The enduring impact of childhood maltreatment on grey matter development

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Abstract:

Childhood maltreatment doubles an individual's risk of developing a psychiatric disorder, yet the neurobiological nature of the enduring impact of childhood maltreatment remains elusive. This thesis explores the long-term effect of childhood maltreatment on grey matter. The primary aims of this thesis are to discern the spatial extent, temporal profile and physiological breadth of the developmental impact of childhood maltreatment amongst young people with emerging mental disorder. Chapter II comprises of a meta-analysis of thirty-eight published articles and demonstrates that adults with a history of childhood maltreatment most commonly exhibit reduced grey matter in the hippocampus, amygdala and right dorsolateral prefrontal cortex, compared to non-maltreated adults. Chapters III-V contain three original studies, involving a cohort of 123 young people, aged 14-26, with emerging mental illness. Chapter III bridges a gap between cross-sectional child and adult studies by longitudinally mapping the developmental trajectory of the hippocampus and amygdala following childhood maltreatment. This study provided the first direct evidence that childhood maltreatment stunts hippocampal development into young adulthood. Chapter IV assesses the utility of the cumulative stress and mismatch hypotheses in understanding the contribution of childhood abuse and recent stress to the structure and function of the limbic system. Mismatched levels of early life and recent stress were associated with reduced hippocampal volume and abnormal hippocampal-prefrontal resting state functional connectivity. Chapter V extends on recent advances in connectome research to examine the effect of childhood maltreatment on structural covariance networks. Childhood maltreatment was associated with reduced grey matter across a structural covariance network that overlapped with the default mode and fronto-parietal networks. Investigation of the correspondence of structural covariance with structural connectivity and functional connectivity revealed that reduced grey matter across the network is likely related to deceased functional coactivation following childhood maltreatment. Chapter VI discusses the significance of these studies in furthering understanding of how maltreatment shapes brain development and why childhood maltreatment increases the risk of psychiatric illness.

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Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Authorship Attribution Statement

Chapter II of this thesis is published as Paquola, C., Bennett, M. R. & Lagopoulos, J. Understanding heterogeneity in grey matter research of adults with childhood maltreatment—A meta-analysis and review. *Neurosci. Biobehav. Rev.* **69,** 299–312 (2016).

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In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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As supervisor of the candidate upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

24/01/2018

Jim Lagopoulos

List of Abbreviations

ACC: anterior cingulate cortex

ANOVA: analysis of variance

BDNF: brain derived neurotrophic factor

BIC: Bayesian Information Criterion

BOLD: bold oxygenation level-dependent

BPD: borderline personality disorder

BPRS: Brief Psychiatric Rating Scale

CA: childhood abuse

cACC: caudal anterior cingulate cortex

CM: childhood maltreatment

CSF: cerebrospinal fluid

CTQ: childhood trauma questionnaire

df: degrees of freedom

dlPFC: dorsolateral prefrontal cortex

DNA: deoxyribonucleic acid

DNMT1: DNA [cytosine-5-]-methyltransferase

DSM: Diagnostic and Statistical Manual of Mental Disorders

DWI: diffusion weighted imaging

FA: fractional anisotropy

FDR: false discovery rate

fMRI: functional magnetic resonance imaging

FOV: field of view

FSL: FMRIB Software Library

HDRS: Hamilton Depression Rating Scale

HPA: hypothalamic-pituitary-adrenal

HS: high stress

IQ: intelligence quotient

K10: Kessler-10

LS: low stress

MELODIC: Multivariate Exploratory Linear Optimized Decomposition into Independent Components

MNI: Montreal Neurological Institute

MP-RAGE: magnetization-prepared rapid gradient-echo

MRI: magnetic resonance imaging

mRNA: messenger ribonucleic acid

NMDA: N-methyl-D-aspartate

NoCM: no childhood maltreatment

NR3C1: nuclear receptor subfamily 3 group C member 1

OASIS: Overall Anxiety Severity and Impairment Scale

PTSD: post-traumatic stress disorder

rACC: rostral anterior cingulate cortex

RDoC: Research Domain Criteria

ROI: region of interest

rsFC: resting state functional connectivity

SCN: structural covariance network

SDN: seed-based d mapping

SOFASs: Social and Occupational Functioning Assessment Scale

TE: echo time

TR: repetition time

VBM: voxel based morphometry

vlPFC: ventrolateral prefrontal cortex

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CHAPTER I

1.1. OVERVIEW

The mammalian brain is sculpted by the experiences of early life. Early life experiences alter the developmental trajectory of the brain and in extreme cases can contribute to the pathogenesis of certain psychiatric disorders. Psychiatric disorders are increasingly being reconceptualised as having a neurodevelopmental origin and it has been reported that almost half of all psychiatric disorders emerge by age 14 and three quarters are present by age 24 (Kessler et al., 2005). Effective early detection and intervention are presently hindered by limited understanding of aetiologies of psychiatric disorders.

Stressful early life experiences, including childhood maltreatment, can potently impact neurodevelopment. Childhood maltreatment increases the risk of lifetime mental illness and produces phenotypically distinct cases of psychopathology (Teicher & Samson, 2013). Previous research has noted varied effects of childhood maltreatment on the adult brain, but has failed to capture the developmental impact nor explicate the biological mechanisms that underpin brain changes resultant from childhood maltreatment. This thesis explores the effect of childhood maltreatment on brain development in young people with emerging mental illness.

1.2. BRAIN DEVELOPMENT

The human brain develops from a neural tube during gestation into a complex conglomeration of one billion synapses (DeFelipe, 1999; Sadler, 2005). The embryo does not simply grow outwards from a preformed version of an adult, as was prominently thought in the 17th and 18th century (Dix, 2014) but undergoes a dynamic nonlinear development which is shaped by genes and the environment.

Typical brain development

Neurohistological research has provided a glimpse into the prenatal stages of this process. In the third week of gestation, the neural plate folds and fuses into a neural tube (Copp, Greene, & Murdoch, 2003). From day 42 of gestation, neurons are birthed from progenitor neuroepithelial cells (Clancy, Darlington, & Finlay, 2001; Haubensak, Attardo, Denk, & Huttner, 2004). Newly formed neurons migrate radially and, to a lesser extent, tangentially to form cortical layers (Noctor, Flint, Weissman, Dammerman, & Kriegstein, 2001; O'Rourke, Dailey, Smith, & McConnell, 1992; Rakic, 1988). A period of developmental exuberance begins in the second trimester in which axonal growth, dendritic arborisation and synaptogenesis are followed by selective pruning (Innocenti & Price, 2005).

Synaptogenesis peaks around birth, at which time gyrification and cortico-cortico axonal connections are complete (Chi, Dooling, & Gilles, 1977).

The neurobiological processes underlying postnatal development are less understood due to a dearth of human histological evidence. In its stead, neuroimaging has provided remarkable insight into postnatal neurodevelopment. The safe and non-invasive nature of magnetic resonance imaging (MRI) has enabled collection of longitudinal data to map structural development of the brain at an individual level. In this respect, the seminal works of Jay Giedd and Nitin Gogtay with the National Institute of Mental Health were instrumental in elucidating the asynchronous maturation of the brain from childhood to early adulthood (Giedd et al., 1999; Gogtay et al., 2004). Imaging studies revealed regionally distinct inverted U shaped developmental trajectories of grey matter. Converging evidence from *post mortem* histology and gene studies demonstrates this pattern of development is at least partly driven by heterochronous balancing of synaptogenesis with synaptic pruning (Goyal & Raichle, 2013; Huttenlocher & Dabholkar, 1997). Total cortical volume peaks at 8 years for girls and 9.3 years for boys, then deceases and stabilises by young adulthood (Raznahan et al., 2011). Phylogenetically older cortical regions, such as the primary sensory and motor regions, as well as polar regions, undergo grey matter loss from early childhood, whereas higher-order association areas, such as the dorsolateral prefrontal cortex, inferior parietal and superior temporal gyrus, reach peak thickness in late adolescence (Gogtay et al., 2004). Subcortical structures also exhibit inverted U shaped developmental trajectories, but estimates of peak volume vary from late childhood to early adulthood (Raznahan et al., 2014; Wierenga et al., 2014). White matter tracts increase in volume from birth into adolescence, with concomitant increases in myelination and axonal packing (Lebel & Beaulieu, 2011; Song et al., 2005). Several association tracts, specifically the inferior longitudinal fasciculus, superior longitudinal fasciculus and the fronto-occipital fasciculus, continue to develop into the late twenties.

Atypical brain development and neurodevelopmental disorders

Typical neurodevelopment is crucial for physical and psychological health. Interference with neuronal proliferation or migration causes hemimegalencephaly, microencephaly or lissencephaly (Hu, Chahrour, & Walsh, 2014). It has been suggested that more subtle aberrations in brain development may cause mental illness. This neurodevelopmental theory of mental illness posits that psychiatric disorder is the end stage of atypical neurodevelopment. Central to this theory is the emergence of the vast majority of mental illnesses during adolescence (Kessler et al., 2005); a vital period for cortical remodelling (Sotiras et al., 2016). The neurodevelopmental theory of mental illness has been extensively studied in the context of schizophrenia, where conversion from prodrome to schizophrenia is associated with accelerated grey matter loss (Cannon et al., 2015; Tsutomu Takahashi et al., 2009). Although specific genetic polymorphisms likely contribute to abnormal

neurodevelopment in psychiatric disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), genetic mutations alone cannot account for the neurodevelopmental origins of psychiatric disorders. Epidemiological studies provide compelling evidence that environmental factors significantly enhance risk of psychiatric disorder (Kessler et al., 2010). Empirical research into the specific neurodevelopmental impacts of early life events is lacking. Understanding the effect of the early life environment on neurodevelopment will shed new light on the aetiology of mental illness.

Environmental influences on brain development

During childhood, low long-term potentiation thresholds promote synaptogenesis between synchronous active neurons (Lohmann & Kessels, 2014). Later in life, long-term potentiation thresholds increase and synaptic plasticity is limited. This developmental sequence of heightened plasticity followed by stabilisation means early life experiences can have profound long-term effects. Adaptation to the early life environment is thought to confer evolutionary advantage, however certain adverse conditions early in life can engender atypical neurodevelopment and produce enduring negative consequences.

Early life experiences sculpt the developing brain via synaptic and epigenetic modifications. Experience-dependent plasticity refers to changes in neuronal wiring and synaptic strength induced by external stimuli. Experience-dependent changes in neuronal activity can bidirectionally tune synaptic strength and induce homeostatic synaptic scaling (Heynen et al., 2003; T. Takahashi, 2003; Turrigiano, Leslie, Desai, Rutherford, & Nelson, 1998). At a macroscopic level, experience-dependent plasticity operates via selective elimination of weak synapses and axonal re-routing (Antonini & Stryker, 1993; Le Bé & Markram, 2006). The early life environment also shapes brain development through alterations to the epigenome. Certain environmental exposures can cause long-lived, but reversible, modifications to nucleotides and chromosomes (LaSalle, Powell, & Yasui, 2013). These modifications, such as DNA methylation, govern the transcriptional responsiveness of genes (Hellman & Chess, 2007; Rauch, Wu, Zhong, Riggs, & Pfeifer, 2009). Given DNA methylation is regulated by neuronal activity (Guo et al., 2011), aberrant experience-driven neuronal activity can cause persistent alterations to gene expression. The precise mechanisms of epigenetic action are still under intense investigation, however evidently epigenetic modifications are sensitive to the early life environment, prime the transcriptional responsiveness of specific genes and profoundly impacting resultant phenotypes.

1.3. STRESS

Stress in the brain

Stress is a biological phenomenon that includes the neurophysiological response to 'stressors', which may have physical or psychological origins. Stressors trigger activation of limbic and ascending-brainstem pathways, which are related to psychological and somatic stress, respectively (de Kloet, Joëls, & Holsboer, 2005). These pathways activate corticotrophin-releasing hormone neurons in the hypothalamic paraventricular nucleus (de Kloet et al., 2005). Corticotrophin-releasing hormone receptor 1 then promotes the synthesis of adrenocorticotrophic hormone in the anterior pituitary, which in turn stimulates the adrenal cortex to secrete glucocorticoids. Glucocorticoids modulate over 200 genes by binding to mineralocorticoid receptors and glucocorticoid receptors (Datson, van der Perk, de Kloet, & Vreugdenhil, 2001). The ubiquitous nature of glucocorticoid receptors and the multitude of cellular processes influenced by glucocorticoids, including cellular metabolism, protein synthesis and signal transduction, give an initial insight into the wide-ranging impacts of stress (Datson et al., 2001; Patel et al., 2000).

Early life stress

Heightened sensitivity to the environment in early life also confers increased vulnerability to stress. Meaney and colleagues first revealed how postnatal maternal care regulates neuroendocrine responses, hippocampal synaptic development and gene expression (Meaney et al., 2013; Meaney & Aitken, 1985). Since then, researchers have instituted numerous rodent models to establish causal links between early life stress and neurodevelopment.

The most common animal model of early life stress involves brief daily maternal separation during the postnatal period. Maternal separation is consistently linked to elevated stress-induced corticosterone (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Ladd, Huot, Thrivikraman, Nemeroff, & Plotsky, 2004). Hypothalamic-pituitary-adrenal axis hyper-reactivity may arise from impaired feedback from the hippocampus, which is moderately supported by mixed evidence of reduced hippocampal glucocorticoid receptor expression and increased hippocampal long-term potentiation thresholds following maternal separation (Arnett et al., 2015; Derks et al., 2016; Ladd et al., 2004; Navailles, Zimnisky, & Schmauss, 2010; Renard, Rivarola, Suárez, & Suarez, 2010; van der Doelen et al., 2014; Viau, Sharma, & Meaney, 1996; Zhu et al., 2017). However, the maternal separation model of early life stress lacks procedural standardisation, such as the length of separation, regularity and pup-handling, and induces compensatory positive maternal behaviour. Limited bedding and nesting is an alternative rodent model which better relates to human experiences of early life stress (Gilles, Schultz, & Baram, 1996). Reduction of bedding and nesting material causes fragmentation of mother-pup interactions, decreased licking/grooming and the emergence of abusive maternal behaviour (Ivy, Brunson, Sandman, & Baram, 2008; Rice, Sandman, Lenjavi, & Baram, 2008; Roth, Lubin, Funk, & Sweatt, 2009). At the conclusion of the protocol, stressed pups exhibit significantly elevated basal corticosterone levels and decreased long term potentiation thresholds in CA1 of the hippocampus

(Avishai-Eliner, Gilles, Eghbal-Ahmadi, Bar-El, & Baram, 2001; Brunson et al., 2005; Derks et al., 2016; Gilles et al., 1996; Ivy et al., 2008). Furthermore, a series of studies from Wei and colleagues demonstrated limited bedding and nesting perturbs neurodevelopment via downregulation of proteins important for synaptic development (Wei et al., 2015; Wei, Simen, Mane, & Kaffman, 2012), as well as epigenetic repression of ribosomal DNA synthesis and receptors involved in neuronal differentiation (Boku et al., 2015; Wei, Hao, & Kaffman, 2014).

This accumulating research shows early life stress potently impacts neurodevelopment via synaptic alterations and epigenetic programming. Early life stress is also consistently linked to depressive and anxiety like behaviour in rodents (Dalle Molle et al., 2012; Molet et al., 2016; Raineki, Cortes, Belnoue, & Sullivan, 2012), however the translatability of psychological phenomena across species is difficult to qualify. Translation of rodent models of early life stress to humans is further complicated by phylogenetic differences in the development of hypothalamic circuitry and glucocorticoid circulation (Fourie & Bernstein, 2011; Ralevski & Horvath, 2015). Thus, human research is essential to obtain an understanding of the effect of early life stress on the brain and in this regard, in humans, the most common form of early life stress is childhood maltreatment.

1.4. CHILDHOOD MALTREATMENT

"Recognizing that the child, for the full and harmonious development of his or her personality, should grow up in a family environment, in an atmosphere of happiness, love and understanding … States Parties shall take all appropriate legislative, administrative, social and educational measures to protect the child from all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation, including sexual abuse, while in the care of parent(s), legal guardian(s) or any other person who has the care of the child" – Convention on the Rights of Child (UN General Assembly, 1989)

Childhood maltreatment is typically categorised into five classes; sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. In the most recent year of reporting, the Australian government noted over 45,000 children were victims of substantiated cases of childhood maltreatment (Australian Institute of Health and Welfare, 2015). Authority-based reports fail to capture the true incidence of childhood maltreatment, however. A meta-analysis of 244 publications found the global prevalence of childhood maltreatment, based on self-report, likely exceeds 40% (Stoltenborgh, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2015). Emotional abuse, defined as non physical forms of hostile treatment, which damage a child's emotional health, is the most prevalent form of childhood maltreatment (36.3%). Childhood physical abuse is reported by approximately a quarter of all adults (22.6%). Childhood sexual abuse, involving a caregiver using a child for sexual gratification,

is significantly more prevalent amongst girls (18%) than boys (7.6%). Finally, failure of the caregiver to provide for the basic physical needs and basic emotional needs of the child, namely physical and emotional neglect, are reported by 16.3% and 18.4% of all adults, respectively.

Children from low socioeconomic backgrounds or with parental psychiatric illness and substance abuse are at greater risk of maltreatment (Gillham et al., 1998; Grella, Hser, & Huang, 2006; Kelley, Lawrence, Milletich, Hollis, & Henson, 2015; Sidebotham & Golding, 2001; Yampolskaya & Banks, 2006), but the issue is not restricted to these high-risk groups. The Royal Commission into Institutional Responses to Child Sexual Abuse, alongside international investigations into sexual abuse perpetrated by Catholic clergy, highlight the vulnerability of all children to maltreatment (Kaufman & Erooga, 2016; Royal Commission into Institutional Responses to Child Sexual Abuse, 2017). Furthermore, as these crimes come to light in Australia, there is a strengthened impetus to understand the long-term effects of childhood maltreatment.

The impact of maltreatment extends beyond the home environment and can drastically alter an individual's life. Childhood maltreatment is associated with worsening grades, increased absenteeism and decreased extra-curricular participation (Leiter & Johnsen, 1997). The authors suggested declining school performance may be related to chronic stress and lack of parental supervision. Educational difficulties also likely interact with cognitive deficits (Geoffroy, Pinto Pereira, Li, & Power, 2016). The difficulty of recovering from childhood maltreatment is further compounded by heightened risk of juvenile incarceration (King et al., 2011; Moore, Gaskin, & Indig, 2013). These trends persist into adulthood. Unemployment and criminal engagement rates are significantly higher amongst adults with a history of childhood maltreatment (Currie & Tekin, 2012; Liu et al., 2013). In total, the economic cost of nonfatal childhood maltreatment, in terms of health care, productivity loss, child welfare, criminal justice and special education, is estimated at US$210,012 per child (Fang, Brown, Florence, & Mercy, 2012).

Childhood maltreatment and vulnerability to psychiatric illness

The most notable consequence of childhood maltreatment is enhanced vulnerability to psychiatric illness. Relative to non-maltreated adults, the odds of a depressive disorder are 202% higher in adults with a history of childhood maltreatment, the odds of an anxiety disorder are 270% higher and the odds of a psychosis-related disorder are 378% higher (Li, D'Arcy, & Meng, 2016; Varese et al., 2012). Childhood maltreatment also predicts an unfavourable course of mental illness. Combining data across sixteen epidemiological studies and ten clinical trials, Nanni, Uher, & Danese (2012) found that adults with a history of childhood maltreatment had 224%, 234% and 140% higher odds of depressive episode recurrence, persistence of depressive episodes and treatment resistance compared to non-maltreated individuals, respectively. These findings were independent of age, even though childhood maltreatment

is also related to earlier age of illness onset (Scott, McLaughlin, Smith, & Ellis, 2012). Teicher & Samson, (2013) suggested maltreated individuals represent a distinct subtype within many psychiatric illnesses, in which symptoms are more severe and resistant to treatment. Although the profound effects of childhood maltreatment on mental health are well documented, uncertainty surrounds the neurobiological basis for enduring risk.

1.5. TECHNICAL APPROACH

MRI is an ideal medium to examine the effect of childhood maltreatment on brain development. Different MRI sequences allow quantification of grey matter, white matter tracts and dynamic patterns of metabolic activity.

T1 weighted images depict the longitudinal relaxation time of tissue following a radio frequency pulse that aligns protons to the transverse plane (Bernstein, King, & Zhou, 2004). T1 weighting imaging is implemented with short repetition times and short times to echo to enable differentiation of tissue based on the speed of proton realignment. The strength of the signal indicates the density of fat and water in the underlying tissue. Protons in fat quickly realign and produce a high signal, whereas protons in water are slower to realign and produce a low signal. In the brain, T1-weighted sequences provide a clear delineation of grey matter from white matter, due to the higher signal intensity obtained from white matter. Complementary analytical neuroimaging tools are used to estimate grey matter volume in subcortical structures, cortical thickness and voxel-wise grey matter density. Importantly, inter-individual differences in grey matter can help explicate differences in human behaviour and cognition (Kanai & Rees, 2011).

Insight into relationship of grey matter differences to communication in brain networks may be deduced from diffusion weighted imaging (DWI) and functional MRI (fMRI). DWI is often used in parallel to T1-weighted imaging to highlight white matter tracts. In a DWI sequence, multiple gradient pulses are applied to vary the homogeneity of the magnetic field and the movement of water molecules between pulses is quantified (Stieltjes, Brunner, Fritzsche, & Laun, 2013). The signal produced by DWI represents the freedom of movement of water molecules. Water molecules move more freely along the axon, while motion perpendicular to the axon is constrained. Thus the orientation of white matter tracts can be deduced from the apparent diffusivity of water particles, where diffusivity parallel to the fibre produces a higher signal than diffusivity perpendicular to the fibre (Basser, Mattiello, & LeBihan, 1994). Furthermore, the restriction of water at each brain voxel, or *fractional anisotropy (FA)*, may be quantified by fitting a diffusion tensor model. Fractional anisotropy is broadly sensitive to differences in axons and myelination (Nair et al., 2005; Song et al., 2002).

Dynamic patterns of metabolic activity across the brain may be inferred from fMRI. In fMRI, the difference in magnetic susceptibility between diamagnetic oxyhaemoglobin and paramagnetic deoxyhaemoglobin is represented as the bold oxygenation level-dependent (BOLD) contrast (Ogawa, Lee, Kay, & Tank, 1990). During resting-state fMRI, the BOLD contrast depicts endogenous changes in oxygenation of haemoglobin. The correlation of distinct regions' timeseries of the BOLD signal (commonly referred to as "functional connectivity") is suggested to indicate a dynamic interaction between the underlying neuronal populations (Friston, 1994). The development of functional connectivity networks from childhood to adulthood is thought underpin increases in cognitive efficiency (Poldrack, 2010), but disturbances in functional network architecture commonly appear in psychiatric disorder (Kambeitz et al., 2016; Park et al., 2014).

1.6. SCOPE OF THE THESIS

The main aim of this body of work was to measure the long-term effect of childhood maltreatment on grey matter. The guiding hypothesis was that childhood maltreatment alters brain development. The following chapters address this hypothesis and three specific aims; namely to discern the spatial extent, temporal profile and physiological breadth of the developmental impact of childhood maltreatment.

Chapter II contains a meta-analysis of two decades of human neuroimaging studies and illustrates the grey matter regions most commonly reduced amongst adults with a history of childhood maltreatment. The clinical and demographic characteristics of the cohorts examined in previous studies varied widely, as did the findings. Subsequent sub-group meta-analyses were conducted to inform on the influence of certain cohort characteristics, such as age and psychiatric health. This synthesis of cross-sectional studies implicates the hippocampus and amygdala as key regions of interest which are essential in understanding the effect of childhood maltreatment.

Chapters III and IV involve region of interest analyses to uncover the temporal profile of the effect of childhood maltreatment on the hippocampus and amygdala. **Chapter III** illustrates differential developmental trajectories of the hippocampus and amygdala amongst young people with and without a history of childhood maltreatment. A mixed cross-sectional longitudinal design was implemented to determine the onset and progression of childhood maltreatment related effects on subcortical volumes. Given the enduring impact of childhood maltreatment evidenced by Chapter III and extant literature, **Chapter IV** explores the nature of the developmental impact of childhood maltreatment through evaluation of two competing stress theories. The theories diverge on whether the effects of childhood maltreatment are related to cumulative life stress or early life programming. The potential functional sequelae of grey matter differences subsequent to childhood maltreatment were also elaborated upon by complementing grey matter volume estimates with functional connectivity analyses.

