098	-.405*
	Sig. (2-tailed)	3.24E-12	-	.640	.049
	N	25	25	25	24
IESR_log	Pearson Correlation	.270	.098	1	-.236
	Sig. (2-tailed)	.192	.640	-	.266
	N	25	25	25	24
CONSEQ	Pearson Correlation	-.511*	-.405*	-.236	1
	Sig. (2-tailed)	.011	.049	.266	-
	N	24	24	24	24
Total Intracranial Volume (TIC)	Pearson Correlation	-.006	-.082	.031	.195
	Sig. (2-tailed)	.979	.696	.885	.362
	N	25	25	25	24
Whole Brain Volume (WBV)	Pearson Correlation	-.184	-.226	-.105	-.013
	Sig. (2-tailed)	.380	.277	.619	.950
	N	25	25	25	24
Left HC Surface Area	Pearson Correlation	-.062	-.108	.050	.040
	Sig. (2-tailed)	.767	.607	.813	.852
	N	25	25	25	24
Right HC Surface Area	Pearson Correlation	.017	-.070	.182	.030
	Sig. (2-tailed)	.936	.740	.383	.889
	N	25	25	25	24
Left HC Surface Area / TIC	Pearson Correlation	-.069	-.015	.026	-.208
	Sig. (2-tailed)	.744	.944	.903	.329
	N	25	25	25	24
Right HC Surface Area / TIC	Pearson Correlation	.014	.008	.170	-.186
	Sig. (2-tailed)	.947	.968	.415	.385
	N	25	25	25	24
Left HC Surface Area / WBV	Pearson Correlation	.180	.187	.176	.068
	Sig. (2-tailed)	.389	.371	.400	.753
	N	25	25	25	24
Right HC Surface Area / WBV	Pearson Correlation	.216	.182	.272	.051
	Sig. (2-tailed)	.299	.384	.189	.812
	N	25	25	25	24
Total Left HC	Pearson Correlation	-.080	-.154	.259	.099
	Sig. (2-tailed)	.702	.462	.212	.644
	N	25	25	25	24
Left CA1	Pearson Correlation	-.120	-.131	.260	.168
	Sig. (2-tailed)	.568	.532	.209	.432
	N	25	25	25	24
Left CA2 CA3	Pearson Correlation	-.123	-.275	.234	.070
	Sig. (2-tailed)	.558	.184	.260	.746
	N	25	25	25	24
Left CA4 & DG	Pearson Correlation	-.051	-.193	.158	-.085
	Sig. (2-tailed)	.810	.356	.451	.694
	N	25	25	25	24

Left Subiculum	Pearson Correlation	.007	.078	.053	.180
	Sig. (2-tailed)	.972	.712	.802	.399
	N	25	25	25	24
Left SR SL SM	Pearson Correlation	-.045	-.124	.318	.117
	Sig. (2-tailed)	.831	.555	.121	.587
	N	25	25	25	24
Total Right HC	Pearson Correlation	-.056	-.038	.008	.132
	Sig. (2-tailed)	.790	.855	.971	.539
	N	25	25	25	24
Right CA1	Pearson Correlation	-.048	.044	.036	.249
	Sig. (2-tailed)	.820	.834	.866	.241
	N	25	25	25	24
Right CA2 & CA3	Pearson Correlation	-.357	-.340	-.367	.008
	Sig. (2-tailed)	.080	.096	.071	.969
	N	25	25	25	24
Right CA4 & DG	Pearson Correlation	.012	-.084	.077	-.112
	Sig. (2-tailed)	.954	.691	.714	.604
	N	25	25	25	24
Right Subiculum	Pearson Correlation	.188	.176	.131	.247
	Sig. (2-tailed)	.367	.399	.533	.244
	N	25	25	25	24
Right SR SL SM	Pearson Correlation	-.143	-.082	-.049	.090
	Sig. (2-tailed)	.497	.698	.815	.674
	N	25	25	25	24
Total Left HC / TIC	Pearson Correlation	-.090	-.114	.266	-.031
	Sig. (2-tailed)	.670	.587	.199	.887
	N	25	25	25	24
Left CA1 / TIC	Pearson Correlation	-.137	-.102	.272	.060
	Sig. (2-tailed)	.513	.627	.188	.781
	N	25	25	25	24
Left CA2 CA3 / TIC	Pearson Correlation	-.144	-.275	.261	-.022
	Sig. (2-tailed)	.491	.183	.207	.919
	N	25	25	25	24
Left CA4 & DG / TIC	Pearson Correlation	-.047	-.151	.165	-.202
	Sig. (2-tailed)	.823	.471	.432	.343
	N	25	25	25	24
Left Subiculum / TIC	Pearson Correlation	-.008	.097	.035	.062
	Sig. (2-tailed)	.971	.646	.870	.773
	N	25	25	25	24
Left SR SL SM / TIC	Pearson Correlation	-.046	-.083	.331	.003
	Sig. (2-tailed)	.829	.692	.106	.990
	N	25	25	25	24
Total Right HC / TIC	Pearson Correlation	-.056	.017	.000	-.009
	Sig. (2-tailed)	.791	.936	.999	.968
	N	25	25	25	24
Right CA1 / TIC	Pearson Correlation	-.045	.089	.036	.133
	Sig. (2-tailed)	.833	.672	.866	.536
	N	25	25	25	24
Right CA2 & CA3 / TIC	Pearson Correlation	-.381	-.331	-.400*	-.070
	Sig. (2-tailed)	.060	.106	.048	.743
	N	25	25	25	24
Right CA4 & DG / TIC	Pearson Correlation	.019	-.038	.083	-.229