Following on from the findings in region of interest analyses of Chapters III and IV, **Chapter V** employs structural covariance networks to examine whether childhood maltreatment affects brain network development. The affected network was further characterised by cross-modal coupling. This approach shed new light on the correspondence of structural covariance with structural connectivity and functional connectivity and elucidated potential physiological bases of childhood maltreatment-related effects on grey matter.

Finally, **Chapter VI** includes a brief synthesis of the preceding chapters. The findings will be discussed towards determining regional sensitivity to childhood maltreatment, the temporal profile of childhood maltreatment-related effects and the functional abnormalities that accompany grey matter changes. The concluding chapter addresses the clinical significance of characterising the biological phenotype of childhood maltreatment-related psychiatric illness and the important conceptual insights provided by such a naturalistic human study of neurodevelopment.

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CHAPTER II

Over the past twenty years, researchers have explored the impact of child abuse and neglect on brain structure across a range of cohorts. Discerning the commonalities across studies

aids targeted investigations in the future, while explication of discrepancies between studies can inform on influential demographic and clinical factors.

The following chapter provides a review and quantitative meta-analysis on the associations between childhood maltreatment and adulthood grey matter. The analyses centred on the hippocampus and amygdala, given the prominence of these brain structures in the field, whereby commonalities and discrepancies in extant literature were assessed in a series of subgroup meta-analyses. Additionally, seed based differential mapping was utilised to determine areas that have been consistently associated with childhood maltreatment in whole brain voxel based morphometric studies.

Three key findings emerge from the meta-analysis. Firstly, childhood maltreatment is definitively related to reduced hippocampal volume. The degree of the effect appears to vary between healthy and clinical cohorts, with larger childhood maltreatment related reductions observed amongst individuals with mental illness. Secondly, the relationship of childhood maltreatment to amygdala volume was moderated by mean age of the cohort. This finding may indicate that the impact of childhood maltreatment has a delayed onset or is compounded by later life events. Thirdly, childhood maltreatment is frequently associated with reductions in prefrontal grey matter density. The precise prefrontal location of childhood maltreatment related reductions varied between studies. In concert, these findings promote the targeted investigation of the hippocampus and amygdala, including the relationship of childhood maltreatment to age-related changes in volume, as well as more exploratory approaches to examining alterations in prefrontal grey matter.

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Understanding heterogeneity in grey matter research of adults with childhood maltreatment—A meta-analysis and review

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ABSTRACT

Childhood trauma has been associated with long term effects on prefrontal-limbic grey matter. A literature search was conducted to identify structural magnetic resonance imaging studies of adults with a history of childhood trauma. We performed three meta-analyses. Hedges' g effect sizes were calculated for each study providing hippocampal or amygdala volumes of trauma and non-trauma groups. Seed based differential mapping was utilised to synthesise whole brain voxel based morphometry (VBM) studies. A total of 38 articles (17 hippocampus, 13 amygdala, 19 whole brain VBM) were included in the meta-analyses. Trauma cohorts exhibited smaller hippocampus and amygdala volumes bilaterally. The most robust findings of the whole brain VBM meta-analysis were reduced grey matter in the right dorsolateral prefrontal cortex and right hippocampus amongst adults with a history of childhood trauma. Subgroup analyses and meta-regressions showed results were moderated by age, gender, the cohort's psychiatric health and the study's definition of childhood trauma. We provide evidence of abnormal grey matter in prefrontal-limbic brain regions of adults with a history of childhood maltreatment.

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1. Introduction

Childhood trauma is associated with poor social, academic, mental and physical health outcomes (McLeod et al., 2014; Rapoza et al., 2014; Romano et al., 2015). Exposure to severe stress in childhood, through interpersonal, socioeconomic or natural trauma, more than doubles the risk of developing a mental illness by adulthood (Chapman et al., 2004; Varese et al., 2012). The prefrontal-limbic system (a network encompassing the prefrontal cortex, hippocampus and amygdala) is a corner stone for mental health (Godsil et al., 2013). The interaction of these three regions is essential for emotion and stress regulation. It has been suggested that childhood trauma-induced structural abnormalities in the prefrontal-limbic system may underpin functional deficits and confer enhanced psychiatric risk subsequent to childhood trauma (Teicher and Samson, 2013).

One of the earliest brain regions targeted by neuroanatomical research into childhood trauma was the hippocampus, a limbic structure involved in memory forming, organizing, and storing (Opitz, 2014). Preclinical evidence of stress-induced impairments to hippocampal dendrites and cell organisation (Sapolsky et al., 1990; Uno et al., 1989) prompted the notion that hippocampal development could be altered by early life stress. This hypothesis was bolstered by early evidence of reduced hippocampal volume in adults with post-traumatic stress disorder (PTSD) (Bremner et al., 1995). Although a large number of studies have since reported an association of childhood trauma with decreased hippocampal volume (Brambilla et al., 2004; Bremner et al., 1997, 2003; Carballedo et al., 2012; Chaney et al., 2014; Dannlowski et al., 2012; Driessen et al., 2000; Opel et al., 2014; Pederson et al., 2004; Stein et al., 1997; Vythilingam et al., 2002; Weniger et al., 2008), this finding has not been consistently replicated in all studies and sub-group analyses (Aas et al., 2012; Baker et al., 2013; Carballedo et al., 2012; Chaney et al., 2014; Cohen et al., 2006; Lenze et al., 2008; Liao et al., 2013; Weniger et al., 2008).

Childhood trauma has also been correlated with abnormalities of the amygdala, a subcortical structure associated with memory, decision making and emotional reactions (Janak and Tye, 2015), though findings have been mixed thus far. The first MRI study in this field used the amygdala as a comparison region for the hippocampus (Bremner et al., 1997). Later, the amygdala was chosen as a region of interest (ROI) due its involvement in borderline personality disorder (BPD) and PTSD pathologies, its close neuroanatomical association with the hippocampus and its involvement in memory and fear. While some studies have shown amygdala volume to be significantly decreased in adults with a history of childhood trauma (Aas et al., 2012; Hoy et al., 2012), others have reported increased volume (Baldaçara et al., 2014; Kuhn et al., 2015; Pechtel et al., 2013) or no link between amygdala volume and childhood trauma (Andersen et al., 2008; Brambilla et al., 2004; Bremner et al., 1997; Cohen et al., 2006; Driessen et al., 2000; Schmahl et al., 2003).

The most common finding to arise from whole brain analyses has been decreased prefrontal grey matter in relation to childhood trauma (Chaney et al., 2014; Kumari et al., 2013; Sheffield et al., 2013; Thomaes et al., 2010; Tomoda et al., 2009b; van Harmelen et al., 2010). The prefrontal cortex (functionally important for coordinated neural responses and executive functions (Funahashi and Andreau, 2013)) may be sensitive to childhood trauma due to its protracted development, as well as its connections to the hypothalamic-pituitary-adrenal axis, hippocampus and amygdala. The prefrontal subregions linked to childhood trauma have varied between studies, however, and not all whole brain analyses have detected a relationship between prefrontal grey matter and childhood trauma (Benedetti et al., 2012; Labudda et al., 2013; Lu et al., 2013; Tomoda et al., 2009b; Van Dam et al., 2014). A large number of studies have attempted to understand the long term neuro-structural consequences of childhood trauma. By using a meta-analytical approach, we aim to determine the robustness of the proposed relationship between childhood trauma and adult prefrontal-limbic grey matter.

Inconsistencies in neuroimaging findings may be due to variability in research parameters such as cohort demographics, definition of childhood trauma, and the choice between investigating healthy or psychiatric cohorts. Investigating healthy individuals aids understanding of the effects of childhood maltreatment independent of psychiatric illness and illustrates grey matter alterations that underpin psychiatric resilience following childhood trauma (Baker et al., 2013; Carballedo et al., 2012; Cohen et al., 2006; Dannlowski et al., 2012; Lu et al., 2013; Walsh et al., 2014). On the other hand, to address the strong association of childhood trauma with the development of a psychiatric illness, some researchers have investigated individuals with mental illnesses and a history of childhood maltreatment. To reduce the effect of disorder-specific pathologies, high and low trauma groups are often matched for psychiatric health (Chaney et al., 2014; Liao et al., 2013; Sheffield et al., 2013). Furthermore, one group has conducted several studies with heterogeneous psychiatric cohorts (Tomoda et al., 2009a, 2011, 2012). These trans-diagnostic investigations aid understanding of the general effects of childhood maltreatment in vulnerable individuals, yet they require additional control of confounding factors related to psychiatric health. The combination of these three approaches (healthy, psychiatrically matched and mixed psychiatric cohorts) is leading to a more comprehensive understanding of how childhood maltreatment confers psychiatric risk and the different brain regions involved. Further investigation is required to overcome the variability of these findings and to elucidate the different relationships of childhood trauma to grey matter within disorder-specific groups.

Childhood trauma encompasses any severely stressful event occurring before the age of 16, including neglect, abuse, natural disasters and major family disturbances. Studies have used psychiatrist led interviews and retrospective questionnaires to measure childhood trauma. Depending on the tools implemented, childhood trauma has been variably restricted to experiences of abuse or neglect, only abuse, only non-emotional abuse (physical or sexual) and only sexual abuse. Differential patterns of behavioural problems and neuroendocrine activity have been reported depending on type of childhood trauma (Cicchetti and Rogosch, 2001; van der Put et al., 2015). In juvenile offenders, sexual abuse has been linked to internalising problems whereas physical maltreatment has been linked to externalising problems and violent crimes (van der Put et al., 2015). Additionally, boys with a history of sexual abuse were far more likely to have committed a sexual offence. Physically and sexually abused children have also been shown to have greater morning cortisol than non-maltreated, emotionally maltreated or neglected children (Cicchetti and Rogosch, 2001). In terms of the effect on brain structure, one group has hypothesised that childhood trauma has a general effect on stress-related systems and trauma-specific effects on sensory systems (Tomoda et al., 2012). This proposition is based on evidence of reduced visual cortex volume in adults exposed to domestic violence in childhood and increased superior temporal gyrus grey matter in adults that experienced severe parental verbal abuse (Tomoda et al., 2011, 2012). Additionally, in a study looking at the differential effects of childhood trauma types on the cortex, childhood sexual abuse was linked to thinning of the genital region of the somatosensory cortex, whereas childhood emotional abuse was linked to thinning of the face region (Heim et al., 2013). Thus, the type of childhood trauma used to define groups must be acknowledged as a potential moderating factor in meta-analytical approaches.

Three meta-analyses have previously been conducted on grey matter abnormalities in individuals with a history of childhood

trauma. Woon and Hedges (2008) focused on hippocampal and amygdala ROI studies of PTSD subsequent to childhood abuse. Due to strict inclusion parameters, only four adult studies were used in the meta-analysis. They found adult abused cohorts exhibited reduced bilateral hippocampi, however this finding is not generalizable to individuals without PTSD. Riem et al. (2015) presented evidence for peak hippocampal sensitivity to childhood maltreatment occurring in middle childhood. Furthermore, they found the combined effect size of childhood maltreatment on reduction of hippocampal volume was significant in studies measuring multiple types of maltreatment, but not in studies measuring solely sexual abuse, emotional abuse or deprivation. A recent meta-analysis of whole brain VBM studies reported distributed frontal and temporal grey matter reductions in individuals with a history of childhood maltreatment, as well as increased grey matter in right superior frontal and left middle temporal gyri (Lim et al., 2014). The latter two meta-analyses included a study of PTSD with an unknown number of traumas occurring in childhood or young adulthood (Landre et al., 2010). All three meta-analyses showed the exclusion of child studies altered their main findings, which aligns with the hypothesis of childhood trauma altering the developmental trajectory of brain volumes rather than causing a deleterious insult.

Systematic and critical reviews have been more plentiful (Frodl and O'Keane, 2013; Grassi-Oliveira et al., 2008; Hart and Rubia, 2012; McCrory et al., 2011; Teicher et al., 2003). In these reviews, the prefrontal-limbic system has been identified as most likely to be affected by childhood trauma, both structurally and functionally. Authors have placed emphasis on the complexity of the relationship between childhood trauma and structural abnormalities. In each review authors advise caution when interpreting individual study results and for future studies to account for psychiatric comorbities, genetic influences, HPA axis function and/or gender.

The purpose of this investigation is to review the current state of structural neuroimaging research of adults with a history of childhood trauma. We aim to gain insight into grey matter abnormalities subsequent to childhood trauma and explore reasons for variable findings. Three meta-analyses were performed to address the most common methodologies, namely hippocampus ROI, amygdala ROI and whole brain VBM. The cohort's psychiatric states and the type of childhood trauma experienced were explored as moderating variables, alongside age, gender and use of psychotropic medications. In order to gain a clearer insight into the long term effects of childhood trauma we have chosen to exclude all studies with individuals younger than 18 years. Such a review is important to enhance our understanding of the devastating neurobiological effects of childhood trauma and guide early, targeted intervention programs. Our findings may also serve as a platform for the elaboration of biomarkers that link childhood trauma and specific mental illnesses.

2. Methods

2.1. Study selection

A computerised literature search was conducted with PubMed, Scopus and Web of Science databases in October 2015. Key words used were "childhood maltreatment", "childhood trauma", "child abuse" or "early life stress" in combination with "grey matter", "voxel based morphometry", "structural magnetic resonance imaging", "hippocampal volume" or "amygdala volume". Titles and abstracts were screened to determine whether articles involved human magnetic resonance imaging studies on the effects of childhood trauma; defined as exposure to severe stress before the age of 16, including neglect, abuse, natural disasters and major family disturbances. The overarching inclusion criteria, based on the PRISMA guidelines (Moher et al., 2009), were (i) includes original data, (ii) measures grey matter and (iii) conducted in an adult sample (minimum age > 18 years).

2.2. Region of interest meta-analyses

The final inclusion criteria for the ROI meta-analysis, based on Comprehensive Meta-Analysis requirements (Borenstein et al., 2011), were (i) includes a hippocampal or amygdala ROI, (ii) compares a childhood trauma with a no-trauma group and (iii) provides mean and standard deviation volumes of each group or provides p values.

Using the Comprehensive Meta-Analysis software package (version 2.2.046), we compared the left, right and combined volume of each ROI between trauma and no-trauma groups. Common effect sizes were not assumed, as data was accumulated from highly variable study protocols. Consequently, mean effect sizes were calculated using a random-effects model. Effect sizes were reported by Hedges' g (Hedges and Olkin, 1985), in which a negative score indicates a smaller volume in adults with a history of childhood trauma. A chi-squared test of heterogeneity was performed. Q statistics and I^2 were reported, with I^2 of 0.25, 0.5 and 0.75 denoting small, moderate and high levels of heterogeneity, respectively (Higgins and Thompson, 2002). Mean age of study cohort and percentage of females in study cohort were examined as potential confounders through fixed effect meta-regression. Publication bias was assessed using the fixed effect regression Egger's Test (Egger et al., 1997). We tested the moderating effects of psychiatric health (psychotropic medication use, diagnosis matched control groups and presence of individuals with PTSD, mood disorder or BPD) and the definition of trauma (any severe stressor, abuse/neglect, abuse, physical/sexual abuse, sexual abuse and multiple trauma types) on the effects of childhood trauma on hippocampal and amygdala grey matter, where applicable. Within the random-effects model, a significant $Q_{contrast}$ statistic between subgroups indicated that the effect size was significantly different.

2.3. Whole brain VBM meta-analysis

Further selection criteria for this section of the meta-analysis, in accordance with Seed-based *d* Mapping (SDM) requirements (Radua and Mataix-Cols, 2012), were (i) conduct whole brain VBM analysis and (ii) provide peak or centroid coordinates of significant cluster in MNI or Talairach space.

The methodological advantages and drawbacks of SDM have been discussed in detail elsewhere (Radua and Mataix-Cols, 2009; Radua et al., 2014), and are only briefly summarised here. First, individual study maps were recreated by assigning voxels values based on their proximity to peak coordinates (Note: centroid coordinates were used where peak coordinates were not available and clusters were contained within an anatomical region). Next, the mean value of each voxel across all studies, weighted for sample size, was calculated and used to produce a meta-analytic map. Finally, standard randomisation tests were performed at a whole brain level using 500 Monte Carlo simulations and a significance threshold of $p < 0.05$. To test the robustness of the findings we conducted a jack knife sensitivity analysis, in which the same analysis is repeated excluding one study at a time. Effect size estimates were extracted from the primary region of each significant cluster to determine which studies contributed to each cluster. Meta-regression analyses on age and percentage of females were also conducted. A random effects general linear model was implemented to test the moderating effects of psychiatric health (psychotropic medication use, diagnosis matched control groups and presence of individuals with psychiatric diagnoses) and the definition of trauma (any severe stressor, abuse/neglect, abuse, physical/sexual abuse, sexual abuse and multiple trauma types). The Q statistic was calculated

for each voxel within each subgroup and contrasted to determine regions with significantly different effect sizes between subgroups.

3. Results

3.1. Hippocampal volume meta-analyses

Seventeen studies were used in the hippocampus meta-analyses, as illustrated by the PRISMA flow diagram in Fig. 1. A total of 1998 subjects were included, of which 1042 were categorised as having experienced childhood trauma. Due to insufficient data, two studies were excluded from the hemisphere specific analyses (see Supplementary Table 1 for studies included in each test). The demographic and experimental characteristics are displayed in Table 1.

Significant reductions in left, right and combined hippocampal volume were found in the trauma group, compared to the no-trauma group (Table 2, Supplementary Fig. 1). Heterogeneity was significant in all three analyses (Supplementary Table 3). Publication bias was significant in the combined analysis (Supplementary Table 4). Meta-regressions showed age and percentage of females did not significantly affect results (Age: left: $Q=0.33$, $p=0.57$, right: $Q=0.79$, $p=0.38$, combined: $Q=1.76$, $p=0.18$. Gender: left: $Q=0.13$, $p=0.72$, right: $Q=1.58$, $p=0.21$, combined: $Q=1.31$, $p=0.25$).

Reduced hippocampal volume amongst trauma groups was evident regardless of psychotropic medication use or implementation of diagnosis matched controls (Table 2). Amongst healthy cohorts, right and combined hippocampal volumes were reduced in the trauma group (Table 2). Although childhood trauma was only linked to reduced right hippocampal volume within PTSD studies, the left, right and combined hippocampal volume effect sizes did not significantly differ from studies of healthy individuals (Table 2). The difference in left, right and combined hippocampal volumes between trauma and non-trauma groups was significantly greater in mood disorder and BPD studies, compared to healthy cohort studies. Furthermore, within mood disorder studies, right and combined hippocampal volumes were significantly reduced in trauma groups and within BPD studies, left, right and combined hippocampal volumes were significantly reduced in individuals with childhood trauma (Table 2).

The difference in hippocampal volume between physical/sexual abuse groups and non-abused counterparts was significantly greater than studies measuring other types of childhood trauma (Table 2). A significant reduction in hippocampal volume was not evident in trauma groups, compared to no-trauma groups, amongst studies measuring abuse/neglect, abuse, sexual abuse or multiple traumas (Table 2).

3.2. Amygdala volume meta-analyses

Thirteen studies were used for the amygdala meta-analyses (as illustrated by the PRISMA flow diagram in Fig. 1). A total of 1042 subjects were included, of which 499 were categorised as having suffered childhood trauma. Due to insufficient data three studies (Korgaonkar et al., 2013; Kuo et al., 2012; Sodre et al., 2014) were excluded from the hemisphere specific analyses (See Supplementary Table 2 for studies included in each test). The demographic and study characteristics are displayed in Table 1.

Significant reductions in left, right and combined amygdala volumes were detected in the trauma group, compared to the no-trauma group (Table 3, Supplementary Fig. 2). Heterogeneity was significant in all three analyses (Supplementary Table 3). Publication bias was significant in right and combined analyses (Supplementary Table 4). Meta-regressions showed larger effects sizes were present in the combined amygdala meta-analysis amongst studies of greater mean age and fewer females (Age: $Q=5.30$, $p=0.02$. Gender: $Q=6.88$, $p=0.001$). Age and gender did not significantly affect the left amygdala tests (Age: $Q=2.79$, $p=0.12$. Gender: $Q=2.09$, $p=0.15$). Effect sizes in the right amygdala tests were greater in predominantly male studies ($Q=6.95$, $p=0.001$), but unaffected by mean age ($Q=2.37$, $p=0.12$).

Amongst amygdala studies, all cohorts containing individuals with psychiatric diagnoses also contained individuals taking psychotropic medications. Thus at the cohort level, medication status was synonymous with psychiatric health. Within psychiatric cohorts, the left, right and combined amygdala tests revealed reduced volume in trauma groups compared to no-trauma groups. No association of childhood trauma with amygdala volume was evident within healthy cohorts, however, and the effect size of such studies was significantly less than studies using psychiatric individuals (Table 3). The use of psychiatrically matched controls did not appear to moderate the relationship of childhood trauma and amygdala volume (Table 3). Combined amygdala volumes were significantly reduced in trauma groups, regardless of the definition of childhood trauma (Table 3). In contrast, left and right amygdala volumes were only reduced amongst studies defined by physical or sexual abuse (Table 3). The greatest reductions in left, right and combined amygdala volume were evident amongst adults with a history of physical or sexual abuse (Table 3).

3.3. Whole brain voxel based morphometry

The whole brain VBM search yielded 19 studies, as illustrated by the PRISMA flow diagram in Fig. 1 (Moher et al., 2009). A total of 1095 subjects were included, of which 406 subjects were categorised as having experienced childhood trauma, 460 subjects having no history of childhood trauma and 229 subjects were used in correlation analyses with varied levels of childhood trauma. The demographic characteristics of participants in each study are displayed in Table 1.

Childhood trauma was associated with reduced grey matter in three clusters. The affected regions were identified as the right dorsolateral prefrontal cortex (dlPFC), right hippocampus and right postcentral gyrus (Table 4, Fig. 2). A jack-knife sensitivity analysis showed the hippocampal cluster was highly robust, while the dlPFC and postcentral clusters were rendered non-significant by Dannlowski et al. (2012) exclusion. Effect size estimates showed 7 studies contributed to the right dlPFC cluster, 5 studies to the hippocampal cluster, and 2 studies to the postcentral cluster (Supplementary Table 5). Weighted regression analyses showed the postcentral and dlPFC clusters were related to age and gender (Supplementary Table 6), in such that greatest reductions in grey matter were evident in studies with high mean ages and more females. The hippocampal cluster was not strongly related to age or gender (Supplementary Table 6). Healthy trauma groups exhibited significantly greater reductions in dlPFC and postcentral grey matter, compared to trauma groups composed of individuals with psychiatric diagnoses (Supplementary Table 6). A significant shift in the peak coordinates of the right hippocampal cluster was evident upon comparison of healthy and psychiatric cohorts. Amongst healthy cohorts, trauma groups exhibited greatest grey matter reductions in an anterior, lateral region of the hippocampus. In contrast, within psychiatric cohorts, the association of childhood trauma with grey matter loss was strongest in a posterior, medial region of the right hippocampus (Supplementary Table 6). Studies defined by abuse/neglect displayed significantly greater effect sizes in each cluster, compared to other studies. Additionally, groups with a history of physical or sexual abuse displayed significantly greater reductions in hippocampal grey matter, compared to other trauma type groups (Supplementary Table 6).

Table 1
Study characteristics.

Author, year	Test	CT definition	Childhood trauma					No childhood trauma				
			N	Age(mean ± sd)	% F	DSM (%)	Meds	N	Age (mean ± sd)	% F	DSM (%)	Meds
Bremner et al. (1997)	H, A	Sexual or physical abuse	17	40.1 ± 5.7	29	PTSD (100) MDD (29) Anxiety (nr)	nr	17	42.4 ± 7.3	29	Nil	nr
Stein et al. (1997)	H	Sexual abuse	21	32.0 ± 6.3	100	PTSD (71) Dissociative (71) MDD (29) Social anxiety (5) OCD (5)	nr	21	30.2 ± 6.4	100	Nil	nr
Vythilingam et al. (2002)	H	Sexual or physical abuse	21	33 ± 6	100	MDD (100) PTSD (24) Anxiety (nr)	Nil	25	30.1 ± 6.4	100	MDD (44) Anxiety (nr)	Nil
Vythilingam et al. (2002)[c]	H	Sexual or physical abuse	21	33 ± 6	100	MDD (100) PTSD (24) Anxiety (nr)	Nil	11	34 ± 8	100	MDD (100) Anxiety (nr)	Nil
Bremner et al. (2003)	H	Sexual abuse	22	33.4 ± 7.2	100	PTSD (45) MDD (9) Panic (14)	Nil	11	38 ± 7	100	Nil	Nil
Brambilla et al. (2004)	H	Sexual or physical abuse	6	26.3 ± 5.7	83	BPD (100) MDD (17) Dysthymia (33)	Nil	20	34.9 ± 8.1	30	Nil	Nil
Pederson et al. (2004)	H	1 trauma	34	25.8 ± 5.9	100	PTSD (50)	nr	15	23.8 ± 5.6	100	Nil	nr
Cohen et al. (2006)	H, A	2 adverse events	102	39.9 ± 17.2[a]	50[a]	Nil	Nil	80	39.9 ± 17.2[a]	50[a]	Nil	Nil
Soloff et al. (2008)	V	Sexual abuse	14	26.1 ± 8.0[a]	100	BPD (100) Dep (50)[a] PTSD (5)[a] Anxiety (18)[a]	Nil	8	26.1 ± 8.0[a]	100	BPD (100) Dep (50)[a] PTSD (5)[a] Anxiety (18)[a]	Nil
Weniger et al. (2008)	H, A	Sexual and physical abuse	23	30.9 ± 7.0	100	BPD (100) Dissociative (57) PTSD (43)	Yes	25	33 ± 7	100	Nil	Nil
Tomoda et al. (2009b)	V	Harsh corporal punishment	23	21.74 ± 2.22	35	Nil	Nil	22	21.68 ± 1.84	73	Nil	Nil
Tomoda et al. (2009a)	V	Sexual abuse	23	20.2 ± 1.3	100	MDD (17) PTSD (17)	Nil	14	19.0 ± 1.1	100	Nil	Nil
Thomaes et al. (2010)	V	Sexual or physical abuse	33	35.3 ± 9.8	100	PTSD (100) Anxiety (70) MDD (64)	Yes	30	35.2 ± 12.3	100	Nil	Nil
Sala et al. (2011)	H	Sexual or physical abuse	6	32.8 ± 7.6[a]	73[a]	BPD (100) MDD (nr)	Yes	9	32.8 ± 7.6[a]	73[a]	BPD (100) MDD (nr)	Yes
Tomoda et al. (2011)	V	Parental verbal abuse	21	21.2 ± ns	57	Yes (nr)	Nil	19	21.1 ± ns	63	Nil	Nil
Aas et al. (2012)	H, A	2 traumas	18	27.4 ± 7.9[a]	37[a]	Psychosis (100)	Yes	7	27.4 ± 7.9[a]	37[a]	Psychosis (100)	Yes
Benedetti et al. (2012)	V	Above median on RFQ	20	34.15 ± 9.00	65	OCD (100)	Yes	20	36.80 ± 11.0	65	OCD (100)	Yes
Carballedo et al. (2012)	V	Mild emotional abuse	10	37.25 ± 14.3[a]	65[a]	Nil, family history of MDD	Nil	10	37.25 ± 14.3[a]	65[a]	Nil, family history of MDD	Nil
Carballedo et al. (2012)	V	Mild emotional abuse	10	35.65 ± 11.7[a]	65[a]	Nil	Nil	10	35.65 ± 11.7[a]	65[a]	Nil	Nil
Clark et al. (2012)	H, A	3 adverse events	27	42.0 ± 10.3	48	Nil	Nil	20	46.0. ± 12.8	50	Nil	Nil
Dannlowski et al. (2012)[b]	V	CTQ	145	33.8 ± 10.4	46	Nil	Nil					
Kuo et al. (2012)	A	1 trauma	39	48.0 ± 9.6[a]	93[a]	PTSD (67) MDD (46)[a] Anxiety (nr)	nr	48	48.0 ± 9.6[a]	93[a]	PTSD (33) MDD (30)[a] Anxiety (ns)	nr
Malykhin et al. (2012)	A	Sexual or physical abuse	19	36.2 ± 8.4	79	MDD (100) Anxiety (37)	Yes	20	32.5 ± 7.9	70	MDD (100) Anxiety (35)	Yes

Table 1 (*Continued*)

Author, year	Test	CT definition	Childhood trauma					No childhood trauma				
			N	Age(mean ± sd)	% F	DSM (%)	Meds	N	Age (mean ± sd)	% F	DSM (%)	Meds
Tomoda et al. (2012)	V	Witness domestic violence	22	21.8 ± 2.4	73	Yes (nr)	Nil	30	21.6 ± 2.2	73	Nil	Nil
Baker et al. (2013)	H, A	1 trauma	97	34.8 ± 15.2	49	Nil	Nil	76	33.7 ± 19.2	58	Nil	Nil
Fonzo et al. (2013)	V	Above CTQ median	16	40.44 ± 8.18	100	PTSD (100) MDD (40) Panic (40) GAD (40)	Nil	17	38.18 ± 8.82	100	PTSD (100) MDD (75) Panic (19) GAD (43.8)	Nil
Korgaonkar et al. (2013)	H, A	3 traumas	74	>18	68	Nil	Nil	150	>18	51	Nil	Nil
Kumari et al. (2013)[b]	V	Psycho-social deprivation	56	33.17 ± 6.96	0	SCZ (50) ASPD (23)						
Labudda et al. (2013)	V	Above CTQ cut off on 4 or 5 scales	20	30.51 ± 11.57[a]	100	BPD (100)	Yes	19	30.51 ± 11.57[a]	100	BPD (100)	Yes
Lu et al. (2013)	V	Above any CTQ subscale cutoff	24	21.5 ± 3.98	63	Nil	Nil	24	21.5 ± 3.69	63	Nil	Nil
Sheffield et al. (2013)	V	Sexual abuse	24	41.7 ± 11.9	67	Psychosis (100)	Yes	23	36.3 ± 13.5	52	Psychosis (100)	Yes
Chaney et al. (2014)	H, V	Above any CTQ subscale cutoff	30	41.7 ± 12.1	43	MDD (67)	Yes	53	36.3 ± 10.7	68	MDD (32)	Yes
Aust et al. (2014)	H, A	nr	25	34.4 ± 9.9[a]	48[a]	Nil	Nil	25	34.4 ± 9.9[a]	48[a]	Nil	Nil
Sodre et al. (2014)	A	nr	16	nr	nr	Bipolar (100)	nr	10	nr	nr	Bipolar (100)	nr
Van Dam et al. (2014)	V	Above any CTQ subscale cutoff	69	36.3 ± 6.8	42	SUD (64)	Nil	108	35.5 ± 4.3	32	SUD (32)	Nil
Walsh et al. (2014)	V	Adverse family Environment	27	18.4 ± 0.6	63	Nil	Nil	31	18.4 ± 0.7	48	Nil	Nil
Cancel et al. (2015)[b]	V	CTQ emotional neglect	28	32.1 ± 8.3	29	SCZ (100)	Yes					
Gerritsen et al. (2015)	H	At least 1 type of CM (NEMESIS)	96	38.8 ± 10.2[a]	78[a]	MDD (100) Anxiety (nr)	Yes	64	38.8 ± 10.2[a]	78[a]	MDD (100) Anxiety (nr)	Yes
Gerritsen et al. (2015)	H	At least 1 type of CM (NEMESIS)	39	38.8 ± 10.2[a]	78[a]	Nil	Nil	63	38.8 ± 10.2[a]	78[a]	Nil	Nil
Gerritsen et al. (2015)	H	At least 1 type of CM (NEMESIS)	11	61.5 ± 9.6[a]	19[a]	MDD (100)	Yes	37	61.5 ± 9.6[a]	19[a]	MDD (100)	Yes
Gerritsen et al. (2015)	H	At least 1 type of CM (NEMESIS)	119	61.5 ± 9.6[a]	19[a]	Nil	Nil	469	61.5 ± 9.6[a]	19[a]	Nil	Nil
Opel et al. (2015)	V	Above any CTQ subscale cutoff	20	34.1 ± 14.0	50	Nil	Nil	20	36.3 ± 12.1	50	Nil	Nil
Veer et al. (2015)	H, A	Interpersonal trauma	12	28.1 ± 7.2	100	PTSD (100) MDD (42) Anxiety (nr)	Yes	12	26.8 ± 6.6	100	Nil	Nil

CT: childhood trauma. % F: Percentage of females. DSM: DSM diagnoses within group. Meds: medications. nr = Not reported. H: Hippocampal ROI meta-analysis. A: Amygdala ROI meta-analysis. V: Whole brain VBM meta-analysis. CTQ: Childhood trauma questionnaire (Bernstein et al., 1997). RFQ: Risky family questionnaire (Felitti et al., 1998). NEMESIS: Nemesis Trauma Interview (Spijker et al., 2002).
Diagnosis abbreviations: ASPD: antisocial personality disorder, BPD: borderline personality disorder. Dep: Depressive disorder. GAD: generalized anxiety disorder. MDD: major depressive disorder. OCD: obsessive compulsive disorder. PTSD: post-traumatic stress disorder. SCZ: schizophrenia. SUD: substance use disorder.

[a] Approximated from larger sample.
[b] One group correlative analysis.
[c] Subset of above study.

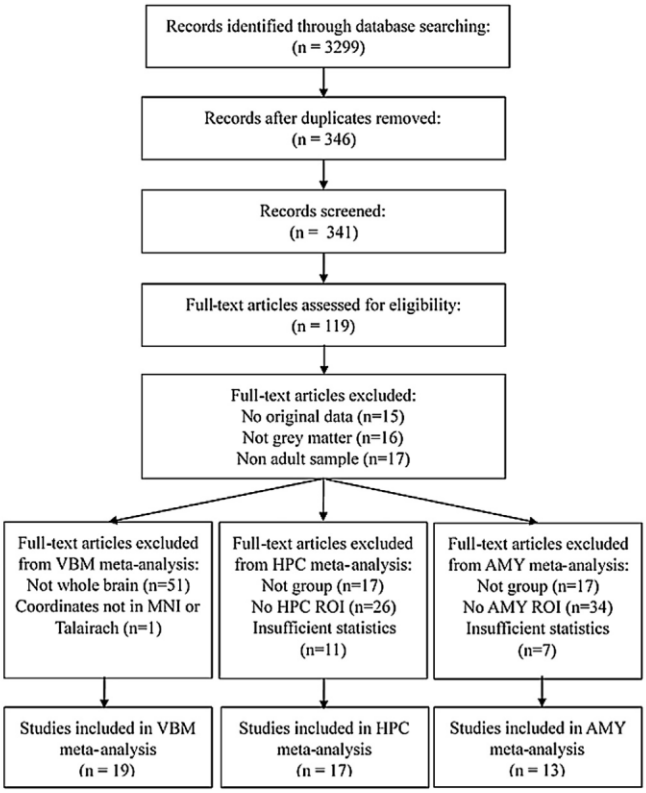

Fig. 1. Flow diagram of study selection, based on PRISMA guidelines.
Legend: VBM = voxel based morphometry. ROI = region of interest. HPC = hippocampus. AMY = amygdala.

Table 2
Main effect of childhood trauma on adult hippocampal volume and subgroup meta-analyses. Hedges' g, p values and Q statistics provided where appropriate.

	Left	Right	Combined
A. Main effect of maltreatment	**g = −0.642, p = 0.001**	**g = −0.616, p < 0.001**	**g = −0.517, p < 0.001**
B1. Medicated cohorts	**g = −0.883, p = 0.011**	**g = −0.778, p = 0.002**	**g = −0.693, p < 0.001**
B2. Unmedicated cohorts	**g = −0.945, p = 0.007**	**g = −0.790, p = 0.003**	**g = −0.793, p < 0.001**
Difference between B1 and B2	Q = 1.355, p = 0.244	Q = 0.753, p = 0.386	Q = 2.692, p = 0.101
C1. Groups not matched for diagnosis	**g = −0.407, p = 0.001**	**g = −0.449, p = 0.003**	**g = −0.410, p < 0.001**
C2. Psychiatrically matched groups	**g = −0.803, p = 0.008**	**g = −0.521, p < 0.001**	**g = −0.481, p < 0.001**
Difference between C1 and C2	Q = 1.489, p = 0.222	Q = 1.036, p = 0.309	Q = 1.768, p = 0.184
D1. Healthy cohort	g = −0.176, p = 0.062	**g = −0.293, p = 0.002**	**g = −0.206, p = 0.001**
D2. PTSD cohort	g = −0.214, p = 0.570	**g = −0.344, p = 0.033**	g = −0.288, p = 0.128
Difference between D1 and D2	Q = 0.010, p = 0.922	Q = 0.073, p = 0.787	Q = 0.170, p = 0.680
D3. BPD cohort	**g = −1.619, p = 0.010**	**g = −1.059, p < 0.001**	**g = −1.349, p < 0.001**
Difference between D1 and D3	**Q = 5.155, p = 0.024**	**Q = 6.847, p = 0.009**	**Q = 12.359, p < 0.001**
D4. Mood disorder cohorts	g = −1.385, p = 0.130	**g = −1.000, p = 0.003**	**g = −1.127, p = 0.001**
Difference between D1 and D4	Q = 1.726, p = 0.189	**Q = 4.128, p = 0.042**	**Q = 7.723, p = 0.005**
E1. Any stressor	**g = −0.223, p = 0.007**	**g = −0.339, p = 0.002**	**g = 0.258, p < 0.001**
Difference between E1 to not E1	**Q = 4.156, p = 0.041**	**Q = 4.078, p = 0.043**	**Q = 10.069, p = 0.002**
E2. Abuse or neglect	g = −0.220, p = 0.578	g = −0.325, p = 0.413	g = −0.382, p = 0.192
Difference between E2 and not E2	Q = 1.169, p = 0.280	Q = 0.613, p = 0.434	Q = 0.670, p = 0.413
E3. Abuse	g = −0.341, p = 0.247	g = −0.094, p = 0.749	g = −0.216, p = 0.297
Difference between E3 and not E3	Q = 0.982, p = 0.322	Q = 3.081, p = 0.079	Q = 2.895, p = 0.089
E4. Physical or sexual abuse	**g = −2.064, p = 0.002**	**g = −1.487, p < 0.002**	**g = −1.761, p < 0.001**
Difference between E4 and not E4	**Q = 8.042, p = 0.005**	**Q = 5.540, p = 0.019**	**Q = 14.800, p < 0.001**
E5. Sexual abuse	g = −0.210, p = 0.738	**g = −0.540, p = 0.036**	g = −0.179, p = 0.662
Difference between E5 and not E5	Q = 2.349, p = 0.125	Q = 0.137, p = 0.711	Q = 1.504, p = 0.220
E6. Multiple traumas	g = −0.290, p = 0.399	g = −0.410, p = 0.383	g = −0.271, p = 0.124
Difference between E6 and not E6	Q = 1.220, p = 0.269	Q = 0.291, p = 0.589	Q = 3.205, p = 0.073

4. Discussion

To our knowledge, this is the first meta-analysis to examine hippocampal and amygdala volumes following childhood trauma across psychiatric disorders and the first to be conducted exclusively in adults. This is also the largest VBM meta-analysis of adults with childhood trauma. Results revealed reduced hippocampal and amygdala grey matter amongst individuals exposed to childhood trauma. The most robust finding of the whole brain VBM meta-analysis was reduced grey matter in the right dlPFC. Repetitive transcranial magnetic stimulation studies have recently elucidated the role of the right dlPFC in regulating attention to emotional stimuli by increasing amygdala activity (De Raedt et al., 2010; Leyman et al., 2009; Vanderhasselt et al., 2011; Zwanzger et al., 2014).

Table 3
Main effect of childhood maltreatment on adult amygdala volume and subgroup meta-analyses. Hedges' g, p values and Q statistics provided where appropriate.

	Left	Right	Combined
A. Main effect	**g = −0.482, p = 0.006**	**g = −0.668, p = 0.002**	**g = −0.559, p < 0.001**
B1. Psychiatric cohorts	**g = −0.926, p < 0.001**	**g = −1.234, p < 0.001**	**g = −1.020, p < 0.001**
B2. Healthy cohorts	g = −0.104, p = 0.356	g = −0.125, p = 0.187	g = −0.107, p = 0.076
Difference between B1 and B2	**Q = 10.378, p = 0.001**	**Q = 9.327, p = 0.002**	**Q = 20.496, p < 0.001**
C1. Groups not matched for diagnosis	**g = −0.731, p = 0.023**	**g = −0.960, p = 0.003**	**g = −0.848, p < 0.001**
C2. Psychiatrically matched groups	g = −0.366, p = 0.061	**g = −0.529, p = 0.034**	**g = −0.446, p < 0.001**
Difference between C1 and C2	Q = 0.941, p = 0.332	Q = 1.106, p = 0.293	Q = 2.706, p = 0.100
D1. Any stressor	g = −0.160, p = 0.223	g = −1.483, p = 0.138	**g = −0.140, p = 0.016**
Difference between D1 and not D1	**Q = 5.834, p = 0.016**	**Q = 5.460, p = 0.019**	**Q = 15.706, p < 0.001**
D2. Physical or sexual abuse	**g = −1.109, p < 0.001**	**g = −1.408, p = 0.011**	**g = −1.245, p < 0.001**
Difference between D2 and not D2	**Q = 12.152, p < 0.001**	**Q = 4.498, p = 0.034**	**Q = 12.632, p < 0.001**
D3. Multiple traumas	g = −0.444, p = 0.193	g = −0.568, p = 0.085	**g = −0.420, p = 0.013**
Difference between D3 and not D3	Q = 0.046, p = 0.830	Q = 0.190, p = 0.663	Q = 1.138, p = 0.286

Table 4
Meta-analysis results of VBM studies on childhood maltreatment.

Region	Peak voxel	No. of voxels	SDM value	p value
Right dorsolateral prefrontal cortex	24,38,32	170	−1.897	0.000206411
Right hippocampus	30,−32,−10	129	−1.718	0.000738025
Right postcentral gyrus	60,−22,32	112	−1.582	0.001506984

Note: SDM value represents difference in grey matter, with negative scores for trauma < non trauma. Peak voxel given in MNI coordinates.

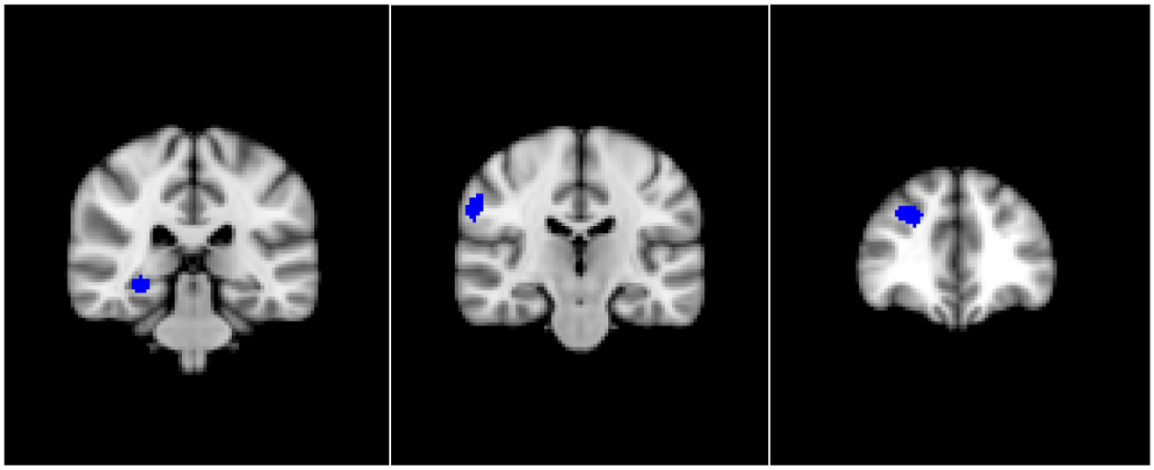

Fig. 2. Results of whole brain VBM meta-analysis on childhood trauma. Clusters shown in coronal view at peak voxel. Right hippocampus (y = −32), right postcentral gyrus (y = −22) and right dorsolateral prefrontal cortex (y = 38).

Grey matter reductions in this region may underlie reduced dlPFC blood oxygenation level dependent response to traumatic scripts and abnormal dlPFC functional connectivity amongst individuals with a history of childhood trauma (Herringa et al., 2013; Philip et al., 2014; Schmahl et al., 2004). Although the dlPFC was the most robust finding of the VBM meta-analysis, grey matter abnormalities have not been consistently detected in this region. Overall there is great variability in the literature on childhood trauma induced structural abnormalities. We take this opportunity to review these differences and reflect upon the factors from which they arise.

4.1. Age

Regression of mean age in meta-analyses revealed group differences in amygdala grey matter were greater amongst older cohorts. Child studies of maltreatment have frequently reported greater amygdala volumes in neglected children (Lupien et al., 2011; Mehta et al., 2009; Tottenham et al., 2010), however no difference in amygdala volume has been evident in abused children with PTSD (De Bellis et al., 2001, 1999, 2002). Typically, the amygdala increases in volume throughout adolescence (Wierenga et al., 2014). One longitudinal study has shown reduced amygdala growth throughout mid-adolescence in individuals with high childhood maltreatment (Whittle et al., 2014). This finding supports the notion that abnormal amygdala development results in smaller amygdala volumes in adults with childhood trauma. Reduced grey matter in the right dlPFC and right postcentral gyrus also appeared to be driven by older cohorts, as they were no longer significant following regression of mean age. Although no studies have focused on the longitudinal changes in these regions following childhood trauma, it is possible alterations to the developmental trajectory of grey matter only become apparent later in life.

4.2. Gender

The effect of gender was significant in the right amygdala, right dlPFC and right post central gyrus. Effect sizes for each region were greater in predominantly male studies. Gender has been shown to moderate the effect of childhood trauma on depressive symptoms in adulthood (Khan et al., 2015), internalisation problems (Godinet et al., 2014), affective processing (Crozier et al., 2014) and cerebral, corpus callosum and ventricular development (De Bellis and Keshavan, 2003). Gender differences may arise from the synergistic actions of stress and sex hormones on grey matter plasticity (McEwen, 2010). Alternatively, differences in the prevalence of maltreatment types for boys and girls could lead to different effects on grey matter development (Christoffersen et al., 2013; Radford et al., 2013).

4.3. Diagnosis and type of maltreatment

The differential effect of childhood trauma on grey matter volume depending on psychiatric grouping and maltreatment type stems from a multitude of neurobiological and genetic factors. An individual's genetic susceptibility to a certain mental illness plays an important role in determining the effect of childhood trauma. Genes involved in monoaminergic, neurotrophic and stress systems are the primary candidates of where early life environment influences grey matter development. For example, expression of BDNF genes has been shown to mediate the effect of stress hormones on dendritic spines (Bennett and Lagopoulos, 2014). A full discussion of these systems is not within the scope of this review, but it is important to note the relationship (for examination of this link in psychosis see van Winkel et al., 2013).

In addition, preclinical studies have shown the neurobiological effects of stress differ depending on stressor type. In adult mice, chronic immobilisation stress enhances arborisation of excitatory neurons in the basal amygdala and leads to atrophy of basal dendrites in CA3 of the hippocampus. On the other hand, chronic unpredictable stress results in atrophy of amygdala interneurons and no change in CA3 pyramidal neurons (Vyas et al., 2002). Furthermore, only chronic immobilisation stress significantly increases anxiety behaviour; suggesting the type of stress experienced can affect psychiatric outcomes. Here we report greatest hippocampal and amygdala reductions when comparing individuals based on exposure to childhood physical or sexual abuse. In contrast, decreased dlPFC and postcentral grey matter was most prevalent in studies defined by any childhood trauma. Therefore, stressor type appears to be an important factor in determining the structural consequences of childhood trauma and should be thoroughly examined in future studies.

4.3.1. Hippocampus

The hippocampus has been the central focus of grey matter childhood trauma studies. The ROI meta-analysis showed the hippocampus to be consistently smaller in childhood trauma cohorts and five whole brain VBM studies contributed to a right hippocampal cluster of reduced grey matter (Supplementary Table 5).