	Sig. (2-tailed)	.927	.856	.695	.281
	N	25	25	25	24
Right Subiculum / TIC	Pearson Correlation	.190	.212	.125	.173
	Sig. (2-tailed)	.364	.308	.550	.418
	N	25	25	25	24
Right SR SL SM / TIC	Pearson Correlation	-.137	-.034	-.058	-.035
	Sig. (2-tailed)	.513	.870	.784	.869
	N	25	25	25	24
Total Left HC / WBV	Pearson Correlation	.076	.030	.357	.121
	Sig. (2-tailed)	.718	.886	.080	.572
	N	25	25	25	24
Left CA1 / WBV	Pearson Correlation	.014	.028	.359	.201
	Sig. (2-tailed)	.946	.893	.078	.345
	N	25	25	25	24
Left CA2 CA3 / WBV	Pearson Correlation	-.009	-.137	.284	.078
	Sig. (2-tailed)	.966	.514	.168	.717
	N	25	25	25	24
Left CA4 & DG / WBV	Pearson Correlation	.091	-.037	.269	-.080
	Sig. (2-tailed)	.664	.860	.194	.711
	N	25	25	25	24
Left Subiculum / WBV	Pearson Correlation	.110	.184	.112	.162
	Sig. (2-tailed)	.600	.379	.594	.449
	N	25	25	25	24
Left SR SL SM / WBV	Pearson Correlation	.095	.039	.400*	.130
	Sig. (2-tailed)	.652	.853	.048	.544
	N	25	25	25	24
Total Right HC / WBV	Pearson Correlation	.111	.155	.107	.146
	Sig. (2-tailed)	.598	.460	.609	.496
	N	25	25	25	24
Right CA1 / WBV	Pearson Correlation	.092	.197	.121	.247
	Sig. (2-tailed)	.660	.345	.563	.245
	N	25	25	25	24
Right CA2 & CA3 / WBV	Pearson Correlation	-.373	-.322	-.416*	.000
	Sig. (2-tailed)	.066	.116	.039	1.000
	N	25	25	25	24
Right CA4 & DG / WBV	Pearson Correlation	.165	.087	.182	-.105
	Sig. (2-tailed)	.430	.681	.385	.626
	N	25	25	25	24
Right Subiculum / WBV	Pearson Correlation	.226	.221	.150	.208
	Sig. (2-tailed)	.277	.288	.475	.329
	N	25	25	25	24
Right SR SL SM / WBV	Pearson Correlation	-.006	.084	.028	.093
	Sig. (2-tailed)	.978	.690	.893	.665
	N	25	25	25	24

*p < .05; **p < .01

Note. Storm32: Objective Hardship questionnaire (full); Storm24: Objective Hardship questionnaire (partial); IES-R: Impact of Event Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 41

Pearson's correlation coefficients between predictors and hippocampal measures for girls in the prenatal maternal stress cohort