Firstly, hippocampal volume appeared to be slightly reduced in healthy childhood trauma cohorts. It should be noted, due to a lack of data, one group study could not be included, which did not find a significant difference in hippocampal volume between trauma and non-trauma groups (van Harmelen et al., 2010). Additionally, in 6 of eight associative studies, a significant negative correlation of childhood trauma severity with hippocampal volume was detected (Dannlowski et al., 2012; Driessen et al., 2000; Gatt et al., 2009; Gorka et al., 2014; Lenze et al., 2008; Opel et al., 2014; Riem et al., 2015; Samplin et al., 2013). When viewed in whole, it appears slight decreases in each study were emphasised in the meta-analysis to show hippocampal volume to be significantly reduced in healthy childhood trauma cohorts.

The effect size of hippocampal differences between individuals with PTSD subsequent to childhood trauma and healthy individuals without childhood trauma was similar to the comparison of healthy traumatised individuals and healthy no-trauma individuals. Reduced hippocampal volume has been repeatedly reported in adult PTSD, but controversy exists whether smaller hippocampi represent a risk factor or acquired feature of the illness (Pitman et al., 2012). Without studies implementing PTSD matched controls, it is difficult to discern whether reduced hippocampal volume among adults with PTSD secondary to childhood abuse is linked to diagnosis or childhood trauma. Studies composed of three adult groups – PTSD secondary to childhood abuse, history of childhood abuse without PTSD and neither PTSD or childhood abuse – have presented conflicting results (Bremner et al., 2003; Pederson et al., 2004; Weniger et al., 2009). All three studies found both abused groups to have smaller mean hippocampal volumes than the healthy-non abused group (however these were not significantly different in all studies). Only two studies found the PTSD group to exhibit smaller hippocampi than the non PTSD abused group. Furthermore, high levels of early life trauma have been linked to greater hippocampal volumes in individuals with PTSD from urban violence (Baldaçara et al., 2014), suggesting an interaction of childhood trauma and adulthood PTSD on hippocampal volume. From this evidence and our meta-analysis, it appears childhood trauma is linked to similar reductions in adult hippocampal volumes in healthy individuals and individuals with PTSD, relative to healthy adults without a history of childhood trauma. Larger studies with PTSD matched control groups could be valuable in the quest to discern how hippocampal volume is affected by childhood abuse and the subsequent development of PTSD.

Reduced hippocampal volume in depressed individuals with childhood trauma compared to depressed non-maltreated counterparts has been consistently detected (Chaney et al., 2014; Opel et al., 2014; Vythilingam et al., 2002), however this was not replicated in a study of emotional and physical neglect (Frodl et al., 2010). The interaction of early life adversity and hippocampal volume has been shown to be predictive of the number of depressive episodes later in life (Rao et al., 2010) and cumulative illness duration (Frodl et al., 2010). Additionally, regression analyses have revealed the difference in hippocampal volume between healthy and depressed individuals can be accounted for by childhood trauma (Opel et al., 2014). It has been suggested reduced hippocampal volumes evident in major depression (Schmaal et al., 2016) may stem from the combination of childhood maltreatment and a genetic susceptibility to hippocampal decline, with further hippocampal volume loss occurring throughout disorder course (Frodl et al., 2010). In line with this notion, a negative correlation of the number of stressful early life events with hippocampal volume was detected amongst depressed Val66Met carriers of the BDNF gene, but not depressed Val/Val carriers (Gatt et al., 2009). This gene-environment interaction on hippocampal volume was also found in a psychosis cohort (Aas et al., 2014), but was not evident when healthy individuals were included (Gerritsen et al., 2015; Molendijk et al., 2012). Investigation of other genetic mutations implicated in depression, such as those within the monoaminergic system, may help us understand the mediating effect childhood trauma has on hippocampal development (Won and Ham, 2015).

The definition of childhood trauma and/or the type of experimental design implemented clearly have an effect on the findings of BPD studies. Whereas hippocampal volume is consistently reduced in abused groups compared to non-abused groups (Brambilla et al., 2004; Sala et al., 2011; Weniger et al., 2009), associative studies have not detected a relationship of child abuse/neglect severity with hippocampal volume (Bøen et al., 2014; Driessen et al.,

2000; Kuhlmann et al., 2013). Hippocampal differences may only be observed in severe or abusive cases of childhood maltreatment amongst individuals who develop BPD.

Finally, although insufficient studies were available to perform a subgroup analysis on psychosis cohorts, it should be noted that no studies of first episode psychosis have detected a main effect of childhood trauma on hippocampal volume (Aas et al., 2014, 2012; Hoy et al., 2012; Sheffield et al., 2013). However, after accounting for BDNF met carriers or age of psychosis onset, regression analyses including severity of childhood trauma have been able to account for the variation in hippocampal volume (Aas et al., 2014; Hoy et al., 2012). The commonality of hippocampal reduction in psychosis cohorts may overshadow the effect of childhood trauma (van Erp et al., 2015).

4.3.2. Amygdala

The second ROI meta-analysis showed trauma groups exhibited reduced amygdala volume. This finding was not consistent across subgroup meta-analyses. A number of factors appear to play a role in this variability.

Amongst the healthy/unmedicated cohorts, no difference in amygdala volume was evident. In agreement with this result, no correlation between childhood trauma and amygdala volume has been reported in studies of healthy participants (Gerritsen et al., 2015; Gorka et al., 2014) or unmedicated individuals with BPD (Driessen et al., 2000; Kuhlmann et al., 2013). In our meta-analysis, the greatest difference in amygdala volume between maltreatment groups was evident in two mood disorder studies (Malykhin et al., 2012; Sodre et al., 2014) (Supplementary Fig. 2). Decreased amygdala volume in association with childhood abuse has also been consistently detected in psychosis groups (Aas et al., 2012; Hoy et al., 2012). Although smaller amygdala volumes are commonly found in psychosis (van Erp et al., 2015) but not mood disorders (Hajek et al., 2009), all four studies show childhood trauma to be associated with decreased amygdala volume when compared within individuals with similar psychiatric illnesses. Thus, illustrating the necessity of using psychiatrically matched controls in amygdala studies.

Researchers originally hypothesised amygdala volume would be greater in individuals with a history of childhood trauma, due to evidence of greater amygdala volumes in PTSD. However, only three studies have reported increased amygdala volume in adults with a history of childhood trauma (Baldaçara et al., 2014; Kuhn et al., 2015; Pechtel et al., 2013). Rather, the presence of childhood trauma appears to direct the effect of adulthood traumatic stress on amygdala volume. Kuo et al. (2012) reported a negative correlation between combat exposure and amygdala volume in war veterans with a history of childhood trauma, but a positive correlation was exhibited amongst war veterans without a history of childhood trauma. In support of this notion, compared to healthy controls, individuals with PTSD exhibit right amygdala enlargement only after controlling for severity of childhood trauma (Baldaçara et al., 2014). Additionally, a recent meta-analysis showed no significant difference in amygdala volume of individuals with PTSD compared to trauma-exposed controls (O'Doherty et al., 2015), suggesting adulthood trauma rather than diagnosis determines amygdala volume. Therefore, the interaction of childhood trauma with high levels of adulthood stress (prevalent in psychiatric cohorts (Eckert et al., 2006; Navarro-Mateu et al., 2015)) appears to lead to reduced amygdala volume. On the other hand, in healthy cohorts where adulthood trauma is less common, amygdala volume does not appear to be determined by childhood trauma. In conjunction, these studies show the importance of investigating childhood trauma within a psychiatric group and accounting for adulthood stress to gain an understanding of the additive or interactive effects of childhood maltreatment and disease progression on amygdala volume.

4.3.3. Prefrontal cortex

The relationship of childhood trauma to prefrontal grey matter, as well as the subregions affected, appears to vary widely depending on experimental design. The most consistent report of prefrontal abnormalities in healthy maltreated cohorts has been of grey matter reductions in the ventromedial prefrontal cortex/anterior cingulate (Carballedo et al., 2012; Cohen et al., 2006; Dannlowski et al., 2012; Frodl et al., 2010; Gorka et al., 2014). This finding was not replicated in studies defining childhood maltreatment by one trauma or an adverse family environment (Gerritsen et al., 2012; Lu et al., 2013; Walsh et al., 2014). In terms of psychiatric cohorts, no prefrontal differences related to childhood trauma have been observed amongst individuals with BPD (Kuhlmann et al., 2013; Labudda et al., 2013) or in the majority of mixed mood and anxiety cohorts (Tomoda et al., 2009a, 2012, 2011) (the exception being (Tomoda et al., 2009b)). Individuals with PTSD subsequent to childhood trauma appear to have decreased grey matter in dorsal prefrontal regions (Fonzo et al., 2013; Thomaes et al., 2010). Prefrontal grey matter reductions are present in psychosis cohorts with childhood maltreatment. The regional specificity of this reduction is unclear however, as different prefrontal ROIs have been utilised (Kumari et al., 2013; Sheffield et al., 2013). Finally, studies of individuals with depression have been mixed. Evidence of decreased, increased or no difference in prefrontal grey matter in depressed adults with a history of childhood trauma has been reported (Chaney et al., 2014; Frodl et al., 2010; Treadway et al., 2009). Due to a paucity of common results few conclusions can be drawn. Prefrontal cortex abnormalities must be further explored and contextualised in terms of diagnosis and maltreatment type.

4.4. Considerations and limitations

The postcentral gyrus which was shown to be significantly reduced in relation to childhood trauma in the whole brain VBM meta-analysis was driven by two studies with large effect sizes. This region has not been identified in any correlational or ROI studies of childhood trauma. Without replication, speculation on its involvement in childhood trauma related pathology would be premature.

Our meta-analyses revealed the right hippocampus and right dlPFC to be more sensitive to childhood maltreatment than the respective regions in opposite hemispheres. However, conclusions regarding laterality need to be made with caution as significant effects were noted bilaterally in the largest ROI meta-analysis and reduced left dlPFC has been implicated in childhood maltreatment (Sala et al., 2011). Hemisphere specific sensitivity may stem from differences in development and functionality. The right hippocampus reaches peak volume earlier than the left hippocampus (Uematsu et al., 2012), suggestive of greater vulnerability earlier in life. The complementary functions of the left and right counterparts of the hippocampus and dlPFC may be another point of difference. While activity in the left hippocampus predicts egocentric mapping, activity in the right hippocampus is associated with allocentric representation (Igloi et al., 2010) and the dual coding theory posits memory encoding is reliant on the left dlPFC while the right dlPFC is involved in retrieval strategies (Paivio, 1991).

A limitation of the present study was the inability to directly compare group and correlational studies in ROI meta-analyses. We attempted to mitigate this issue through thorough examination of the literature. This approach also enabled us to compensate for the significant publication bias in the ROI meta-analyses (Supplementary Table 4) by discussing the results in context of non-significant findings.

4.5. Concluding remarks

The aim of this meta-analysis and review was to provide new insights into the variability that exists in grey matter research relating to childhood trauma. Our meta-analyses confirm childhood trauma affects limbic grey matter and that the findings in this field are greatly influenced by participant and experimental characteristics. A primary goal of this field is to understand how childhood trauma confers psychiatric risk and to use this knowledge to develop effective, targeted intervention strategies. To this end, we urge authors to discuss their results in context of psychiatric diagnosis and trauma types as effects may be highly specific and generalisation to wider populations problematic.

4.6. Future directions

Immense difficulty arises when attempting to disentangle the effects of childhood trauma from psychiatric illness. However, recent studies have shown great promise in dealing with these issues by carefully matching maltreatment groups and investigating regression effects (such as Van Dam et al., 2014; Opel et al., 2014). While whole brain VBM approaches may be helpful in novel psychiatric groups (for example eating disorder cohorts), targeted prefrontal-limbic protocols are preferential to exploratory analyses at this point. The interaction of genetic and/or epigenetic modifications with childhood trauma on grey matter will be a tremendously interesting avenue of research in coming years. A handful of recent studies have already broached the issue with BDNF (Aas et al., 2014; Bennett and Lagopoulos, 2014; Gatt et al., 2009), but many more genetic links are able to be investigated. Finally, longitudinal studies are essential if causal conclusions on the effects of childhood trauma during periods of peak psychiatric vulnerability are to be made.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.08.011.

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CHAPTER III

Since discovering the long-term effect of childhood maltreatment on grey matter, researchers have endeavoured to understand how early life stress engenders later abnormalities. Preclinical evidence shows that early life stress alters neurodevelopment via synaptic alterations and epigenetic programming, however, cross-sectional studies have been unable to capture the neurodevelopmental impact of childhood maltreatment in humans. In the following study, I present longitudinal evidence that childhood maltreatment negatively impacts hippocampal development.

The first published neuroimaging study of childhood maltreatment asserted *"Traumatic stress early in development may have an impact on brain development that results in a reduction in size of some brain regions"* (Bremner *et al.*, 1997). As evidence mounted that childhood maltreatment leads to reduced adult hippocampal volume, researchers called for longitudinal studies to empirically determine the impact of childhood maltreatment on the development of the hippocampus. Additionally, in the preceding Chapter, childhood maltreatment related reductions in amygdala volume appeared to have a temporal quality, being more consistently observed in older cohorts. Only two longitudinal studies previously examined the impact of childhood maltreatment on hippocampal and amygdala development (De Bellis *et al.*, 2001; Whittle *et al.*, 2013). These studies were conducted in children and young adolescents and neither found that hippocampal development was significantly affected by childhood maltreatment. The following chapter steps forward to late adolescence and young adulthood. Hippocampal and amygdala volume development were mapped in 123 individuals (14-28 years) using between one and five scanning time points. In doing so, the first empirical evidence that childhood maltreatment stunts right hippocampal growth is uncovered.

Having established the importance of childhood maltreatment in shaping hippocampal development, new challenges arise in determining the nature and consequences of the developmental impact of childhood maltreatment. This chapter highlights the importance of late adolescence and young adulthood in the emergence of observable effects of childhood maltreatment. Late adolescence and young adulthood are marked by drastic changes in the social environment, hormonal biochemistry as well as neural wiring. Further research is necessary to expound how underlying perturbations caused by childhood maltreatment interact with environmental and biological changes during late adolescence and young adulthood. Additionally, counter to our hypothesis, neither hippocampal or amygdala development were associated with psychiatric symptom severity. Although the hippocampus is clearly affected by childhood maltreatment, further research is clearly still necessary to understand how the hippocampus and its interactions with other brain regions may underpin psychiatric illness.

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Hippocampal development in youth with a history of childhood maltreatment

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ABSTRACT

Childhood maltreatment (CM) is associated with enhanced risk of psychiatric illness and reduced subcortical grey matter in adulthood. The hippocampus and amygdala, due to their involvement in stress and emotion circuitries, have been subject to extensive investigations regarding the effect of CM. However, the complex relationship between CM, subcortical grey matter and mental illness remains poorly understood partially due to a lack of longitudinal studies. Here we used segmentation and linear mixed effect modelling to examine the impact of CM on hippocampal and amygdala development in young people with emerging mental illness. A total of 215 structural magnetic resonance imaging (MRI) scans were acquired from 123 individuals (age: 14–28 years, 79 female), 52 of whom were scanned twice or more. Hippocampal and amygdala volumes increased linearly with age, and their developmental trajectories were not moderated by symptom severity. However, exposure to CM was associated with significantly stunted right hippocampal growth. This finding bridges the gap between child and adult research in the field and provides novel evidence that CM is associated with disrupted hippocampal development in youth. Although CM was associated with worse symptom severity, we did not find evidence that CM-induced structural abnormalities directly underpin psychopathology. This study has important implications for the psychiatric treatment of individuals with CM since they are clinically and neurobiologically distinct from their peers who were not maltreated.

1. Introduction

Child abuse and neglect are widespread global phenomena (Stoltenborgh et al., 2015) and represent a major public health challenge due to the enduring negative impact they have on social, academic, mental and physical health outcomes (McLeod et al., 2014; Rapoza et al., 2014; Romano et al., 2014). Maltreated children have double the risk of developing a psychiatric illness in adulthood (Scott et al., 2010; Spauwen et al., 2006). Furthermore, amongst people with depressive, bipolar, psychosis or anxiety disorder, childhood maltreatment (CM) has been linked to worse symptom severity and poor treatment response (Kuhn et al., 2015; Miniati et al., 2010; Nanni et al., 2012; Simon et al., 2009).

Across studies of the past two decades CM has been strongly related to reduced hippocampal volume in adulthood (for meta-analysis see Paquola et al. (2016)), however the largest study to date did not find CM to be associated with hippocampal volume in healthy and depressed individuals (Frodl et al., 2017). There has been no evidence of differences in hippocampal volume between children with abuse related post-traumatic stress disorder (PTSD) and healthy non-abused children (De Bellis and Keshavan, 2003; De Bellis et al., 1999; De Bellis et al., 2002). Additionally, while numerous studies of institutionally-raised children have shown enlarged amygdala volumes (Lupien et al., 2011; Mehta et al., 2009; Tottenham et al., 2010), only two studies have reported greater amygdala volumes in adults with a history of CM (Kuhn et al., 2015; Pechtel et al., 2013). Conversely, several studies have shown no difference (Andersen et al., 2008; Brambilla et al., 2004; Bremner et al., 1997; Cohen et al., 2006; Driessen et al., 2000; Frodl et al.,

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2017; Schmahl et al., 2003) or smaller amygdala volumes (Aas et al., 2012; Hoy et al., 2012; Malykhin et al., 2012; Sodre et al., 2014) among adults with a history of CM. Furthermore, our recent meta-analysis revealed greater CM-related reductions in amygdala volume amongst older cohorts (Paquola et al., 2016). During normal brain development, amygdala and hippocampal volumes increase throughout adolescence (Lenroot and Giedd, 2010; Ostby et al., 2009).

To date, only three longitudinal studies have investigated the impact of CM on the development of subcortical brain structures. One small longitudinal study of 10–13 years old children did not detect any difference in hippocampal or amygdala volume changes between healthy children and those with PTSD secondary to child abuse (De Bellis et al., 2001). In contrast, Whittle et al. (2013) reported that young teens with high levels of CM had reduced left amygdala growth compared to non-maltreated counterparts. In the same study the authors reported that there was no difference in hippocampal development. This result was replicated in a recent extension of the study to late teens, which also assessed development of hippocampal subregions (Whittle et al., 2016). Childhood maltreatment was, however, found to be indirectly related to reduced left hippocampal development via increased risk of psychopathology (Whittle et al., 2013).

Numerous links have been established between CM and subcortical volumes (Paquola et al., 2016), between CM and psychiatric risk (Scott et al., 2010; Spauwen et al., 2006) and between subcortical volume and mental health (Schmaal et al., 2016; van Erp et al., 2016). However, few studies have investigated the three factors in conjunction (for an interesting exception see Rao et al. (2010)). It has been suggested that abnormal subcortical development during youth may confer enhanced psychiatric risk and contribute to the clinical differentiation of individuals with a history of CM from those without (Teicher and Samson, 2013). This effect may be particularly important between late adolescence and young adulthood when the symptoms and diagnosis of three quarters of lifetime psychiatric disorders emerge (Kessler et al., 2005) and subcortical development is coupled to pubertal changes (Goddings et al., 2012).

The primary aim of the present study was to determine whether CM impacts hippocampal and amygdala development in young people with emerging mental illness. In addition, we aimed to quantify the clinical differentiation of individuals with CM, and examine whether clinical differences were related to aberrant hippocampal or amygdala development. To this end we performed a mixed cross sectional/longitudinal study of 123 young people exhibiting an admixture of psychiatric symptoms and reporting varied CM histories. We used linear mixed effect modelling to explore the differences in subcortical development and clinical trajectories of young people with high and low levels of reported CM. Furthermore, we assessed whether subcortical development was related to symptom severity. We hypothesised that people with CM would have reduced rates of hippocampal grey matter growth compared to people without CM, and that this reduced rate of brain development would be related to worse psychiatric symptoms.

2. Method

2.1. Participants

Participants were recruited from a specialised clinic ('headspace') for assessment and early intervention of mental health problems in young people (Scott et al., 2012) at the Brain and Mind Centre, Sydney, Australia. Given the instability and high co-morbidity of psychiatric diagnoses in young people (Hafner et al., 2008), we followed the Research Domain Criteria recommendations of the National Institute of Mental Health (Cuthbert and Insel, 2013) and recruited a wide range of individuals from a specialised mental health clinic for young people. The advantages of using this trans-diagnostic approach in research are discussed at length elsewhere (Casey et al., 2013; Cuthbert, 2014; Cuthbert and Insel, 2013). The present study included 215 MRI scans from 123 individuals, of whom 52 were scanned at least twice (see Supplementary Table 1 for further information). All patients were receiving clinician-based case management and relevant psychosocial interventions at the time of assessment. Patients who were treated with psychotropic medications were assessed under 'treatment as usual' conditions, that is, medications were not interrupted in any way. Exclusion criteria for all participants were medical instability (as determined by a psychiatrist), history of neurological disease (e.g. tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g. cancer, electroconvulsive therapy in last 3 months), intellectual and/or developmental disability (a predicted IQ score < 70), insufficient English for testing or psychiatric assessment and current substance dependence. The study was carried out in accordance with the Declaration of Helsinki, was approved by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent.

2.2. Clinical assessment

At baseline a retrospective self-report questionnaire, the Childhood Trauma Questionnaire (CTQ) short form, was used to measure exposure to maltreatment prior to the age of 16 (Bernstein et al., 1997). The CTQ separately assesses experiences of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect using a rating system along a five point Likert scale from 1 (never true) to 5 (very often true). Each participant produces a score from 5 to 25 for each subscale and an additive score from 25 to 125 for total CTQ. Participants were assigned to the CM group if they exceeded the moderate-severe cutoff score on one or more CTQ subscales; sexual abuse $\geq$8, physical abuse $\geq$10, emotional abuse $\geq$13, physical neglect $\geq$10 and emotional neglect $\geq$15. Thirteen participants reported sexual abuse, 24 participants reported physical abuse, 50 participants reported emotional abuse, 30 participants reported physical neglect and 34 participants reported emotional neglect. Notably, 55 participants did not report any CM, 25 participants reported one type of CM, 17 participants reported three types of CM, 10 participants reported four types of CM and 2 participants reported five types of CM.

At each time point a trained research psychologist conducted the clinical assessment (in a semi-structured interview format) to inform the diagnostic classification and to determine the nature and history of any mental health problems (see Supplementary Table 1 for more information on clinical data acquired at each time point). Primary diagnoses of participants included depressive ($n = 58$), bipolar ($n = 32$), psychosis ($n = 17$), and anxiety disorders ($n = 16$). Since 84% of the participants presented with a co-morbid axis-1 psychiatric disorder, we characterised the cohort on the basis of having any mood disorder diagnosis, any psychosis disorder diagnosis and any anxiety disorder diagnosis. Age of illness onset was collected for 94 participants. 64 participants experienced early disorder onset; defined as disorder onset at or before 15 years of age. 30 participants experienced late disorder onset; defined as disorder onset after 15 years of age. The assessment also included the Hamilton Depression Rating Scale (HDRS, 17-item) (Hamilton, 1967) to quantify current mood symptoms, the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) to quantify current general psychiatric symptoms and the Social and Occupational

Functioning Assessment Scale (SOFAS) (Goldman et al., 1992); where a patient's functioning is rated from 0 to 100.

2.3. Magnetic resonance imaging

Subjects underwent MRI scanning on a 3-Tesla GE MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) at the Brain and Mind Centre, Sydney, Australia. We acquired a customized MP-RAGE 3D T1-weighted imaging sequence with the following parameters: 0.9 mm isotropic resolution; repetition time (TR) = 7264 msec; echo time (TE) = 2784 msec; flip angle = 15°; coronal orientation; field of view (FOV) = 230 mm; matrix of 256 × 256; total slices = 196.

2.4. Image analysis

Imaging analyses were performed using FMRIB Software Library (FSL) v5.0 (Smith et al., 2004). Bilateral amygdalae and hippocampi were selected as regions of interest (ROI) based on extant literature and measured using FIRST software on T1-weighted images (Patenaude et al., 2011). Firstly, images were registered to MNI152 standard space using FMRIB's Linear Image Registration Tool (FLIRT). Then, the surface mesh of each subcortical structure was extracted and transformed back to original MRI space, filled and boundary corrected. A blinded neuroimaging expert visually inspected the hippocampal and amygdala boundaries for gross errors by overlaying the segmentation on the original T1 weighted scan. Finally, the volume of each structure for each subject was calculated in cubic millimetres and exported into SPSS 21.0 (SPSS Corp., 2012). Additionally, total intracranial volume was estimated using FSL's SIENAX (Smith et al., 2002). The process involved extraction of brain and skull images from a single whole head T1 weighted image, registration of the brain image to MNI152 standard space and tissue type segmentation with partial volume estimation.