Variables		Storm32	Storm24	IESR_log	CONSEQ
Storm32	Pearson Correlation	1	.941**	.303	-.178
	Sig. (2-tailed)	-	8.69E-13	.132	.384
	N	26	26	26	26
Storm24	Pearson Correlation	.941**	1	.342	-.015
	Sig. (2-tailed)	8.69E-13	-	.087	.943
	N	26	26	26	26
IESR_log	Pearson Correlation	.303	.342	1	-.221
	Sig. (2-tailed)	.132	.087	-	.277
	N	26	26	26	26
CONSEQ	Pearson Correlation	-.178	-.015	-.221	1
	Sig. (2-tailed)	.384	.943	.277	-
	N	26	26	26	26
Total Intracranial Volume (TIC)	Pearson Correlation	-.146	.004	-.034	.155
	Sig. (2-tailed)	.476	.983	.870	.449
	N	26	26	26	26
Whole Brain Volume (WBV)	Pearson Correlation	-.143	-.013	-.002	.053
	Sig. (2-tailed)	.486	.949	.992	.796
	N	26	26	26	26
Left HC Surface Area	Pearson Correlation	.136	.348	.099	.360
	Sig. (2-tailed)	.508	.081	.630	.071
	N	26	26	26	26
Right HC Surface Area	Pearson Correlation	.122	.278	.145	.286
	Sig. (2-tailed)	.552	.169	.479	.157
	N	26	26	26	26
Left HC Surface Area / TIC	Pearson Correlation	.290	.355	.117	.227
	Sig. (2-tailed)	.150	.075	.570	.265
	N	26	26	26	26
Right HC Surface Area / TIC	Pearson Correlation	.261	.283	.156	.153
	Sig. (2-tailed)	.198	.162	.447	.456
	N	26	26	26	26
Left HC Surface Area / WBV	Pearson Correlation	.277	.353	.084	.298
	Sig. (2-tailed)	.171	.077	.683	.139
	N	26	26	26	26
Right HC Surface Area / WBV	Pearson Correlation	.248	.283	.123	.219
	Sig. (2-tailed)	.222	.161	.549	.283
	N	26	26	26	26
Total Left HC	Pearson Correlation	.176	.340	.168	.404*
	Sig. (2-tailed)	.390	.089	.412	.041
	N	26	26	26	26
Left CA1	Pearson Correlation	.206	.363	.170	.352
	Sig. (2-tailed)	.314	.069	.406	.078
	N	26	26	26	26
Left CA2 CA3	Pearson Correlation	.001	.029	-.173	.215
	Sig. (2-tailed)	.996	.890	.398	.293
	N	26	26	26	26
Left CA4 & DG	Pearson Correlation	.121	.261	.075	.410*
	Sig. (2-tailed)	.555	.197	.717	.038
	N	26	26	26	26

Left Subiculum	Pearson Correlation	.221	.414*	.290	.349
	Sig. (2-tailed)	.278	.035	.151	.081
	N	26	26	26	26
Left SR SL SM	Pearson Correlation	.111	.224	.179	.288
	Sig. (2-tailed)	.590	.271	.380	.153
	N	26	26	26	26
Total Right HC	Pearson Correlation	.109	.316	.122	.421*
	Sig. (2-tailed)	.594	.116	.554	.032
	N	26	26	26	26
Right CA1	Pearson Correlation	.106	.292	.028	.433*
	Sig. (2-tailed)	.605	.148	.890	.027
	N	26	26	26	26
Right CA2 & CA3	Pearson Correlation	-.088	-.017	-.077	.088
	Sig. (2-tailed)	.668	.935	.708	.671
	N	26	26	26	26
Right CA4 & DG	Pearson Correlation	.159	.336	.122	.328
	Sig. (2-tailed)	.438	.094	.553	.102
	N	26	26	26	26
Right Subiculum	Pearson Correlation	.152	.330	.291	.422*
	Sig. (2-tailed)	.458	.100	.149	.032
	N	26	26	26	26
Right SR SL SM	Pearson Correlation	.018	.195	.083	.306
	Sig. (2-tailed)	.929	.340	.688	.128
	N	26	26	26	26
Total Left HC / TIC	Pearson Correlation	.272	.350	.178	.323
	Sig. (2-tailed)	.180	.080	.384	.108
	N	26	26	26	26
Left CA1 / TIC	Pearson Correlation	.320	.395*	.197	.289
	Sig. (2-tailed)	.111	.046	.334	.153
	N	26	26	26	26
Left CA2 CA3 / TIC	Pearson Correlation	.061	.042	-.155	.147
	Sig. (2-tailed)	.768	.837	.450	.473
	N	26	26	26	26
Left CA4 & DG / TIC	Pearson Correlation	.192	.254	.073	.317
	Sig. (2-tailed)	.346	.210	.725	.115
	N	26	26	26	26
Left Subiculum / TIC	Pearson Correlation	.335	.490*	.389*	.338
	Sig. (2-tailed)	.094	.011	.050	.091
	N	26	26	26	26
Left SR SL SM / TIC	Pearson Correlation	.190	.235	.180	.224
	Sig. (2-tailed)	.353	.249	.379	.270
	N	26	26	26	26
Total Right HC / TIC	Pearson Correlation	.206	.327	.130	.352
	Sig. (2-tailed)	.313	.103	.526	.078
	N	26	26	26	26
Right CA1 / TIC	Pearson Correlation	.210	.326	.039	.399*
	Sig. (2-tailed)	.304	.104	.850	.043
	N	26	26	26	26
Right CA2 & CA3 / TIC	Pearson Correlation	-.037	-.013	-.100	.056
	Sig. (2-tailed)	.858	.950	.626	.784
	N	26	26	26	26
Right CA4 & DG / TIC	Pearson Correlation	.231	.325	.120	.251