2.5. Statistical analysis

First, we performed independent sample t-tests and chi-squared tests to compare baseline age, proportion of females, prevalence of diagnoses, age of illness onset, illness duration and CTQ scores in the No-CM and CM groups. Next, we implemented linear mixed effect modelling, which is a flexible and powerful tool for the analysis of unbalanced, longitudinal data (Verbeke and Molenberghs, 2000). We used the MIXED procedure in SPSS 21.0 (SPSS Corp., 2012) to investigate: (1) the impact of CM on clinical trajectory, (2) the impact of CM on ROI developmental trajectories and (3) whether the relationship in (2) differs depending on clinical outcomes (See Supplementary Methods).

Univariate feature selection was implemented to determine which demographic or clinical variables would be used in the ROI analyses (Supplementary Methods and Supplementary Table 2). In each analysis, model selection was completed in three steps and determined on the basis of Bayesian Information Criterion (BIC). First, the functional form of the trajectory was determined by comparing linear, quadratic and cubic growth terms. The best-fit growth term was used in subsequent analyses. Next we explored the impact of moderators by testing whether a full model (including main and interaction effects) explained greater variance than a simple model (including only main effects). In the final step, the best fit of the full or simple model was compared to the best-fit age term. The best-fit model for each measure (age term, age and CM model or age and CM interaction model) thus explained the greatest variance accounting for the number of parameters in the model (for further details see Supplementary Methods). After the best-fit model was selected, we inspected fixed effects. Tests were considered significant if $p < 0.05$. Finally, where applicable, we tested whether clinical outcomes mediated the effect of CM on ROI development. To do so, clinical outcomes associated with CM [as determined by analysis (1)] and the ROI volume (as shown in Supplementary Table 2) were added to the best fit model as a fixed main effect. Potential mediation was determined based on changes to significance of individual fixed effects. To visually inspect the data, individual changes as well as the best fit trajectory of each group were mapped in a spaghetti plot using GraphPad Prism (GraphPad, 2014).

3. Results

3.1. Demographics and clinical characteristics

Demographics of the participants are reported in Table 1. The two groups did not differ significantly in terms of baseline age, sex, diagnoses or illness duration. The best-fit model for HDRS was a simple linear age and CTQ model, in such that more severe CM was associated with greater depressive symptoms ($p < 0.001$, Table 2, Fig. 1). The best-fit model for BPRS was a simple linear age and CM model, in such that CM was associated with greater general psychiatric symptoms ($p = 0.015$, Table 2, Fig. 1). Although linear age provided the best-fit model for SOFAS and medication use, neither measure was significantly associated with age (Table 1).

3.2. Effect of CM on hippocampal and amygdala development

Best-fit models for each ROI are presented in Table 3. All ROIs increased in a linear fashion throughout youth. An interaction of CM with age indicated that individuals with CM had a reduced rate of right hippocampal grey matter growth compared to non-maltreated individuals ($p = 0.011$, Table 3, Fig. 2). Given HDRS was associated with both CM (Table 2) and right hippocampal volume (Supplementary Table 2), we tested whether symptom severity could mediate the effect of CM on right hippocampal development. In the extended mediator model, greater depressive symptoms were associated with greater right hippocampal volume ($\beta = 10.00$, $p = 0.011$). The interaction of CM with age remained significant ($F = 4.346$, $p = 0.039$); suggesting depressive symptoms most likely do not mediate the effect of CM on right hippocampal volume. Linear age provided the best-fit model for the left amygdala, right amygdala and left hippocampus volumes: CM did not moderate the development of these regions during youth (Table 3, for outcome of complex model see Supplementary Table 3).

4. Discussion

In this mixed cross-sectional/longitudinal study of young people, exposure to CM was associated with reduced rates of right hippocampal grey matter development compared to non-maltreated people. This results bridges the gap between child and adult research findings and provides novel evidence that CM is associated with disrupted hippocampal development in youth. Irrespective of CM and symptom severity, left hippocampal and bilateral amygdala volume increased linearly throughout youth similarly to non-maltreated people and what has been previously reported in health brain development. We found severity of CM to be associated with worse depressive and general psychiatric symptoms, but CM groups did not appear to have different clinical trajectories.

The hippocampal growth observed in the present study is consistent with previous evidence of the region's prolonged development (Gogtay et al., 2006; Ostby et al., 2009; Uematsu et al.,

Table 1
Group differences in demographic and clinical characteristics.

	All subjects (n = 123)			Longitudinal group (n = 52)		
	No-CM (n = 55)	CM (n = 68)	Group difference	No-CM (n = 18)	CM (n = 34)	Group difference
Age, years	19.8 ± 3.2	19.9 ± 3.4	t = −0.159, p = 0.874	20.6 ± 2.9	19.5 ± 3.6	t = 1.110, p = 0.272
Females	35 (63.6%)	44 (64.7%)	χ^2 = 0.015, p = 0.902	11 (61.1%)	22 (64.7%)	χ^2 = 0.066, p = 0.798
Any diagnosis						
Mood	51 (92.7%)	64 (94.1%)	χ^2 = 0.097, p = 0.756	17 (94.4%)	32 (94.1%)	χ^2 = 0.002, p = 0.962
Psychosis	12 (21.8%)	20 (29.4%)	χ^2 = 0.911, p = 0.340	6(33.3%)	11(32.4%)	χ^2 = 0.005, p = 0.943
Anxiety	34 (61.8%)	35 (51,5%)	χ^2 = 1.322, p = 0.250	9(50%)	18(52.9%)	χ^2 = 0.041, p = 0.840
Early disorder onset[a]	11(20%)	19 (27.9%)	χ^2 = 1.463, p = 0.226	14 (100%)	16 (47.1%)	**χ^2=7.795, p=0.005**
Illness duration[a]	5.7 ± 4.7	5.3 ± 4.6	t = 0.350, p = 0.727	6.7 ± 3.6	4.3 ± 4.0	t = 1.844, p = 0.073
Total CTQ	33.0 ± 4.9	54.2 ± 12.3	**t=-13.006, p<0.001**	32.4 ± 4.7	54.5 ± 11.7	**t=-9.681, p<0.001**
Sexual abuse subscore	5.2 ± 0.5	7.0 ± 4.7	**t=-3.209, p<0.001**	5.1 ± 0.2	6.5 ± 4.0	**t=-2.149, p<0.001**
Physical abuse subscore	5.5 ± 0.9	9.0 ± 4.2	**t=-6.705, p<0.001**	5.5 ± 0.9	9.5 ± 4.1	**t=-5.530, p<0.001**
Emotional abuse subscore	7.8 ± 2.0	14.7 ± 4.4	**t=-11.621, p<0.001**	7.8 ± 2.2	14.9 ± 4.5	**t=-7.573, p<0.001**
Physical neglect subscore	6.1 ± 1.4	9.0 ± 3.0	**t=-7.172, p<0.001**	6.0 ± 1.4	9.5 ± 2.8	**t=-5.946, p<0.001**
Emotional neglect subscore	8.6 ± 3.2	14.5 ± 5.0	**t=-7.982, p<0.001**	8.1 ± 2.5	14.1 ± 5.0	**t=-5.833, p<0.001**

Mean ± standard deviation or n (percentage of cohort) given where appropriate. Percentages are indicative of the proportion within the group.
Significance of $p < 0.05$ is indicated in bold.
[a] Age of illness onset was collected from a limited number of participants. From all subjects: No-CM n = 43 and CM n = 51. From longitudinal group: No-CM n = 14 and CM n = 27. CTQ: childhood trauma questionnaire.

Table 2
Best fit models for clinical variables.

Measure	Best fit model	Intercept	Age	CTQ	CM
HDRS	Linear age and CTQ model	F = 14.2 β = 6.76 ***	F = 0.144 β = 0.01	F = 13.22 β = 0.14 ***	
BPRS	Linear age and CM model	F = 2659.35 β = 42.32 ***	F = 2.1 β = −0.03		F = 6.08 β = −3.86*
SOFAS	Linear age	F = 3211.31 β = 63.63 ***	F = 0.63 β = −0.02		
Medication use	Linear age	F = 2190.09 β = 40.57***	F = 3.32 β = −0.04		

Significance depicted by *:$p < 0.05$, **:$p < 0.01$, ***:$p < 0.001$. HDRS: Hamilton Depression Rating Scale. BPRS: Brief Psychiatric Rating Scale. SOFAS: Social and Occupational Functioning Assessment Scale.

2012; Wierenga et al., 2014). It has been difficult to determine the timing of the peak of hippocampal grey matter, however, estimates range from 11 years (Uematsu et al., 2012) to after 30 years of age (Ostby et al., 2009). These discrepancies may be underpinned by the heterogeneity of hippocampal subregion development (Gogtay et al., 2006), methodological differences (i.e.: correction for intracranial volume), and, as we show in the present manuscript, exposure to CM. The enduring impact of CM on the hippocampus likely stems from alterations to the epigenome [see Provençal and Binder (2015) for review]. For example, Boku et al. (2015) recently identified a pathway involving DNA [cytosine-5-]-methyltransferase (DNMT1) and retinoic acid receptor α that mediates the reduced capacity of adult progenitor cells in the dentate gyrus of late adolescent rats to differentiate following maternal separation. Although the translatability of maternal separation rodent models to cases of human child abuse and neglect has been questioned (Molet et al., 2014), certain epigenetic similarities have been discovered such as enhanced DNA methylation of NR3CR1 (Suderman et al., 2012). Additionally, in line with our recent meta-analysis (Paquola et al., 2016), we found the effect of CM on the hippocampus to be lateralized to the right hemisphere. The greater sensitivity of the right, compared to the left, hippocampus may stem from differences in developmental peaks (Uematsu et al., 2012) or function (Igloi et al., 2010).

Individuals with CM did not present with abnormal amygdala development. The clinical heterogeneity of our sample may have diminished the observable effect of CM on amygdala volume as CM related reductions in amygdala grey matter have been detected exclusively in studies that compare psychiatrically matched groups (Paquola et al., 2016). Alternatively, the effects of CM on the amygdala may be primarily functional. Enhanced amygdala activation to emotional faces is consistently detected amongst individuals with a history CM (Bogdan et al., 2012; Grant et al., 2011; van Harmelen et al., 2013). Since findings on the impact of CM on

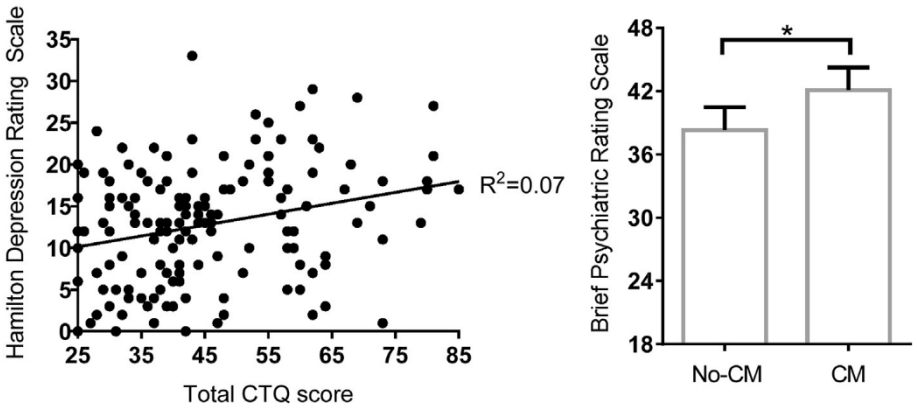

Fig. 1. Childhood maltreatment is related to worse depressive and psychiatric symptoms *Left*: Scatter plot and regression line depicting the relationship of total Childhood Trauma Questionnaire (CTQ) with Hamilton Depression Rating Scale score. Each point represents an individual time point. *Right*: Column graph depicting the difference in Brief Psychiatric Rating Scale score of individuals without (No-CM) and with a history of childhood maltreatment (CM). *Note*: Subject repetition and age were controlled for within statistical analysis but are not accounted for in the above graphs.

Table 3
Best fit models for grey matter volumes.

Region	Best fit model	Intercept	Age	CM	Age × CM	Mood	Psychosis	Anxiety	eTIV
Left amygdala	Linear age	F = 37.93 β = 1548.90***	F = 3.88 β = 0.78 *			ns	ns	ns	ns
Right amygdala	Linear age	F = 14.46 β = 999.71***	F = 5.77 β = 0.97 *				ns	ns	ns
Left hippocampus	Linear age	F = 125.46 β = 4282.48***	F = 6.62 β = 1.90 *			ns	ns	ns	ns
Right hippocampus	Linear age and CM interaction model	F = 142.51 β = 4608.25***	ns	ns	F = 4.87 β = 3.28*	ns	ns	ns	ns

CM: childhood maltreatment. Mood: any mood diagnosis. Psychosis: any psychosis diagnosis. Anxiety: any anxiety diagnosis. eTIV: estimated intracranial volume. Significance depicted *:p < 0.05, **:p < 0.01, ***:p < 0.001.

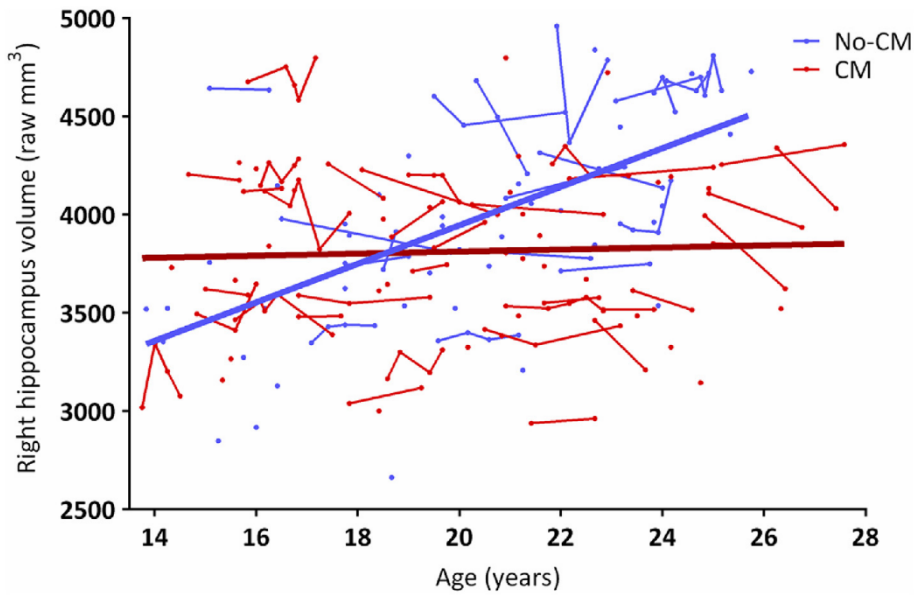

Fig. 2. Distinct right hippocampal developmental trajectories of individuals with and without childhood maltreatment. Each point represents right hippocampal volume at an individual time point and connections between points represent an individual's right hippocampal development across time points. Trend lines depict average right hippocampal growth of individuals without childhood maltreatment (No-CM, blue, y = 98.04x + 1986) and individuals with childhood maltreatment (CM, red, y = 5.229x + 3708). Inspection of model fixed effects revealed that there was significant growth in the No-CM group (F = 43.90, p < 0.0001), but no significant change over time in the CM group (F = 0.22, p = 0.64). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adult amygdala volume have been mixed (Paquola et al., 2016) future longitudinal research into the effects of CM on the amygdala would benefit from including functional MRI.

CM has been repeatedly linked to psychiatric illness in adulthood (Kuhn et al., 2015; Scott et al., 2010; Spauwen et al., 2006). Our findings support and extend on this work by demonstrating a dose-dependent relationship between severity of CM and severity of depressive symptoms. Although CM and depressive

symptoms were found to be independently related to hippocampal volume, the three-way relationship between CM, depression and hippocampal volume appears to be more complex than previously hypothesised (Teicher et al., 2016).

This study is not without limitations. Firstly, the retrospective nature of the CTQ may lead to inaccurate reports of CM. The validity of the CTQ, in comparison with psychiatrist-led interviews, has been established by a large body of literature (Bernstein et al., 1997; Karos et al., 2014; Spinhoven et al., 2014), and as such is a useful tool for research projects in its simplicity and robustness. The complexity of the statistical model limited our ability to formally test for mediation of clinical outcomes. More simple models using set time points and dichotomous classification of illness, such as Whittle et al. (2013), may be more appropriate for mediation analyses. Next, although the HDRS, BPRS and SOFAS are well validated in clinical settings they may lack the sensitivity to characterise clinical trajectories. Future studies may benefit from the inclusion of more accurate predictors of clinical trajectory and additional measures that capture more symptom clusters, such as anxiety. Finally, the use of a heterogeneous psychiatric cohort provides insight into the general effect of CM in psychiatrically vulnerable individuals, but this research needs to be extended into healthy cohorts and diagnosis specific groups to fully characterise the impact of CM on subcortical brain development during youth.

In conclusion, this is the first longitudinal study to show CM is associated with disrupted hippocampal development in youth. This study has significant implications for the treatment of individuals with CM since they are clinically (and neurobiologically) distinct from non-maltreated counterparts in terms of the severity of symptoms and hippocampal development. Future studies should work to characterise the complex relationship between CM, grey matter and psychiatric risk within more homogenous cohorts and to translate neuroimaging findings to clinical practice.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2017.03.019.

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CHAPTER IV

"Adaptation to our surroundings is one of the most important physiologic reactions in life; one might even go so far as to say that the capacity of adjustment to external stimuli is the most characteristic feature of live matter." – Hans Selye, 1951

From Hans Selye to the present day, increased understanding of biological stress can shed light on the capacity of the child to adjust to an abusive or neglectful environment. Shifting perspectives in stress research have historically been driven by animal studies, but the clinical utility of stress theories is dependent upon their translation to natural human settings.

Hans Selye first constructed a conceptual and theoretical framework for investigating biological stress in 1936 (Selye, 1936). Based on observations of mouse responses to noxious agents, Selye (1936) described the "General Adaptation Syndrome" as the non-specific biochemical reactions to various stressors. He asserted that persistent stress elicits a transition from an "alarm reaction" to a "stage of resistance", where the animal adapts to the stressor, then to a "stage of exhaustion", where the acquired adaptation is lost (Selye, 1946). Selye attributed the aetiology of numerous illnesses to abnormal adaptive reactions in this stress process (Selye, 1951). These conceptions shaped stress research for the subsequent decades and presently held theories of stress remain reminiscent of Selye's claims. McEwen and Stellar (1993) described biological stress and stress-related disease in terms of allostasis, the process of achieving homeostasis. Repeated physiological accommodations to stress were theorised to increase an organisms' "allostatic load" and cause "wear and tear". This theory, commonly referred to as the cumulative stress hypothesis, was bolstered by evidence that stress induced increases in glucocorticoids gradually damage hippocampal neurons (Sapolsky, Krey and McEwen, 1986). The cumulative stress theory explains how stress responses that occur within a millisecond to a minute can lead to changes throughout a human lifespan. The elucidation of the epigenome and critical periods of development prompted a paradigmatic shift in the way we think of adaptation on a longer time scale, however. The long-term development of the brain is influenced by early life modifications to the epigenome and events during critical periods. In light of this knowledge, the mismatch hypothesis postulates that early life stress, rather than adding to allostatic load, can trigger an adaptive developmental trajectory which engenders resilience to later stress (Schmidt, 2011). While these theories are commonly applied in animal experiments, their translation to human research has been limited.

This chapter evaluates the cumulative stress and mismatch hypotheses in respect to the impact of childhood abuse and recent stress on clinical symptoms, brain structure and brain function. The aim was to shed light on the mechanisms that underpin brain alterations following childhood maltreatment. Severity of psychiatric symptoms mirrored the cumulative stress hypothesis, whereas left hippocampal volume and prefrontal-hippocampal functional connectivity were predicted by the mismatch

hypothesis. These findings suggest that limbic circuitry adapts to the early life environment, but this adaptation is not necessarily beneficial to psychiatric health. The divergence of clinical from neuroimaging findings also reflects a shift in the field from corresponding mental function with localised brain differences to network-level alterations (Xia *et al.*, 2017). Further research into the impact of childhood maltreatment on structural and functional brain networks could help elucidate the relationship to mental function.

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Utility of the Cumulative Stress and Mismatch Hypotheses in Understanding the Neurobiological Impacts of Childhood Abuse and Recent Stress in Youth with Emerging Mental Disorder

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Abstract: Childhood abuse has an enduring impact on the brain's stress system. Whether the effects of childhood abuse and adulthood stress are additive (cumulative stress hypothesis) or interactive (mismatch hypothesis) is widely disputed, however. The primary aim of this study was to test the utility of the cumulative stress and mismatch hypotheses in understanding brain and behaviour. We recruited 64 individuals (aged 14–26) from a specialised clinic for assessment and early intervention of mental health problems in young people. A T1-weighted MRI, a resting state fMRI and clinical assessment were acquired from each participant. Grey matter estimates and resting state functional connectivity (rsFC) of the hippocampus, amygdala and anterior cingulate cortex (ACC) were determined using segmentation and seed-to-voxel rsFC analyses. We explored the effects of childhood abuse and recent stress on the structure and function of the regions of interest within general linear models. Worse psychiatric symptoms were significantly related to higher levels of life time stress. Individuals with mismatched childhood and recent stress levels had reduced left hippocampal volume, reduced ACC-ventrolateral prefrontal cortex rsFC and greater ACC-hippocampus rsFC, compared to individuals with matched childhood and recent stress levels. These results show specific utility of the cumulative stress hypothesis in understanding psychiatric symptomatology and of the mismatch hypothesis in modelling hippocampal grey matter, prefrontal rsFC, and prefrontal-hippocampal rsFC. We provide novel evidence for the enduring impact of childhood abuse on stress reactivity in a clinical population, and demonstrate the distinct effects of stress in different systems. *Hum Brain Mapp 38:2709–2721, 2017.*

Key words: childhood abuse; stress; MRI; grey matter; resting state

INTRODUCTION

The brain regions involved in emotion and stress undergo both dendritic and synaptic remodelling in response to a psychologically traumatic event. The effects differ depending on the frequency, severity and timing of the stressor(s) (for review, see McEwen et al. [2015]). Human neuroimaging studies have found that adults with a history of childhood maltreatment and even those with a recent exposure to

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trauma have reduced hippocampal, amygdala and anterior cingulate cortex (ACC) grey matter, compared to individuals without any history of trauma [Aas et al., 2012, Ansell et al., 2012, Chaney et al., 2014, Cohen et al., 2006, Dannlowski et al., 2012, Hoy et al., 2012, Kuo et al., 2012, Malykhin et al., 2012, Opel et al., 2014, Papagni et al., 2011, Sodre et al., 2014, Vythilingam et al., 2002, Woon et al., 2010]. Childhood maltreatment has also been associated with reduced functional connectivity between regions involved in stress [Birn et al., 2014, Chugani et al., 2001, Herringa et al., 2013, Thomason et al., 2015]. In contrast, high adulthood stress has been linked to elevated hippocampal-ventromedial prefrontal cortex connectivity [Admon et al., 2013a], as well as reduced anterior cingulate functional connectivity [Kennis et al., 2015].