	Sig. (2-tailed)	.257	.105	.559	.217
	N	26	26	26	26
Right Subiculum / TIC	Pearson Correlation	.234	.360	.352	.387
	Sig. (2-tailed)	.249	.070	.078	.051
	N	26	26	26	26
Right SR SL SM / TIC	Pearson Correlation	.095	.197	.074	.251
	Sig. (2-tailed)	.645	.335	.718	.217
	N	26	26	26	26
Total Left HC / WBV	Pearson Correlation	.271	.357	.158	.371
	Sig. (2-tailed)	.180	.073	.442	.062
	N	26	26	26	26
Left CA1 / WBV	Pearson Correlation	.321	.406*	.176	.343
	Sig. (2-tailed)	.110	.040	.389	.086
	N	26	26	26	26
Left CA2 CA3 / WBV	Pearson Correlation	.062	.050	-.164	.172
	Sig. (2-tailed)	.765	.810	.423	.402
	N	26	26	26	26
Left CA4 & DG / WBV	Pearson Correlation	.192	.260	.056	.354
	Sig. (2-tailed)	.346	.199	.784	.076
	N	26	26	26	26
Left Subiculum / WBV	Pearson Correlation	.339	.501**	.372	.382
	Sig. (2-tailed)	.090	.009	.062	.054
	N	26	26	26	26
Left SR SL SM / WBV	Pearson Correlation	.194	.246	.162	.269
	Sig. (2-tailed)	.342	.225	.429	.184
	N	26	26	26	26
Total Right HC / WBV	Pearson Correlation	.205	.334	.110	.403*
	Sig. (2-tailed)	.315	.096	.593	.041
	N	26	26	26	26
Right CA1 / WBV	Pearson Correlation	.208	.332	.022	.454*
	Sig. (2-tailed)	.307	.097	.917	.020
	N	26	26	26	26
Right CA2 & CA3 / WBV	Pearson Correlation	-.034	-.004	-.101	.088
	Sig. (2-tailed)	.869	.986	.623	.669
	N	26	26	26	26
Right CA4 & DG / WBV	Pearson Correlation	.229	.331	.106	.290
	Sig. (2-tailed)	.260	.099	.606	.151
	N	26	26	26	26
Right Subiculum / WBV	Pearson Correlation	.238	.369	.338	.414*
	Sig. (2-tailed)	.242	.064	.091	.036
	N	26	26	26	26
Right SR SL SM / WBV	Pearson Correlation	.096	.206	.058	.300
	Sig. (2-tailed)	.639	.311	.777	.137
	N	26	26	26	26

*p < .05; **p < .01

Note. Storm32: Objective Hardship questionnaire (full); Storm24: Objective Hardship questionnaire (partial); IES-R: Impact of Event Scale Revised; CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 42

Pearson's correlation coefficients between predictors and hippocampal measures for boys in the early life maternal stress cohort