Childhood abuse is strongly associated with adulthood mental illness. For example, a Canadian study of over 23,000 individuals found physical or sexual abuse in childhood tripled the risk of a psychiatric diagnosis in adulthood [Afifi et al., 2014]. Despite the compelling evidence that early life plays a large role in determining emotional processing, stress sensitivity and psychiatric risk in adulthood [Buchmann et al., 2014, Poon and Knight, 2012, van Vugt et al., 2014, Young and Widom, 2014, Scott et al., 2010, Spauwen et al., 2006], the interaction of childhood and adulthood stress on brain structure and function has not been thoroughly researched in humans. Two opposing views have emerged that attempt to describe how early life stress programs an individual's response to later life stress [Nederhof and Schmidt, 2012]. The cumulative stress hypothesis suggests greater exposure to trauma increases disease risk and neurobiological abnormalities in a dose dependent manner. Under this model, childhood and adulthood stress have an additive effect, which is supported by numerous reports of a correlation between lifetime stress and risk of mental illness [Kuhn et al., 2015, Myers et al., 2015, Toussaint et al., 2016, Vinkers et al., 2014]. On the other hand, the mismatch hypothesis suggests an individual is programmed by their early life environment to be suited to a similar environment later in life. The interactive effect of childhood and adulthood stress is central to this theory, in such that an individual with a history of childhood abuse would be at heighted disease risk only if their adulthood environment was not stressful [Santarelli et al., 2014]. Support or rejection of these hypotheses may enhance our understanding of stress sensitivity following childhood abuse. In turn, we can gain insight into the association of childhood abuse with enhanced psychiatric risk. Furthermore, by identifying the neurobiological consequences of childhood abuse and recent stress, we can provide a concrete basis for early intervention strategies and aid development of targeted treatment programs.

Previous neuroimaging studies have not provided clear support for either theory. Amongst veterans with a history of childhood maltreatment, greater combat exposure was correlated with reduced amygdala volume and reduced ACC thickness [Kuo et al., 2012, Woodward et al., 2013]. However, for veterans without childhood maltreatment, their combat exposure was not related to amygdala volume or ACC thickness. In another study, increased combat exposure and more severe childhood maltreatment were independently associated with enhanced blood oxygenation level dependent (BOLD) response of two anatomically distinct regions of the dorsal ACC upon angry face presentation [Herringa et al., 2013]. Together, this evidence suggests amygdala and ACC grey matter are more vulnerable to adulthood stress following childhood maltreatment, while the impacts of childhood maltreatment and adulthood stress on emotion induced functional reactivity of the ACC are independent.

Our primary aim was to test the utility of the cumulative stress and mismatch hypotheses in modelling hippocampal, amygdala and ACC structure and function. Our secondary aim was to extend research on the interaction of childhood and recent stress to individuals in the early stages of mental disorder. Given the instability and high co-morbidity of psychiatric diagnoses in young people [Hafner et al., 2008], we followed the Research Domain Criteria recommendations of the National Institute of Mental Health [Cuthbert and Insel, 2013] and recruited a wide range of individuals from a specialised mental health clinic for young people. The advantages of using this trans diagnostic approach in research, in contrast to categorical diagnostic grouping, are discussed at length elsewhere [Casey et al., 2013, Cuthbert, 2014, Cuthbert and Insel, 2013]. Thirdly, we wished to ascertain whether variability in childhood trauma neuroimaging research stems from differences in recent stress. For example, childhood maltreatment has been linked to both increased and decreased amygdala volumes in adults [Aas et al., 2012, Cisler et al., 2013, Dean et al., 2014, Frodl et al., 2010, Pechtel et al., 2013, Aust et al., 2014, Hoy et al., 2012, Veer et al., 2015]. To do so, we designed a study in line with the proposal of Nederhof and Schmidt [2012]. Sixty-four young people were split into four groups depending on exposure to childhood sexual or physical abuse (present/absent) and number of recent stressful events (high/low). Childhood sexual and physical abuse are particularly pervasive forms of childhood maltreatment. They have been associated with greater grey matter reductions [Paquola et al., 2016] and greater internalising problems [Pears et al., 2008], compared to other forms of childhood maltreatment. We assessed the independent and interactive effects of childhood abuse and recent stressful events on hippocampal, amygdala and ACC grey matter and resting state functional connectivity (rsFC), as well as psychiatric symptoms. We hypothesised, in line with Kuo et al. [2012] and Woodward et al. [2013], that grey matter volumes would be most reduced in individuals with childhood abuse *and* high levels of recent stressful events. We expected to detect abnormal ACC rsFC in individuals with childhood abuse and/or high stress, however, we did not expect to

TABLE I. Group differences in demographic characteristics

	NoCM-LS [n =17] Group 1	NoCM-HS [n =16] Group 2	CA-LS [n =13] Group 3	CA-HS [n =18] Group 4	One way ANOVA	Post hoc pairwise
Age, years	20.5 (2.9)	20.1 (3.3)	20.5 (2.9)	20.1 (3.5)	ns	
Females	12	10	10	11	ns	
Any mood disorder	15	14	13	18	ns	
Any psychosis disorder	4	4	1	4	ns	
Any anxiety disorder	12	10	6	12	ns	
Illness duration, years	5.4 (3.5)	6.6 (3.6)	4.7 (5.0)	6.4 (4.8)	ns	
Antidepressant use	9	9	7	6	ns	
Mood stabilizer use	2	3	1	4	ns	
Antipsychotic use	4	2	2	8	ns	
CTQ score	31.2 (5.3)	33.6 (5.3)	57.3 (14.7)	62.1 (12.2)	$F(3,60) = 42.01$	1,2 < 3,4
Sexual abuse score	5.0 (0.0)	5.1 (0.5)	8.4 (6.6)	9.3 (6.5)	$F(3,60) = 3.99$	1 < 3,4 2 < 4
Physical abuse score	5.0 (0.0)	5.0 (0.0)	11.5 (4.7)	11.9 (4.6)	$F(3,60) = 22.99$	1,2 < 3,4
Emotional abuse score	7.3 (2.2)	8.3 (1.9)	14.4 (5.4)	16.9 (4.3)	$F(3,60) = 27.78$	1,2 < 3,4
Physical neglect score	6.1 (1.4)	6.1 (1.6)	8.5 (3.4)	9.1 (3.2)	$F(3,60) = 6.75$	1,2 < 3,4
Emotional neglect score	7.8 (2.7)	9.1 (2.9)	14.5 (6.9)	14.8 (4.6)	$F(3,60) = 10.97$	1,2 < 3,4
Recent stressful life events	0.5 (0.5)	2.8 (1.0)	1.2 (0.8)	3.9 (1.3)	$F(3,60) = 42.38$	1,3 < 2<4
Intracranial volume, mm^3	1553810 (141360)	1472616 (173062)	1455437 (146439)	1511983 (116276)	ns	

Mean (standard deviation) or n provided where relevant. F, DoF and r are presented for contrasts in which $P < 0.05$ FDR corrected. Legend: noCM: no childhood maltreatment. CA: childhood abuse. LS: low stress. HS: high stress. CTQ: Childhood trauma questionnaire. ns: not significant.

observe an interaction of childhood abuse and recent stress (in line with Herringa et al. [2013]). Finally, in support of the cumulative stress model, we expected psychiatric symptoms to be most severe in individuals with the greatest life stress.

METHOD

Participants

Sixty-four young people (43 women, age range = 14–26 years) were recruited from a specialised clinic (headspace) for assessment and early intervention of mental health problems in young people [Scott et al., 2012] at the Brain & Mind Centre, Sydney, Australia. Inclusion criteria were a history of moderate-severe childhood physical and/or sexual abuse, or no history of childhood maltreatment. All patients were receiving clinician-based case management and relevant psychosocial interventions at the time of assessment. Primary diagnoses (as determined by a trained research psychologist via DSM-IV criteria) included depressive disorder ($n = 34$), bipolar disorder ($n = 15$), psychotic disorder ($n = 7$) and anxiety disorder ($n = 8$). Seventy-five percent of the participants presented with comorbid axis-1 psychiatric diagnoses. To better characterise participants, we have noted the presence of any mood disorder, psychosis disorder or anxiety disorder in Table I. Patients who were treated with psychotropic medications were assessed under 'treatment as usual' conditions, that is, medications were not interrupted in any way. At the time of assessment 29.7% of patients were not taking any psychotropic medications, 51.6% were taking a second-generation antidepressant, 14.1% were taking mood stabilising medication and 23.4% were taking an atypical antipsychotic medication (Table I). Exclusion criteria for all participants were medical instability (as determined by a psychiatrist, on the basis stability of treatment and symptoms), history of neurological disease (e.g. tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g. cancer, electroconvulsive therapy in the last 3 months), intellectual and/or developmental disability (a predicted IQ score < 70), insufficient English for testing or psychiatric assessment, and current substance dependence. The study was approved by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent.

Clinical Assessment

The Childhood Trauma Questionnaire (CTQ) short form, a retrospective self-report questionnaire, was used to measure exposure to maltreatment prior to the age of 16 [Bernstein et al., 1997]. The CTQ separately assesses experiences of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect, using a rating system along a five point Likert scale from 1 (never true) to 5 (very often true). Each participant produces a score from 5 to 25 for each subscale, and an additive score from 25 to 125 for total CTQ. Moderate-severe cut-offs for each subscore were used to classify the presence of childhood maltreatment [Bernstein et al., 1997]; sexual abuse ≥ 8, physical abuse ≥ 10, emotional abuse ≥ 13, physical neglect ≥ 10 and emotional neglect ≥ 15. Recent stressful events were measured with a brief checklist of threatening experiences [Brugha and Cragg, 1990]. Participants were asked

to indicate (yes/no) whether they had experienced each of the twelve life events in the past 12 months.

In addition, a trained research psychologist conducted a clinical assessment (in a semi-structured interview format) to inform the diagnostic classification and to determine the nature and history of any mental health problems. The assessment included the Hamilton Depression Rating Scale (HDRS, 17-item) [Hamilton, 1967] to quantify current (over the last seven days) mood symptoms, the Brief Psychiatric Rating Scale (BPRS) [Overall and Gorham, 1962] to quantify current general psychiatric symptoms, the Kessler-10 (K-10) [Kessler et al., 2002], a brief instrument designed to detect psychological distress [Andrews and Slade, 2001] and the Overall Anxiety Severity and Impairment Scale (OASIS), a brief continuous measure of anxiety-related severity and impairment [Norman et al., 2006].

Magnetic Resonance Imaging Acquisition

Participants underwent MRI scanning using a 3-Tesla GE MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) at the Brain & Mind Centre, Sydney, Australia. From each participant we acquired a high resolution structural image (Customized MP-RAGE 3D T1-weighted sequence (0.9 mm isotropic resolution): repetition time (TR) = 7264ms; echo time (TE) = 2784ms; flip angle = 15°; coronal orientation; field of view (FOV) = 230 × 230 mm; matrix of 256 × 256; total slices =196) and resting state BOLD data (Echo planar imaging sequence: TR = 3000 ms; TE = 36 ms; slice thickness = 3.0 mm; flip angle = 90°; FOV = 240 × 240mm; matrix = 64 × 64; total slices = 20, total volumes = 273). Participants were instructed to rest comfortably with eyes closed without moving or falling asleep for the duration of the scans.

Structural Imaging Analysis

Volumetric analyses were performed using FMRIB Software Library (FSL) v5.0 [Smith et al., 2004]. Bilateral amygdalae and hippocampi were selected as regions of interest (ROI) based on extant literature and measured using FIRST software on T1-weighted images [Patenaude et al., 2011]. Firstly, images were registered to MNI152 standard space using FMRIB's Linear Image Registration Tool (FLIRT). Then, the surface mesh of each subcortical structure was extracted and transformed back to original MRI space, filled and boundary corrected. Boundaries were visually inspected for gross errors. Additionally, total intracranial volume was estimated using SIENAX [Smith et al., 2002]. The process involved extraction of brain and skull images from a single whole head T1 weighted image, registration of the brain image to MNI152 standard space and tissue type segmentation with partial volume estimation. Finally, the volume of each structure for each subject was calculated in cubic millimetres and exported into SPSS 21.0 [SPSS Corp., 2012].

FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu/) was used to obtain cortical thickness measurements. ACC thickness (instead of volume) was measured to make results comparable to extant literature. Processes included motion correction and averaging of two volumetric T1-weighted images [Reuter et al., 2010], removal of non-brain tissue [Segonne et al., 2004], alignment of scans to Talairach space, segmentation of the deep grey matter volumetric structures [Fischl et al., 2002, Fischl et al., 2004], intensity normalization [Sled et al., 1998], tessellation of the grey matter/white matter boundary, topology correction [Fischl et al., 2001, Segonne et al., 2007] and surface deformation to optimally place the grey/white and grey/cerebrospinal fluid borders [Dale et al., 1999, Dale and Sereno, 1993, Fischl and Dale, 2000]. Resulting cortical representations underwent surface inflation [Fischl et al., 1999a], registration to a spherical atlas to align individual cortical folding patterns with group cortical geometry [Fischl et al., 1999b], parcellation of the cortex into gyral and sulcal features [Desikan et al., 2006b, Fischl et al., 2004] and creation of cortical thickness statistical maps, calculated as the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the tessellated surface [Fischl and Dale, 2000]. All images were visually inspected and any inaccuracies in segmentation and parcellation were manually edited. Finally, thickness measurements of bilateral rostral ACC (rACC) and caudal ACC (cACC) were extracted for each individual and exported to SPSS Version 21.0 [SPSS Corp., 2012].

Functional Imaging Analysis

Image preprocessing was performed using the Statistical Parametric Mapping (SPM12) software package (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). Functional images were subjected to slice timing correction and motion realignment before being co-registered to the structural image. Then both structural and functional scans were normalised to MNI space and resampled into a 2 × 2 × 2 mm^3 voxel size. Segmentation was performed on the normalised structural image to yield grey matter, white matter and cerebrospinal fluid masks. Functional images were then smoothed using 8 mm full-width at half-maximum Gaussian.

Functional connectivity was measured via a seed-based correlation method within the CONN-fMRI functional connectivity toolbox [Whitfield-Gabrieli and Nieto-Castanon, 2012]. To mitigate the impact of movement and physiological noise confounds the CONN-fMRI toolbox utilises anatomical component correction to regress principal components of white matter and cerebrospinal fluid from the BOLD time series at a voxel level before the resultant residual time-series are band-pass filtered ($0.008 < f < 0.09$ Hz). Seed regions were defined as the left hippocampus, right hippocampus, left amygdala, right amygdala, left rACC, right rACC, left cACC and right cACC (Fig. 1). Seed regions were masked using

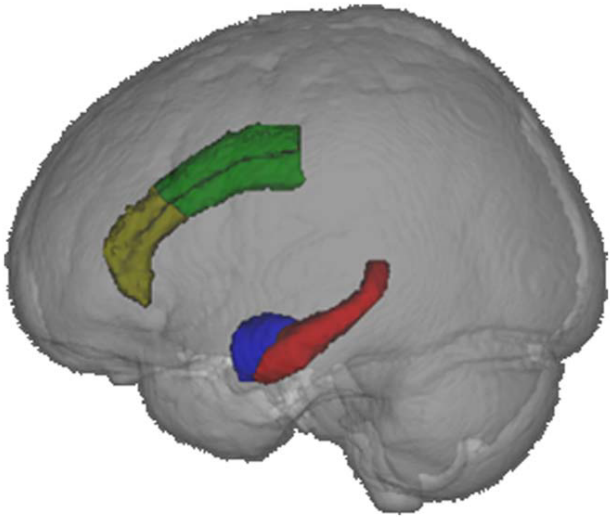

Figure 1.
The left hippocampus (red), left amygdala (blue), left caudal ACC (green) and left rostral ACC (yellow) seed regions, presented from a left view in neurological convention. [Color figure can be viewed at wileyonlinelibrary.com]

automated anatomical labelling [Desikan et al., 2006a, Tzourio-Mazoyer et al., 2002]. Pearson's correlation coefficients were generated between the seed region time series and the time series of all other voxels, and converted to normally distributed z-scores for second level general linear model analyses (described in the following section). Following statistical analysis, we extracted the z standardised correlation coefficients of each significant seed-to-voxel cluster pair for each participant. The correlation coefficients were exported to SPSS Version 21.0 [SPSS Corp., 2012] to estimate effect sizes and exported to GraphPad Prism [GraphPad, 2014] to illustrate group level effects (Fig. 3).

Data Analysis

Participants with moderate-severe childhood physical and/or sexual abuse were classed as the child abuse group (CA). Participants below the moderate-severe cut-off on all five subscores of the CTQ were classed as the no childhood maltreatment group (NoCM). Next, both the CA and NoCM groups were mean split into low recent stress (LS) and high recent stress (HS) groups based on the number of threatening life events experienced in the past year. As a preliminary analysis, we compared age, gender, diagnosis, illness duration, medication use, CTQ scores, number of recent stressful events and intracranial volume across groups using a one-way ANOVA. Significant effects were further investigated with post hoc pairwise comparisons. We performed four statistical tests within general linear models to determine the relationship of clinical outcomes, grey matter and rsFC with childhood abuse and recent stress: (i) Main effect of childhood abuse (NoCM vs CA); (ii) Main effect of recent stressful events (LS vs HS); (iii) Cumulative stress hypothesis (main effect of the sum term of z standardised total CTQ and z standardised number of recent stressful events) and (iv) Mismatch hypothesis (NoCM-LS and CA-HS vs NoCM-HS and CA-LS). Age, gender, diagnosis, medication use and, in grey matter analyses, intracranial volume were entered as covariates in each analysis.

For clinical analyses, contrasts were considered significant if $P < 0.05$ following False Discovery Rate (FDR) correction across the four clinical outcomes (HDRS, BPRS, K10 and OASIS) and the four tests. For structural analyses, contrasts were considered significant if $P < 0.05$ following FDR correction across the eight ROIs and the four tests. In each case, FDR correction for multiple comparisons was performed within R Studio [R Team, 2015] using the method outlined by Benjamini and Hochberg [1995]. For rsFC analyses, we used conservative thresholds of $P < 0.001$ for height (based on Bonferroni adjustment for eight seed regions and four tests) and $P < 0.05$ FDR corrected for cluster size. Pearson's r values were used as a measure of effect size.

RESULTS

Participant Characteristics

Demographic characteristics of the participants are reported in Table I. The four groups did not differ significantly in terms of age, gender, diagnoses or medication use. Greater depressive symptoms (HDRS), general psychiatric symptoms (BPRS), current distress (K10) and anxiety symptoms (OASIS) were associated with higher levels of combined childhood abuse/recent stress (Table II, Fig. 2). Additionally, childhood abuse was associated with significantly worse clinical outcomes (Table II), and high recent stress was associated with greater depressive and general psychiatric symptoms (Table II).

Structural Imaging

CA and NoCM groups did not significantly differ in terms of amygdala volume, hippocampal volume or ACC thickness (Table II). Subjects reporting HS had approximately 7% thinner right rACC compared to subjects reporting LS (Table II). Individuals with mismatched childhood and recent stress levels (NoCM-HS and CA-LS) had approximately 9% smaller left hippocampal volume compared to individuals with matched childhood and recent stress levels (NoCM-LS and CA-HS, Table II).

Functional Imaging

Seed-to-voxel functional connectivity analyses were performed from each ROI (Fig. 1). Childhood maltreatment groups did not differ significantly in terms of rsFC from any ROI to any cluster of voxels. Compared to LS groups,

TABLE II. Relationship of childhood abuse and recent stress to clinical characteristics and grey matter volume/thickness

	NoCM-LS [n =17]	NoCM-HS [n =16]	CA-LS [n =13]	CA-HS [n =18]	Childhood abuse	Recent stressful events	Cumulative stress hypothesis	Mismatch hypothesis
Hamilton Depression Rating Scale	9.6 (7.0)	15.5 (4.9)	16.3 (6.6)	16.9 (7.2)	$F(1,56) = 9.51$, $r = 0.38$	$F(1,56) = 6.39$, $r = 0.32$	$F(1,56) = 14.73$, $r = 0.47$	Ns
Brief Psychiatric Rating Scale	36.2 (9.9)	40.4 (7.2)	38.9 (5.9)	47.6 (10.9)	$F(1,56) = 7.84$, $r = 0.35$	$F(1,56) = 9.21$, $r = 0.38$	$F(1,56) = 9.52$, $r = 0.38$	Ns
Kessler 10	24.4 (8.7)	29.4 (7.7)	30.7 (30.7)	33.0 (8.9)	$F(1,56) = 11.45$, $r = 0.41$	ns	$F(1,56) = 11.40$, $r = 0.44$	Ns
Overall Anxiety Severity and Impairment Scale	6.2 (3.6)	7.4 (4.4)	8.1 (4.0)	10.2 (5.2)	$F(1,56) = 5.95$, $r = 0.31$	ns	$F(1,56) = 14.14$, $r = 0.41$	Ns
Left amygdala, mm^3	1365 (171)	1410 (257)	1347 (178)	1380 (172)	ns	ns	ns	Ns
Right amygdala, mm^3	1351 (186)	1473 (283)	1337 (193)	1368 (164)	ns	ns	ns	Ns
Left hippocampus, mm^3	3732 (396)	3565 (460)	3263 (457)	3730 (289)	ns	ns	ns	$F(1,61) = 11.71$, $r = 0.40$
Right hippocampus, mm^3	3957 (429)	3957 (556)	3618 (411)	3864 (295)	ns	ns	ns	Ns
Left cACC, mm^2	2.86 (0.29)	3.03 (0.22)	2.81 (0.27)	2.88 (0.22)	ns	ns	ns	Ns
Right cACC, mm^2	2.71 (0.21)	2.83 (0.17)	2.83 (0.19)	2.71 (0.28)	ns	ns	ns	Ns
Left rACC, mm^2	3.05 (0.27)	3.00 (0.30)	3.06 (0.32)	3.04 (0.28)	ns	ns	ns	Ns
Right rACC, mm^2	3.05 (0.25)	2.89 (0.23)	3.22 (0.28)	2.93 (0.25)	ns	$F(1,61) = 10.88$, $r = 0.39$	ns	Ns

Mean (standard deviation) or n provided where relevant. F, DoF and r are presented for contrasts in which $P < 0.05$ following FDR correction.
Legend: noCM: no childhood maltreatment. CA: childhood abuse. LS: low stress. HS: high stress. CTQ: Childhood trauma questionnaire. ns: not significant.

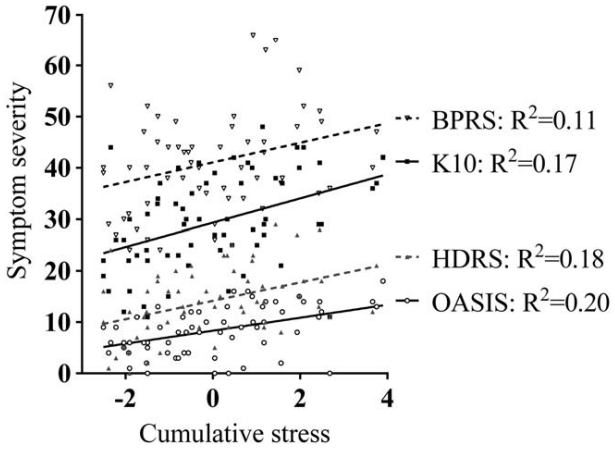

Figure 2.
Greater cumulative life stress is associated with worse psychiatric symptom severity.

individuals reporting HS had enhanced rsFC between the left cACC and bilateral precentral and postcentral gyri (Fig. 3 row 1, Table III). Cumulative stress was not significantly related to rsFC from any ROI to and any cluster of voxels. Mismatched groups had greater rsFC between bilateral rACC and the left hippocampus, compared to matched groups (Fig. 3 row 2, Table III). Additionally, several rsFC pathways from ACC seeds to bilateral ventrolateral prefrontal cortex (vlPFC) and the right supramarginal gyrus were reduced amongst mismatched groups, compared to matched groups (Fig. 3 row 3, Table III).

DISCUSSION

This is the first study to investigate the interaction of childhood abuse and recent stress on brain structure and function in young people. We endeavoured to understand how the cumulative stress and mismatch theories align with human neuroimaging research. In doing so, we provide support for a cumulative stress explanation of clinical symptoms and a mismatch explanation of right hippocampal volume and prefrontal rsFC. We hypothesise, as an extension of Nederhof and Schmidt's [2012] integrated model, that the dichotomy between the observed effects is related to the differential sensitivity of brain-behaviour systems to early life programming. Mismatched early life and later life environments may be most problematic for systems with high sensitivity to early life programming, such as stress induced DNA methylation [Provençal and Binder, 2015]. In the hippocampus, for example, human and rodent studies have shown early life stress is associated with DNA methylation of promotors involved in stress reactivity (NR3C1; [McGowan et al., 2009, Suderman et al., 2012]), synaptic plasticity (protocadherins; [Suderman et al., 2012]) and neuronal differentiation (retinoic acid receptor α; [Boku et al., 2015]). On the other hand, systems with low sensitivity to early life programming are more likely to experience continuous wear and tear due to repeated use of adaptive responses to stress [Lupien et al., 2015].