Variables		Storm24	CONSEQ
Storm24	Pearson Correlation	1	-.303
	Sig. (2-tailed)	-	.150
	N	24	24
CONSEQ	Pearson Correlation	-.303	1
	Sig. (2-tailed)	.150	-
	N	24	24
Total Intracranial Volume (TIC)	Pearson Correlation	-.340	.325
	Sig. (2-tailed)	.104	.121
	N	24	24
Whole Brain Volume (WBV)	Pearson Correlation	-.300	.389
	Sig. (2-tailed)	.155	.060
	N	24	24
Left HC Surface Area	Pearson Correlation	-.111	.342
	Sig. (2-tailed)	.606	.102
	N	24	24
Right HC Surface Area	Pearson Correlation	-.230	.105
	Sig. (2-tailed)	.279	.626
	N	24	24
Left HC Surface Area / TIC	Pearson Correlation	.340	.018
	Sig. (2-tailed)	.104	.935
	N	24	24
Right HC Surface Area / TIC	Pearson Correlation	.158	-.301
	Sig. (2-tailed)	.462	.153
	N	24	24
Left HC Surface Area / WBV	Pearson Correlation	.295	-.116
	Sig. (2-tailed)	.162	.590
	N	24	24
Right HC Surface Area / WBV	Pearson Correlation	.114	-.360
	Sig. (2-tailed)	.595	.084
	N	24	24
Total Left HC	Pearson Correlation	-.096	.116
	Sig. (2-tailed)	.656	.589
	N	24	24
Left CA1	Pearson Correlation	-.056	-.037
	Sig. (2-tailed)	.796	.864
	N	24	24
Left CA2 CA3	Pearson Correlation	.204	.009
	Sig. (2-tailed)	.339	.968
	N	24	24
Left CA4 & DG	Pearson Correlation	-.043	.318
	Sig. (2-tailed)	.841	.130
	N	24	24
Left Subiculum	Pearson Correlation	-.232	.093
	Sig. (2-tailed)	.274	.665
	N	24	24
Left SR SL SM	Pearson Correlation	-.106	.044

	Sig. (2-tailed)	.623	.838
	N	24	24
Total Right HC	Pearson Correlation	-.034	.411*
	Sig. (2-tailed)	.876	.046
	N	24	24
Right CA1	Pearson Correlation	-.037	.431*
	Sig. (2-tailed)	.864	.035
	N	24	24
Right CA2 & CA3	Pearson Correlation	.111	.190
	Sig. (2-tailed)	.604	.375
	N	24	24
Right CA4 & DG	Pearson Correlation	-.011	.433*
	Sig. (2-tailed)	.958	.035
	N	24	24
Right Subiculum	Pearson Correlation	.013	-.008
	Sig. (2-tailed)	.952	.972
	N	24	24
Right SR SL SM	Pearson Correlation	-.115	.390
	Sig. (2-tailed)	.592	.060
	N	24	24
Total Left HC / TIC	Pearson Correlation	.153	-.120
	Sig. (2-tailed)	.477	.576
	N	24	24
Left CA1 / TIC	Pearson Correlation	.171	-.277
	Sig. (2-tailed)	.425	.190
	N	24	24
Left CA2 CA3 / TIC	Pearson Correlation	.337	-.122
	Sig. (2-tailed)	.108	.571
	N	24	24
Left CA4 & DG / TIC	Pearson Correlation	.184	.146
	Sig. (2-tailed)	.390	.495
	N	24	24
Left Subiculum / TIC	Pearson Correlation	-.111	-.028
	Sig. (2-tailed)	.605	.898
	N	24	24
Left SR SL SM / TIC	Pearson Correlation	.068	-.135
	Sig. (2-tailed)	.753	.529
	N	24	24
Total Right HC / TIC	Pearson Correlation	.240	.278
	Sig. (2-tailed)	.258	.189
	N	24	24
Right CA1 / TIC	Pearson Correlation	.225	.326
	Sig. (2-tailed)	.292	.120
	N	24	24
Right CA2 & CA3 / TIC	Pearson Correlation	.223	.096
	Sig. (2-tailed)	.294	.654
	N	24	24
Right CA4 & DG / TIC	Pearson Correlation	.192	.293
	Sig. (2-tailed)	.369	.165
	N	24	24

Right Subiculum / TIC	Pearson Correlation	.154	-.128
	Sig. (2-tailed)	.473	.550
	N	24	24
Right SR SL SM / TIC	Pearson Correlation	.073	.295
	Sig. (2-tailed)	.734	.161
	N	24	24
Total Left HC / WBV	Pearson Correlation	.127	-.180
	Sig. (2-tailed)	.555	.399
	N	24	24
Left CA1 / WBV	Pearson Correlation	.146	-.321
	Sig. (2-tailed)	.497	.127
	N	24	24
Left CA2 CA3 / WBV	Pearson Correlation	.330	-.165
	Sig. (2-tailed)	.115	.442
	N	24	24
Left CA4 & DG / WBV	Pearson Correlation	.165	.079
	Sig. (2-tailed)	.442	.713
	N	24	24
Left Subiculum / WBV	Pearson Correlation	-.119	-.064
	Sig. (2-tailed)	.578	.767
	N	24	24
Left SR SL SM / WBV	Pearson Correlation	.057	-.174
	Sig. (2-tailed)	.793	.416
	N	24	24
Total Right HC / WBV	Pearson Correlation	.227	.197
	Sig. (2-tailed)	.287	.357
	N	24	24
Right CA1 / WBV	Pearson Correlation	.212	.254
	Sig. (2-tailed)	.320	.232
	N	24	24
Right CA2 & CA3 / WBV	Pearson Correlation	.219	.065
	Sig. (2-tailed)	.303	.763
	N	24	24
Right CA4 & DG / WBV	Pearson Correlation	.181	.238
	Sig. (2-tailed)	.398	.262
	N	24	24
Right Subiculum / WBV	Pearson Correlation	.141	-.164
	Sig. (2-tailed)	.512	.445
	N	24	24
Right SR SL SM / WBV	Pearson Correlation	.069	.228
	Sig. (2-tailed)	.748	.284
	N	24	24

*p < .05; **p < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume

Table 43

Pearson's correlation coefficients between predictors and hippocampal measures for girls in the early life maternal stress cohort

Variables		Storm24	CONSEQ
Storm24	Pearson Correlation	1	-.157
	Sig. (2-tailed)	-	.476
	N	23	23
CONSEQ	Pearson Correlation	-.157	1
	Sig. (2-tailed)	.476	-
	N	23	23
Total Intracranial Volume (TIC)	Pearson Correlation	-.134	-.200
	Sig. (2-tailed)	.542	.360
	N	23	23
Whole Brain Volume (WBV)	Pearson Correlation	-.030	-.086
	Sig. (2-tailed)	.892	.695
	N	23	23
Left HC Surface Area	Pearson Correlation	.140	.073
	Sig. (2-tailed)	.524	.742
	N	23	23
Right HC Surface Area	Pearson Correlation	.190	.095
	Sig. (2-tailed)	.386	.665
	N	23	23
Left HC Surface Area / TIC	Pearson Correlation	.389	.375
	Sig. (2-tailed)	.067	.078
	N	23	23
Right HC Surface Area / TIC	Pearson Correlation	.402	.355
	Sig. (2-tailed)	.058	.096
	N	23	23
Left HC Surface Area / WBV	Pearson Correlation	.244	.206
	Sig. (2-tailed)	.262	.346
	N	23	23
Right HC Surface Area / WBV	Pearson Correlation	.275	.201
	Sig. (2-tailed)	.205	.358
	N	23	23
Total Left HC	Pearson Correlation	.217	-.017
	Sig. (2-tailed)	.319	.937
	N	23	23
Left CA1	Pearson Correlation	.240	-.145
	Sig. (2-tailed)	.270	.510
	N	23	23
Left CA2 CA3	Pearson Correlation	-.091	.046
	Sig. (2-tailed)	.679	.835
	N	23	23
Left CA4 & DG	Pearson Correlation	.064	.122
	Sig. (2-tailed)	.772	.579
	N	23	23
Left Subiculum	Pearson Correlation	.455*	.048
	Sig. (2-tailed)	.029	.827
	N	23	23
Left SR SL SM	Pearson Correlation	.196	-.060