Our clinical data was suggestive of greater lifetime stress being related to greater depressive, general psychiatric, distress and anxiety symptoms. Similarly, Kuhn et al. [2015] found that the additive effect of childhood maltreatment and a greater number of recent stressful events was related to increased depressive and anxious temperament in a sample of 1158 healthy young adults. Our findings support and extend upon this work by showing that the cumulative effect of stress on psychiatric symptoms is also evident in a real-world clinical setting. Our results, like those of Kuhn et al. [2015], are correlative in nature however and causal relations are difficult to determine. Although our neuroimaging data did not support the cumulative stress hypothesis, greater life stress has been associated with enhanced stress-induced prefrontal-limbic-striatal BOLD response [Seo et al., 2014] and decreased prefrontal BOLD response during emotion regulation [Kim et al., 2013]. Future studies should investigate whether task-oriented brain function mediates the effect of cumulative stress on psychiatric symptoms.

Young people with mismatched childhood and recent stress levels were shown to have abnormal rsFC in pathways responsible for social and cognitive functioning. The ACC, vlPFC and supramarginal gyrus (as part of the posterior parietal cortex) are important nodes of the brain's social cognition network [Satpute and Lieberman, 2006]. The communication of these regions, alongside the medial temporal lobe and medial prefrontal cortex, is important for self-reflection and self-agency. Reduced rsFC of the ACC with the vlPFC and supramarginal gyrus, as reported in the mismatched groups, may reflect downregulation of this system, and has been specifically linked to worse metacognitive abilities elsewhere [Baird et al., 2013]. In addition, precise communication of the ACC with the hippocampus is necessary for effective learning. Greater rsFC between the rACC and hippocampus has been shown to predict worse learning transfer [Gerraty et al., 2014] and has been associatied with greater difficulty in integrating novel information [van Kesteren et al., 2010]. In sum, reduced rsFC between the ACC and vlPFC combined with enhanced rsFC between the ACC and the hippocampus may provide the neural basis for decreased sociality and hippocampal memory, as has been detected in rodent models of the mismatch hypothesis [Ricon et al., 2012, Santarelli et al., 2014]. Furthermore, the mismatch hypothesis may be especially applicable to social and cognitive brain networks due to their high sensitivity to programming in early life [Marquez et al., 2013, Tzanoulinou et al., 2014].

A mismatch of childhood and recent stress levels was also related to abnormalities in hippocampal structure. This may reflect adaptive programming following childhood abuse, in which hippocampal grey matter is primed for high stress. Preclinical research has shown hormones [Renard et al., 2010, Renard et al., 2007], cell adhesion

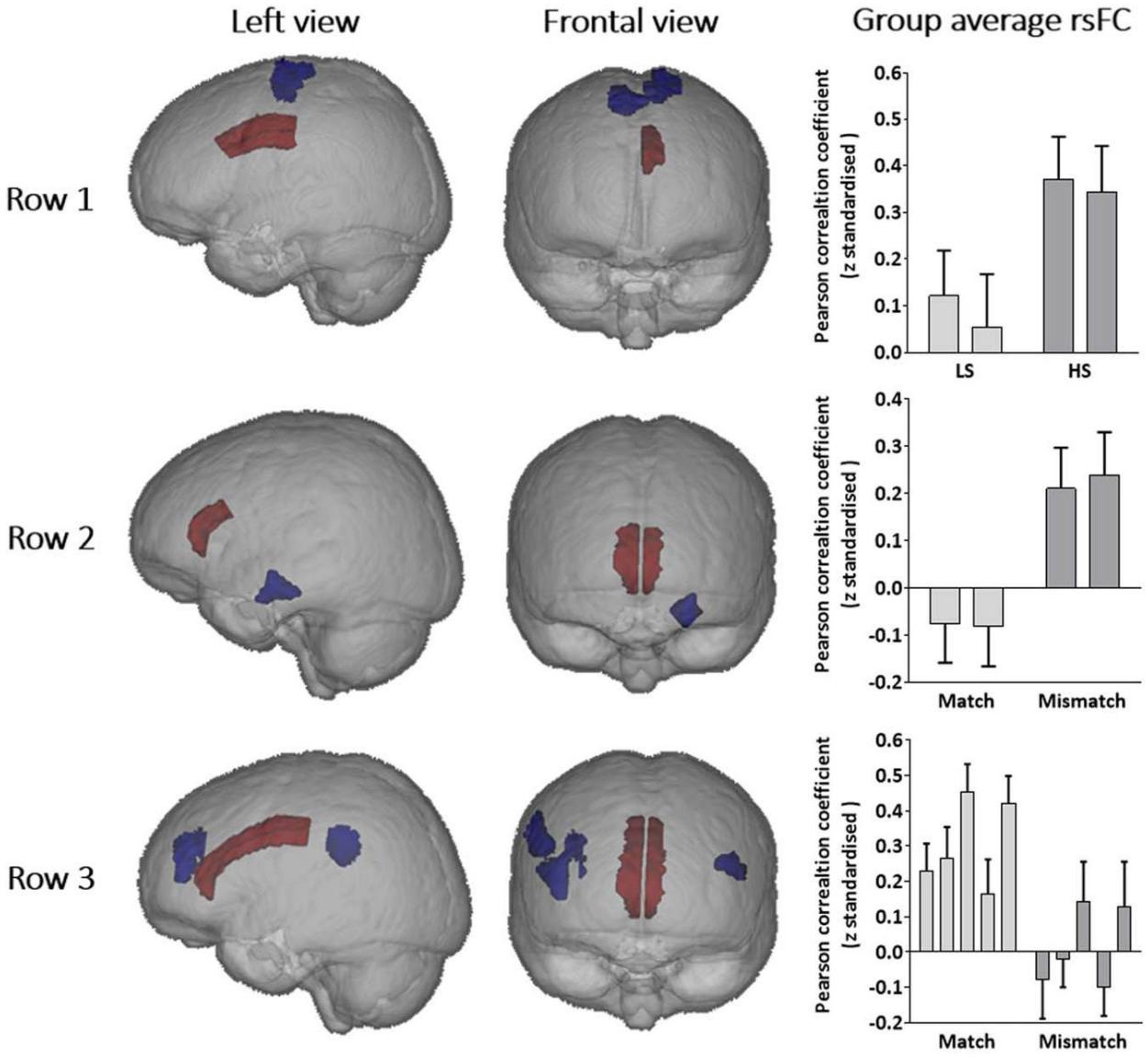

Figure 3.

Each row represents a distinct effect of childhood abuse and/or recent stress on resting state functional connectivity (rsFC). Brains are presented in neurological convention with red representing seeds and blue signifying clusters in which rsFC with a seed region was significantly related to childhood abuse and/or recent stress. In the graphs, columns represent group average z scores of specific seed-to-voxel cluster rsFC, with 95% confidence intervals. *Row 1*: High recent stress was associated with enhanced rsFC of (column i) left cACC-left pre/postcentral gyri and (column ii) left cACC-right pre/postcentral gyri. *Row 2*: Mismatched child and adult stress levels was associated with enhanced rsFC of (column i) right rACC-left hippocampus and (column ii) left rACC-left hippocampus. *Row 3*: Mismatched child and adult stress levels was associated with decreased rsFC of (column i) right rACC-left vlPFC, (column ii) right rACC-right vlPFC, (column iii) right cACC-right supramarginal gyrus, (column iv) left rACC- right vlPFC, (column v) left cACC-right supramarginal gyrus. LS:low recent stress. HS: high recent stress. [Color figure can be viewed at wileyonlinelibrary.com]

molecules [van der Kooij et al., 2015] and epigenetic modifications [Kinnally et al., 2011] mediate the hippocampus' stress sensitivity following early life adversity.

Interestingly, childhood abuse has been repeatedly linked to smaller hippocampal volumes in adults from 18 to 50 years of age [Andersen et al., 2008, Bremner et al., 1997,

TABLE III. Interactive and additive effects of childhood abuse and recent stressful events on seed-to-voxel resting state functional connectivity

Test	Contrast	Seed region	Voxel cluster region	MNI coordinates	Cluster size	*P* value	*r* value
Main effect of childhood abuse	No significant effects						
Main effect of adulthood stress	HS >LS	Left cACC	Left pre/postcentral	−18,-38,66	199	0.003855	0.48
		Left cACC	Right pre/postcentral	12,-22,60	177	0.003855	0.45
Effect of cumulative stress	No significant effects						
Difference between matched and mismatched groups	Mismatch > Match	Right rACC	Left hippocampus	−24,-12,-18	147	0.021685	0.52
		Left rACC	Left hippocampus	−22,-14,-20	161	0.035854	0.52
	Match > Mismatch	Right rACC	Left vlPFC	−40,46,18	151	0.021685	0.57
		Right rACC	Right vlPFC	36,54,16	271	0.003016	0.52
		Right cACC	Right supramarginal	58,-50,36	389	0.000130	0.54
		Left rACC	Right vlPFC	38,48,14	113	0.049409	0.52
		Left cACC	Right supramarginal	56,-46,36	270	0.003427	0.49

P value given at cluster level, FDR corrected.
Legend: LS = low stress. HS = high stress cACC = caudal anterior cingulate cortex. rACC = rostral anterior cingulate cortex, vlPFC = ventrolateral prefrontal cortex.

Bremner et al., 2003, Sala et al., 2011, Stein et al., 1997, Vythilingam et al., 2002, Weniger et al., 2008] but in our study no main effect of childhood abuse was noted. Additionally, in psychosis cohorts, a clear association of childhood maltreatment with hippocampal volume has not been detected [Hoy et al., 2012, Sheffield et al., 2013]. Our study may shed some light on this discrepancy (despite diagnosis not affecting the findings). One possible explanation stems from individuals with psychotic disorders experiencing high levels of trauma [Beards et al., 2013]. Thus, individuals with psychosis may align with the HS groups of our study. In contrast, previous studies which have reported an association of childhood abuse with decreased hippocampal volume may have been primarily composed of individuals with low levels of recent stress. At this point, such an assertion is speculative and further testing of groups matched for psychiatric diagnosis and recent stress is necessary.

In line with Woodward et al. [2013], we found that high recent stress was associated with reduced ACC thickness amongst individuals with childhood maltreatment and that ACC thickness was not related to recent stress amongst individuals without childhood maltreatment. This pattern of results is suggestive of enhanced vulnerability of ACC grey matter to adulthood stress following childhood trauma. Admon et al. [2013b] postulated that reduced rACC following adulthood trauma represents a risk factor for posttraumatic stress disorder. The rACC also plays a central role in emotion regulation [Etkin et al., 2011], and decreased rACC grey matter is associated with anxiety disorders [Shin and Liberzon, 2010] and depressive symptoms [Chen et al., 2007; Lim et al., 2012, Webb et al., 2014]. Given this evidence, abnormal structural remodelling of the rACC in response to stress in CA individuals may underpin enhanced psychiatric vulnerability. To our knowledge, no study has investigated the interaction of childhood trauma on ACC grey matter and subsequent mental health (as has been tested longitudinally in the hippocampus by Rao et al. [2010]).

We detected an association between high recent stress and enhanced rsFC of the cACC with the precentral gyrus. However, this finding contradicts a previous study. Kennis et al. [2015] found that combat exposure was related to reduced rsFC of the cACC and the precentral gyrus, which they proposed was related to motor cortex development following military training. Although our sample differs in numerous ways from the aforementioned study in the type of recent stress experienced, age, gender ratio and psychiatric morbidity, further research is required to understand this anomalous finding.

One limitation of this study is the small size of the four groups. Future studies require larger sample sizes, especially to investigate disorder specific effects. The psychiatric heterogeneity of this cohort is reflective of the clinical service from which participants were recruited [Scott et al., 2012]. However, due to the novelty of this study and the large representation of mood disorders in the cohort, it is difficult to eliminate any potential influence of diagnosis. Replications in other psychiatric cohorts and healthy cohorts are essential to validate the generalizability of these findings. Additionally, the retrospective nature of the CTQ could lead to misrepresentation of childhood maltreatment. The CTQ is a widely used and an effective research tool for cross sectional studies, however, and has been shown to be equally valid to psychiatrist led interviews [Bernstein et al., 1997, Karos et al., 2014, Spinhoven et al., 2014]. Third, susceptibility to early life programming differs greatly between individuals [Ellis et al., 2011], and as such genetic susceptibility should be explored in the future.

CONCLUSION

These results show specific utility of the cumulative stress hypothesis in relation to psychiatric symptoms while the mismatch hypothesis appears to relate to social and cognitive brain systems with high sensitivity to early life programming. These findings highlight the necessity of community-based and clinical programs that reduce stress and improve coping abilities in individuals with a history of childhood abuse, particularly those with major psychiatric disorders. Additionally, the sensitivity of prefrontal-hippocampal networks to stress could be mediated by early intervention social and cognitive training. We hope future studies can continue this avenue of research with the inclusion of genetic susceptibility, which is a key component of the Nederhof and Schmidt [2012] model, as well as longitudinal designs and balanced clinical interventions for fuller characterisation of the effects.

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CHAPTER V

Grey matter research has traditionally been constrained to the investigation of localised inter-individual differences, however, recent innovations allow interrogation of relationships between grey matter regions as well. In this regard, structural covariance analysis offers a unique opportunity to examine the widespread impact of childhood maltreatment on the organisation and development of grey matter networks.

The previous chapters investigated the developmental impact of childhood maltreatment on brain regions involved in stress and emotion. Beyond the specialised functions of individual brain regions, the dynamic interactions between brain regions strongly contribute to the overall functioning of the brain. Complex systems theories are increasingly applied in neuroscience to understand the relationship of inter-regional connections to development and disease (Bassett and Gazzaniga, 2011). Characterisation of the brain as a network of *nodes* (regions) and *edges* (inter-regional relationships) enables a holistic description of the brain. Different aspects of neural structure and function can be described depending on the mode and resolution of network construction. The network approach was recently extended to grey matter, in which structural covariance networks (SCNs) describe the inter-regional covariance of grey matter density or cortical thickness across a population.

The following chapter utilises SCNs to explore the neurodevelopmental impact of childhood maltreatment. By leveraging the association of SCNs to maturation (Alexander-Bloch *et al.*, 2013), the following chapter assesses whether childhood maltreatment affects the development of grey matter networks. The approach involves using SCNs to cluster brain regions together, then statistically evaluating the relationship of childhood maltreatment to grey matter density within each SCN. In doing so, widespread effects of childhood maltreatment may be captured with thousands fewer comparisons than whole brain voxel-based morphometry. Additionally, the SCN framework facilitates complementary structural and functional connectivity analyses to inform on the physiological basis for alterations in the grey matter.

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Structural and functional connectivity underlying grey matter covariance: impact of developmental insult

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5.2 ABSTRACT

Structural covariance networks (SCNs) may offer unique insights into the developmental impact of childhood maltreatment, as structural covariance partly reflects coordinated maturation of distinct grey matter regions. T1-weighted magnetic resonance images were acquired from 121 young people with emerging mental illness. Diffusion weighted and resting state functional imaging was also acquired from a random subset of the participants (n=62). Ten study-specific SCNs were identified using a whole brain grey matter independent component analysis. We assessed the relationship of childhood maltreatment and age with average grey matter density and expression of each SCN. Childhood maltreatment was associated with reduced age-related decline of grey matter density across a SCN that overlapped with the default mode and fronto-parietal networks. Resting state functional connectivity and structural connectivity were calculated in the study-specific SCN and across the whole brain. Grey matter covariance was moderately correlated with rsFC across the SCN, and rsFC fully mediated the relationship between grey matter covariance and structural connectivity in the non-maltreated group. A unique association of grey matter covariance with structural connectivity was detected amongst individuals with a history of childhood maltreatment. Perturbation of grey matter development across the default mode and fronto-parietal networks following childhood maltreatment may have significant implications for mental well-being, given the networks' roles in self-referential activity. Cross-modal comparisons suggest reduced grey matter following childhood maltreatment could arise from deficient functional activity earlier in life.

5.3 INTRODUCTION

Distributed grey matter covariance was first demonstrated in a post mortem study of the visual system, in which the sizes of the optic tract, lateral geniculate nucleus and primary visual area were found to be strongly correlated within individuals, irrespective of hemispheric mass (Andrews, Halpern and Purves, 1997). In the ensuing two decades, advances in neuroimaging have aided the identification of some organising principles of grey matter covariance. The probability of grey matter covariance between two brain regions decreases exponentially with greater anatomical distance (He, Chen and Evans, 2007). However, contralateral homologous regions typically exhibit strong covariance of grey matter volume (Mechelli *et al.*, 2005) and large-scale networks of grey matter covariance, commonly referred to as structural covariance networks (SCNs) have also been identified (Bernhardt *et al.*, 2014) SCNs are highly heritable (Schmitt *et al.*, 2008) and change with age (Zielinski *et al.*, 2010; Li *et al.*, 2013). SCNs provide valuable insight into the organisation of inter-individual differences in grey matter into networks. This approach is critical to understanding grey matter abnormalities in complex brain disorders at a network level.

Biological interpretations of SCNs are presently hindered by the paucity of studies on the correspondence of structural covariance with brain connectivity. Multi-modal imaging takes advantage of the differential sensitivity of neuroimaging modalities to brain physiology and enables a more detailed, integrated understanding of the relationship between brain structure and function. T1-weighted structural MRI scanning allows precise tissue-type segmentation, delineation of subcortical structures and estimation of grey matter volume (van der Kouwe *et al.*, 2008). Diffusion weighted imaging enables characterisation of white matter tracts and, in combination with structural MRI, estimation of the structural connectivity of two grey matter regions. Functional magnetic resonance imaging (fMRI) can be used to estimate patterns of neural activity through proxy measures such as the blood oxygenation level dependent (BOLD) signal. The correlation of distinct regions' BOLD signal (commonly referred to as "functional connectivity") is suggested to indicate a dynamic interaction between the underlying neuronal populations (Friston, 1994). Structural covariance has been demonstrated between regions connected by white matter tracts, such as Broca's area and Wernicke's area (van der Kouwe *et al.*, 2008), however structural covariance does not appear to depend on a direct structural connection. A whole brain comparison of grey matter covariance with structural connectivity reported that only 35-40% of cortical thickness covariance converged with white matter connections (Gong *et al.*, 2012). Cortical thickness covariance is more tightly coupled to resting state functional connectivity (rsFC), especially in cingular, superior temporal, prefrontal and insular areas (Kelly *et al.*, 2012; Alexander-Bloch *et al.*, 2013). Importantly, SCNs are topologically similar to maturational networks; networks characterised by the similarity of regions' developmental trajectories (Alexander-Bloch *et al.*, 2013). In 0-2 year old children, grey matter covariance is preceded by the regions' coordinated maturation, which is in turn

preceded by the emergence of rsFC networks (Geng *et al.*, 2017). The functional basis of SCNs is also evident in their recapitulation of intrinsic connectivity networks derived from resting state fMRI, such as the default mode network (Guo *et al.*, 2015). Age-related changes in SCNs also mirror the development of skills in childhood, including the maturation of language (Zielinski *et al.*, 2010). These parallel lines of evidence have been used to suggest that functional coactivation of distinct grey matter areas prompts coordinated maturation, which drives the development of SCNs (Zielinski *et al.*, 2010; Alexander-Bloch *et al.*, 2013).

Following on from this assertion, it stands to reason that SCNs would be particularly sensitive to developmental insults, such as childhood trauma. Childhood maltreatment, encompassing acts of abuse and neglect prior to the age of sixteen, has an enduring negative impact on sociality, academic performance, psychiatric health as well as physical health (McLeod, Fergusson and Horwood, 2014; Rapoza *et al.*, 2014; Romano *et al.*, 2014). In a recent meta-analysis of 38 articles, adults with a history of childhood maltreatment were found to commonly exhibit reduced hippocampal, amygdala and dorsolateral prefrontal cortex grey matter (Paquola, Bennett, and Lagopoulos 2016). Longitudinal structural MRI studies have shown that childhood maltreatment leads to decreased amygdala growth in young adolescents (12-16 years) and decreased hippocampal growth in youth (14-28 years) (Whittle et al. 2013; Paquola et al. 2017), which suggests childhood maltreatment alters the developmental trajectory of related grey matter regions. Only one study to date has investigated the impact of childhood maltreatment on grey matter covariance (Teicher *et al.*, 2014). Teicher and colleagues utilised graph theory to estimate the centrality (an index of importance) of cortical regions according to the strength and frequency with which the thickness of one region covaried with the thickness of other regions. Childhood maltreatment was associated with a shift in centrality from the anterior cingulate cortex to the precuneus, anterior insula and right parietal-occipital sulcus (Teicher *et al.*, 2014). In line with these findings, fMRI studies have also shown that childhood maltreatment is related to decreased centrality of regions involved in emotion regulation and social cognition (Wang *et al.*, 2014; Cisler *et al.*, 2017).

SCNs also provide unique insight into the spatial extent of childhood maltreatment related effects. For example, reduced grey matter across an SCN would be indicative of a wide spread effect, whereas atypical covariance between regions would be indicative of a more localised effect. In the present study, we use SCNs to assess the impact of childhood maltreatment on grey matter development in young people. In doing, we aim to show the sensitivity of SCNs to developmental insults. We hypothesise that unsupervised detection of SCNs will result in networks similar to intrinsic connectivity networks, and that childhood maltreatment will be related to reduced grey matter across networks involved in stress and emotion. To further elucidate the biological underpinnings of SCNs, we aim to determine the correspondence of grey matter covariance with structural connectivity and functional connectivity at the level of the structural covariance network, intrinsic connectivity network and whole brain. We hypothesise grey matter covariance will be more closely associated with functional connectivity than structural connectivity.

5.4 METHODS

Participants

Demographic and clinical characteristics of the participants are described in Table 1. 121 young people (78 women, age range = 14-26 years) were recruited unbiasedly from a specialised mental health clinic for young people in line with Research Domain Criteria recommendations (Cuthbert and Insel, 2013). This cohort was reflective of a wide range of young people seeking clinical psychiatric assistance. The advantages of such a transdiagnostic approach are discussed at length elsewhere (Casey *et al.*, 2013; Cuthbert and Insel, 2013; Cuthbert, 2014). All patients were receiving clinician-based case management and relevant psychosocial interventions at the time of assessment. Exclusion criteria for all participants were medical instability (as determined by a psychiatrist, on the basis stability of treatment and symptoms), history of neurological disease (e.g. tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g. cancer, electroconvulsive therapy in the last 3 months), intellectual and/or developmental disability (a predicted IQ score < 70), insufficient English for testing or psychiatric assessment, and current substance dependence. The study was approved by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent. Figure 1 provides a general overview of the study design.

Clinical assessment

The Childhood Trauma Questionnaire (CTQ) short form, a retrospective self-report questionnaire, was used to measure exposure to maltreatment prior to the age of 16 (Bernstein *et al.*, 1997). The CTQ separately assesses experiences of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect using a rating system along a five point Likert scale from 1 (never true) to 5 (very often true). Each participant produces a score from 5 to 25 for each subscale, and an additive score from 25 to 125 for total CTQ. SCNs are inherently population based and statistical analyses are based on group comparisons, therefore participants were divided based on exposure to childhood maltreatment. Moderate-severe cut-offs for each sub-score were used to classify the presence of childhood maltreatment; sexual abuse ≥ 8, physical abuse ≥ 10, emotional abuse ≥ 13, physical neglect ≥ 10 and emotional neglect ≥ 15 (Bernstein *et al.*, 1997). Subjects reporting moderate-severe maltreatment in one or more category were allocated to the childhood maltreatment group (CM). Subjects reporting no moderate-severe maltreatment were allocated to the no childhood maltreatment group (No-CM). Additional clinical assessments are described in the Supplementary Material. Group differences in clinical outcomes were measured using t-tests for continuous metrics and chi-squared tests for ordinal metrics. Statistical p values were deemed significant below a threshold of 0.003, which represents a Bonferroni correction for 19 contrasts with an individual alpha level of 0.05.