	Sig. (2-tailed)	.371	.785
	N	23	23
Total Right HC	Pearson Correlation	.096	.078
	Sig. (2-tailed)	.663	.723
	N	23	23
Right CA1	Pearson Correlation	.111	.067
	Sig. (2-tailed)	.615	.761
	N	23	23
Right CA2 & CA3	Pearson Correlation	-.060	.124
	Sig. (2-tailed)	.784	.572
	N	23	23
Right CA4 & DG	Pearson Correlation	.008	.030
	Sig. (2-tailed)	.970	.892
	N	23	23
Right Subiculum	Pearson Correlation	.171	.023
	Sig. (2-tailed)	.434	.917
	N	23	23
Right SR SL SM	Pearson Correlation	.105	.092
	Sig. (2-tailed)	.634	.675
	N	23	23
Total Left HC / TIC	Pearson Correlation	.425*	.142
	Sig. (2-tailed)	.043	.520
	N	23	23
Left CA1 / TIC	Pearson Correlation	.414*	-.048
	Sig. (2-tailed)	.050	.827
	N	23	23
Left CA2 CA3 / TIC	Pearson Correlation	-.030	.207
	Sig. (2-tailed)	.894	.343
	N	23	23
Left CA4 & DG / TIC	Pearson Correlation	.222	.371
	Sig. (2-tailed)	.309	.081
	N	23	23
Left Subiculum / TIC	Pearson Correlation	.477*	.114
	Sig. (2-tailed)	.021	.603
	N	23	23
Left SR SL SM / TIC	Pearson Correlation	.338	.047
	Sig. (2-tailed)	.114	.831
	N	23	23
Total Right HC / TIC	Pearson Correlation	.225	.245
	Sig. (2-tailed)	.302	.259
	N	23	23
Right CA1 / TIC	Pearson Correlation	.236	.201
	Sig. (2-tailed)	.279	.357
	N	23	23
Right CA2 & CA3 / TIC	Pearson Correlation	-.029	.207
	Sig. (2-tailed)	.896	.344
	N	23	23
Right CA4 & DG / TIC	Pearson Correlation	.116	.205
	Sig. (2-tailed)	.598	.348
	N	23	23

Right Subiculum / TIC	Pearson Correlation	.233	.085
	Sig. (2-tailed)	.284	.700
	N	23	23
Right SR SL SM / TIC	Pearson Correlation	.193	.221
	Sig. (2-tailed)	.377	.310
	N	23	23
Total Left HC / WBV	Pearson Correlation	.364	.055
	Sig. (2-tailed)	.088	.805
	N	23	23
Left CA1 / WBV	Pearson Correlation	.355	-.124
	Sig. (2-tailed)	.096	.571
	N	23	23
Left CA2 CA3 / WBV	Pearson Correlation	-.115	.154
	Sig. (2-tailed)	.602	.482
	N	23	23
Left CA4 & DG / WBV	Pearson Correlation	.139	.291
	Sig. (2-tailed)	.528	.179
	N	23	23
Left Subiculum / WBV	Pearson Correlation	.443*	.058
	Sig. (2-tailed)	.034	.792
	N	23	23
Left SR SL SM / WBV	Pearson Correlation	.300	-.017
	Sig. (2-tailed)	.164	.939
	N	23	23
Total Right HC / WBV	Pearson Correlation	.155	.170
	Sig. (2-tailed)	.479	.438
	N	23	23
Right CA1 / WBV	Pearson Correlation	.172	.140
	Sig. (2-tailed)	.434	.525
	N	23	23
Right CA2 & CA3 / WBV	Pearson Correlation	-.064	.175
	Sig. (2-tailed)	.771	.425
	N	23	23
Right CA4 & DG / WBV	Pearson Correlation	.027	.118
	Sig. (2-tailed)	.902	.592
	N	23	23
Right Subiculum / WBV	Pearson Correlation	.198	.037
	Sig. (2-tailed)	.366	.866
	N	23	23
Right SR SL SM / WBV	Pearson Correlation	.146	.166
	Sig. (2-tailed)	.506	.450
	N	23	23

*p < .05; **p < .01

Note. Storm24: Objective Hardship questionnaire (partial); CONSEQ: Cognitive Appraisal (0: negative, 1: neutral or positive); HC: Hippocampus; CA: Cornu Ammonis; DG: Dentate Gyrus; SR SL SM: Stratum Radiatum/ Stratum Lacunosum/ Stratum Moleculare; TIC: Total Intracranial Volume; WBV: Whole Brain Volume