Table 1: Demographic and clinical characteristics of cohort

	All subjects (n=121)			Cross-modal subjects (n=62)		
	No-CM (n=55)	CM (n=66)	Group difference	No-CM (n=31)	CM (n=31)	Group difference
Age, years	19.8 (3.2)	19.9 (3.4)	t(119)=0.08	20.2 (3.0)	20.2 (3.1)	t(60)=0.50
Females	64%	65%	χ^2(119) =0.03	74%	62%	χ^2(60)=1.18
Total CTQ	34.4 (9.4)	53.6 (11.8)	t(119)=9.94 *	34.1 (7.7)	55.5 (11.5)	t(60)=24.04 *
SA	5.3 (1.4)	6.9 (4.7)	t(119)=2.60 *	5.4 (1.8)	7.2 (5.2)	t(60)=11.34 *
PA	5.9 (2.6)	8.8 (3.9)	t(119)=9,80 *	5.8 (1.2)	9.3 (3.9)	t(60)=16.26 *
EA	8.1 (2.9)	14.6 (4.3)	t(119)=9,94 *	7.8 (2.6)	15.3 (4.2)	t(60)=16.91 *
PN	6.2 (1.6)	8.9 (3.0)	t(119)=6.22 *	6.3 (1.6)	9.1 (3.3)	t(60)= 19.06 *
EN	8.9 (3.9)	14.4 (4.9)	t(119)=6.77 *	8.8 (3.6)	14.7 (4.6)	t(60)=17.43 *
Mood disorder	93%	93%	χ^2(119)=0.07	97%	97%	χ^2(60)<0.01
Psychosis disorder	20%	30%	χ^2(119) =1.67	23%	26%	χ^2(60)=0.09
Anxiety disorder	58%	55%	χ^2(119)=0.16	65%	61%	χ^2(60)=0.07
Medication use	81%	72%	χ^2(98)=1.14	85%	80%	χ^2(50)=0.13
HDRS	12.7 (6.5)	15.3 (6.7)	t(106)=2.04	12.5 (6.6)	16.3 (6.3)	t(59)=16.40 *
BPRS	39.8 (9.8)	45.1 (9.5)	t(108)=3.04	38.8 (8.7)	46.8 (9.6)	t(59)=33.00 *
OASIS	7.0 (4.5)	10.8 (4.5)	t(119)=3.69 *	7.1 (4.2)	10.9 (4.2)	t(60)=14.68 *
Kessler-10	28.4 (8.9)	32.5 (9.9)	t(119)=2.37	27.2 (8.8)	33.8 (8.3)	t(63)=25.88 *

Mean (standard deviation) or n (%) provided where relevant. t(df) and Chi squared outcomes are presented, with * indicating $p<0.003$. Clinical data was not available for all participants. The number of participants with available data is equivalent to df+2. Legend: No-CM: no childhood maltreatment. CM: childhood maltreatment. CTQ: Childhood trauma questionnaire. SA: sexual abuse. PA: physical abuse. EA: emotional abuse. PN: physical neglect. EN: emotional neglect. HDRS: Hamilton Depression Rating Scale. BPRS: Brief Psychiatric Rating Scale. OASIS: Overall Anxiety Severity and Impairment Scale

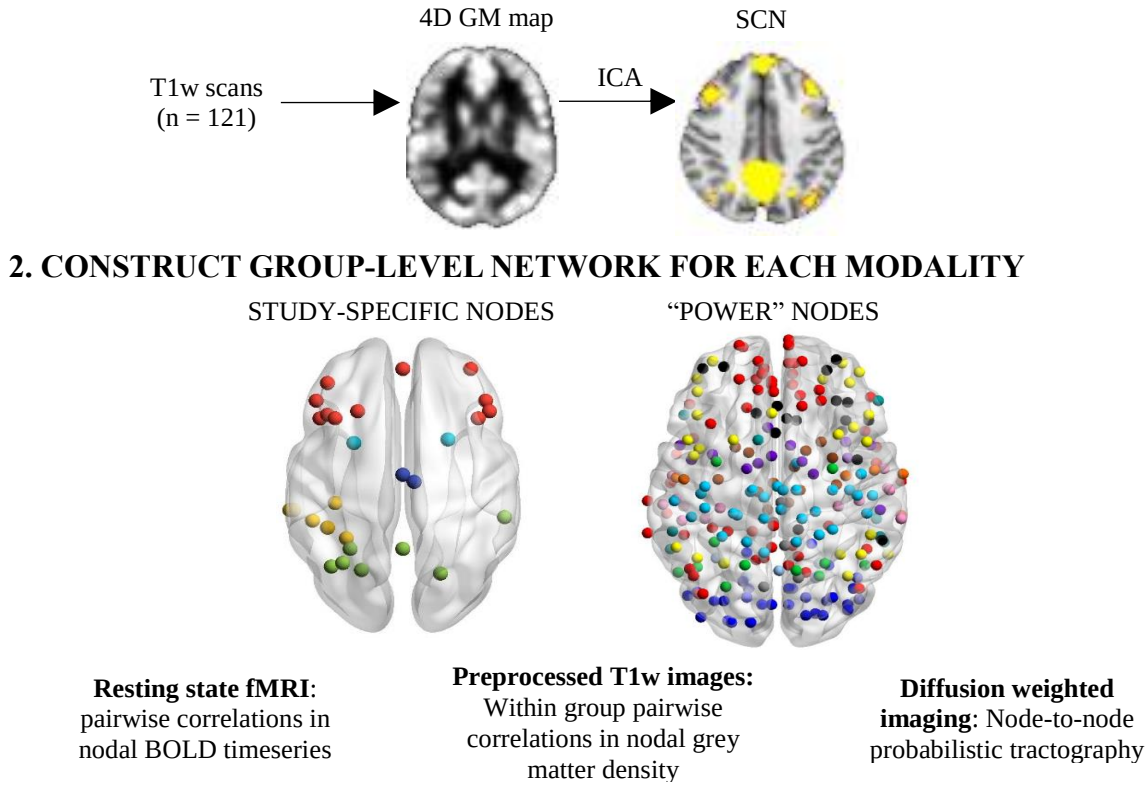

Figure 1: Study design outline. **1)** Derive whole brain structural covariance networks (SCNs) through independent component analysis (ICA) of four-dimensional grey matter (GM) maps. Next, we extracted the average GM density and loading coefficient of each SCN for each subject, and constructed general linear models to statistically examine the effect of childhood maltreatment (CM) and age on SCN GM density and expression. **2)** Two lines of investigation were conducted, with 28 study-specific SCN nodes and with 236 "Power" nodes across the whole brain. The connectivity/correlation of nodes were measured for three modalities: resting state functional connectivity, grey matter and white matter. Average connectivity/correlation matrices were generated within the non-maltreated group (n=31) and the maltreated group (n=31). **3)** Cross-modal correspondence was measured within each group, in line with displayed mediation model.

Image Acquisition

Participants underwent MRI scanning using a 3-Tesla GE MR750 Discovery scanner (GE Medical Systems, Milwaukee, WI) at the Brain & Mind Centre, Sydney, Australia. A high resolution structural image was acquired from all participants with a customized MP-RAGE 3D T1-weighted sequence: repetition time (TR) = 7264ms; echo time (TE) = 2784ms; 0.9 mm isotropic resolution; flip angle=15º; coronal orientation; field of view (FOV) = 230x230 mm; matrix of 256x256; total slices =196. Resting state BOLD data was acquired with an echo planar imaging sequence (TR = 3000ms; TE = 36ms; slice thickness = 3.0mm; 3.75mm isotropic resolution, flip angle = 90º; FOV = 240x240mm; matrix = 64x64; total slices = 20, total volumes = 273). Whole brain diffusion-weighted images were acquired using an echo planar imaging sequence (TR = 7000ms; TE = 68ms; slice thickness = 2.0mm; 0.9 mm isotropic resolution; FOV = 230x230mm; acquisition matrix = 256x256; axial orientation; 69 gradient directions). Eight images without diffusion weighting (b = 0 s/mm2) were acquired prior to the acquisition of 69 images (each containing 55 slices) with spatially uniform diffusion-gradients (b = 1159s/mm2). Participants were instructed to rest comfortably with eyes closed without moving or falling asleep for the duration of the scans.

T1-image processing

All T1-weighted images were analysed using FMRIB's software library (FSL), version 5.0.9 (Smith et al. 2004). First, non-brain matter was removed using FSL's automated brain extraction tool (Jenkinson and Smith, 2001; Smith, 2002). Next, brain extracted images were subjected to tissue-type segmentation. Individual T1 weighted images were linearly registered to the standard 2mm Montreal Neurological Institute (MNI) 152 template, and this registration matrix was used to register the individual grey matter images to MNI space (Jenkinson *et al.*, 2002). Standard space grey matter images were concatenated and averaged to create a study-specific template (Good *et al.*, 2001), then each grey matter image was non-linearly re-registered to the study-specific template and concatenated to produce a four-dimensional grey matter map. To compensate for contraction/enlargement after non-linear registration, each voxel of the grey matter map was multiplied by the Jacobian of the warp field and smoothed with a 3mm Gaussian kernel.

SCNs were identified by an independent component analysis using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) on the modulated four dimensional grey matter map (Beckmann and Smith, 2004; Beckmann *et al.*, 2005; Xu *et al.*, 2009). A ten component model was selected based on a Bayesian dimensionality estimation (Minka, 2000). Ten spatial components of maximal statistical independence, notably not maximal spatial independence, were defined in which the probability of a voxel being noise was less than 50%. Each spatial component represents a network of voxels where grey matter density covaries across subjects, namely a SCN. Each component was thresholded and binarized at 50%, removing voxels with negative weighting or minimal contribution to the network, to create SCN masks (for SCN masks see

Supplementary Figure 1). The ten SCN masks were then cross correlated with ten intrinsic connectivity networks, which were deduced from a MELODIC analysis of 30,000 individuals' resting state functional scans (Smith et al. 2009). The average grey matter density of each SCN was extracted for each participant. The loading coefficients of each component were also extracted to give insight into the strength of SCN "expression" for each participant.

Impact of childhood maltreatment on SCNs

The impact of childhood maltreatment on age related changes in SCNs was assessed in a general linear model as such:

SCN ~ intercept + β_1(age) + β_2(CM group) + β_3(age * CM group) + β_4(sex) + β_5(any mood diagnosis) + β_6(any psychosis diagnosis) + β_7(any anxiety diagnosis) + e_{ij}

The model was repeated with network expression and average grey matter density of each SCN entered as the dependent variable. Statistical p values were deemed significant below a threshold of 0.05 following FDR correction for multiple comparisons across the twenty contrasts. Where β_3 was significantly non-zero, the functional form of age-related changes in the SCN was determined by comparing adjusted R^2 value of linear and quadratic models.

Definition of network nodes

CM was significantly related to grey matter in two SCNs. The two SCNs overlapped substantially (spatial cross-correlation: r=0.43). Further analyses were performed on the SCN that explained greater variance in total grey matter (Supplementary Table 2). "Study-specific nodes" were defined as 5mm spheres around the local maxima of the SCN. The local maxima of the SCN depict the regions that maximally contribute to the SCN. Twenty-eight local maxima were identified and the nodes were labelled per the Harvard-Oxford atlas (Supplementary Figure 1, Supplementary Table 1). The choice of nodes critically influences regional connectivity estimates and network properties (Zalesky *et al.*, 2010). Connectivity of "*study-specific nodes*" informs on the SCN of interest, but the findings may be difficult to interpret in a wider context. To enhance reproducibility and interpretation, we conducted a parallel line of investigation using a previously established parcellation of the whole brain (Power *et al.*, 2011). Power et al., (2011) defined 236 grey matter regions of interest and 28 white matter regions of interest by combining meta-analysis of task-based fMRI and cortical mapping of rsFC. For the present study, 236 "*Power nodes*" were generated as 5mm spheres around the central coordinates of each grey matter region of interest within a functional network defined by Power et al. (2011) using the MarsBaR toolbox (Brett *et al.*, 2002) (Supplementary Figure 1).

Resting state functional MRI analysis

Functional images of 62 participants were pre-processed using the Statistical Parametric Mapping (SPM12) software package (Wellcome Department of Imaging Neuroscience, London, UK;

www.fil.ion.ucl.ac.uk/spm). Functional images were subjected to slice timing correction and motion realignment before being co-registered to the structural image. Then both structural and functional scans were normalised to MNI space and resampled into a 2x2x2 mm^3 voxel size. Segmentation was performed on the normalised structural image to yield grey matter, white matter and cerebrospinal fluid masks. Functional images were then smoothed using 8mm full-width at half-maximum Gaussian. Functional connectivity was measured via a seed-based correlation method within the CONN-fMRI functional connectivity toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). To mitigate the impact of movement and physiological noise confounds the CONN-fMRI toolbox utilises anatomical component correction to regress principal components of white matter and cerebrospinal fluid from the BOLD time series at a voxel level before the resultant residual time-series are band-pass filtered ($0.008<f<0.09$ Hz). Notably, motion artifacts were not significantly related to childhood maltreatment or age (Supplementary Methods). Pearson's correlation coefficients were generated between pairs of nodes, converted to normally distributed z-scores and extracted for further analysis. The functional connectivity procedure was conducted twice per participant, with study-specific nodes and with Power nodes.

Diffusion weighted image processing

Probabilistic tractography was performed on 62 diffusion weighted images using FSL version 5.0.10 (Smith et al. 2004). Diffusion-weighted volumes were eddy current corrected, non-brain tissue removed and a diffusion tensor model was fitted at each voxel. Each resulting tensor map was inspected for the appropriate reconstruction of the major pathways. Using FSL PROBTRACK X, a three-fibre orientation diffusion model was fitted to estimate probability distributions on the direction of fibre populations at each brain voxel in the diffusion space of each subject (Behrens *et al.*, 2007). For each subject, 5000 samples were generated for each node to all other nodes. Structural connectivity probability of two nodes was calculated as the number of fibres projecting from the seed node to the target node, divided by the total number of fibres projecting from the seed node (Gong *et al.*, 2012). Symmetric diffusion connectivity matrices were generated for each participant by taking the larger of a-to-b or b-to-a. The procedure was conducted twice per participant, with study-specific nodes and with Power nodes.

Impact of childhood maltreatment on functional connectivity and structural connectivity networks

To assess whether childhood maltreatment impacted functional and structural connectivity in a similar manner to grey matter covariance, the statistical procedure outlined in "*Impact of childhood maltreatment on SCNs"* was repeated using average functional connectivity and average structural connectivity probability. The procedure was performed for SCN 3, as well as the default mode, left fronto-parietal and right fronto-parietal networks, as defined by Power et al., (2011).

Group-level network construction

Network analyses were conducted in MATLAB and Statistics Toolbox (The MathWorks, 2016) using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) and in-house functions. Brain regions were defined as nodes and correlation/connectivity of brain regions were defined as edges. Participants were categorised into CM and No-CM groups. Group average rsFC and structural connectivity matrices were generated within group for each analysis. Group level grey matter covariance matrices were generated within each group from the Pearson correlation coefficients between each pair of nodes' grey matter density. In line with previous studies, negative edges were removed from group average rsFC and group level grey matter covariance matrices (Gong *et al.*, 2012; Alexander-Bloch *et al.*, 2013; Teicher *et al.*, 2014).

Debate surrounds the use of thresholding and binarisation in graph theory analysis of brain networks (Hinne *et al.*, 2013; Garrison *et al.*, 2015). The primary analyses in the present study were performed using weighted networks for the following reasons: (1) the small size of the networks (28 nodes) conferred low computational demands, (2) optimal thresholding of grey matter covariance networks has not been directly explored and (3) choice of threshold type and sparsity profoundly impacts the results and interpretation of group differences (Garrison *et al.*, 2015). The majority of previous studies have implemented thresholding and binarisation in network construction. Binary graphs are more computationally efficient than weighted networks and likely have fewer false positive connections (van den Heuvel et al. 2017). It has also been argued that thresholding is necessary to model the real sparsity of brain networks (Sporns, 2010). To enable comparison with previous studies, a parallel line of investigation was undertaken using thresholding and binarisation in the network construction. Sparsity based thresholding and binarisation were employed at 1% increments from 5% to 25%, using positive edges only. The range of thresholding was chosen to align with extant literature (Gong *et al.*, 2012; Alexander-Bloch *et al.*, 2013).

Weighted cross-modal correspondence

Structural connectivity probability was resampled for weighted cross-modal analyses to enable statistical comparison to grey matter covariance and rsFC. Non-zero values were resampled to a Gaussian distribution, then rescaled to a mean of 0.5 and standard deviation of 0.1 (Honey *et al.*, 2009). It has also been suggested that this method more closely reflects the true structural connectivity of the brain (Honey *et al.*, 2009).

A series of univariate regressions was performed within each group to establish the degree of cross-modal correspondence. A mediation analysis, outlined in Figure 1, was conducted to test the contribution of rsFC to the correspondence of grey matter covariance and structural connectivity probability (Baron and Kenny, 1986). The mediation analysis was conducted at four levels. First, cross-modal correspondence within the grey matter network affected by childhood maltreatment was assessed using the study-specific nodes. Next, cross-modal correspondence was assessed within the default mode

network and within the fronto-parietal network. Finally, the mediation analysis was repeated for the whole brain to indicate global levels of cross-modal correspondence. Group differences in cross-modal correspondence were assessed by means of non-parametric permutation testing (1000 random group assignments) (Simpson *et al.*, 2013). Statistical p-values were deemed significant using an alpha level of 0.05.

Binary cross-modal convergence

The percentage of cross-modal convergence in two binary networks was defined as the ratio of convergent edges to the number of supra-threshold edges (Gong *et al.*, 2012). In sparse proportionally thresholded networks, this metric informs on the similarity of the network backbones and the similarity of edge strength ranks. The analysis was repeated within each group for grey matter covariance-rsFC, grey matter covariance-structural connectivity probability and rsFC-structural connectivity at 1% increments from 5% to 25% threshold levels. The area under the curve (AUC) was calculated across the thresholds and group comparisons were performed by means of non-parametric permutation testing (1000 random group assignments) (Bullmore *et al.*, 1999; Simpson *et al.*, 2013). Statistical p-values were deemed significant using an alpha level of 0.05.

5.5 RESULTS

Relationship of childhood maltreatment to grey matter across structural covariance networks

Ten SCNs were identified (Supplementary Figure 1). Grey matter density significantly decreased with age in seven SCNs (Supplementary Table 2). Network expression significantly decreased with age in two SCNs (Supplementary Table 2). Neither grey matter density nor network expression significantly increased with age in any SCN. Childhood maltreatment was associated with reduced grey matter in SCN 3 (β=-0.138, se=0.052, t=-2.652, p=0.04 FDR corrected, Figure 2) and SCN 5 (β=-0.148, se=0.049, t=-3.001, p=0.02 FDR corrected). Maltreated and non-maltreated groups exhibited significantly different age-related grey matter loss in SCN 3 (β=0.006, se=0.003, t=2.505, p=0.05 FDR corrected) and SCN 5 (β=0.007, se=0.002, t=2.931, p=0.02 FDR corrected). A spatial cross correlation of SCN 3 and SCN 5 revealed substantial overlap (r=0.43). Further analyses were performed on SCN 3 because it explained greater variance in grey matter covariance than SCN 5 (Supplementary Table 2). The regions covered by SCN 3 are widely distributed (Figure 2). Spatial cross-correlation with resting state intrinsic connectivity networks revealed overlap with the default mode network (r=0.28) and fronto-parietal networks (left: r=0.17, right: r=0.10). We confirmed that childhood maltreatment was associated with reduced grey matter density across the default mode and fronto-parietal networks using a standard atlas of the networks (Power et al., 2011, Supplementary Material). Linear growth in SCN 3 grey matter provided a better fit than quadratic growth in the non-maltreated (linear adjusted

R^2=0.38, quadratic adjusted R^2=0.38) and maltreated group (linear adjusted R^2=0.07, quadratic adjusted R^2=0.05). Post hoc within group regressions revealed that grey matter decreased at a slower rate with age amongst maltreated individuals (β=-0.004, t=-2.432, p=0.018, Figure 3 right) compared to non-maltreated individuals (β=-0.0012, t=-6.100, p<0.0001, Figure 3 left). Subsequent analyses were performed using key nodes of SCN 3 (Supplementary Table 1).

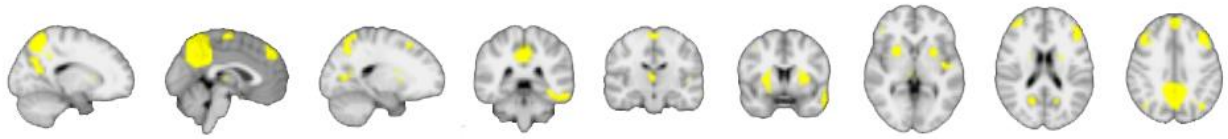

Figure 2: Structural covariance network in which grey matter density is significantly reduced in young people with a history of childhood maltreatment

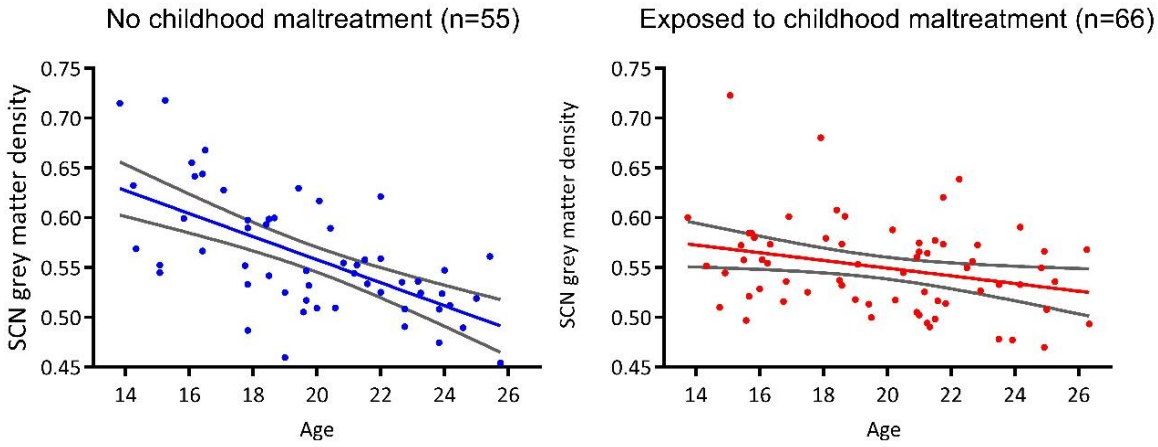

Figure 3: Age-related changes in grey matter density within the SCN significantly differs between youth without childhood maltreatment (left) and youth exposed to childhood maltreatment (right). 95% confidence intervals shown in grey.

Impact of childhood maltreatment on functional and structural connectivity

Average functional connectivity and average structural connectivity probability of the SCN were not significantly related to childhood maltreatment or age (Supplementary Tables 3 and 4).

Cross-modal correspondence in weighted networks

The full statistical outcomes of the mediation analyses are reported in Table 2. rsFC significantly predicted grey matter covariance in non-maltreated and maltreated groups at the level of the SCN, default mode network, fronto-parietal network and whole brain connectome (path b). Interestingly, correspondence of rsFC and grey matter covariance was stronger in the SCN (NoCM: β=0.39. CM: β=0.43) than expected by the global correspondence (NoCM: β=0.18. CM: β=0.15).

Structural connectivity probability significantly predicted rsFC to a small degree in both groups at all levels (path a: $0.06 \leq \beta \leq 0.13$). To a lesser extent, structural connectivity probability also significantly predicted grey matter covariance in both groups at all levels (path c: $0.02 \leq \beta \leq 0.13$). Childhood maltreatment was associated with significantly greater correspondence of structural connectivity probability with grey matter covariance within the SCN ($\beta=0.13$, se=0.019, $t=6.87$, $p<0.001$), relative to the non-maltreated group ($\beta=0.09$, se=0.021, $t=4.37$, $p<0.001$). Conversely, childhood maltreatment was associated with significantly reduced global correspondence of structural connectivity probability and grey matter covariance ($\beta=0.03$, se=0.002, $t=17.50$, $p<0.001$), relative to the non-maltreated group ($\beta=0.03$, se=0.002, $t=19.96$, $p<0.001$). A similar pattern of group differences emerged upon inspection of the unique correspondence of structural connectivity probability with grey matter covariance, controlling for rsFC. In the non-maltreated group, structural connectivity probability did not significantly predict grey matter covariance within the SCN after controlling for rsFC ($\beta=0.03$, se=0.022, $t=1.24$, $p=0.215$); indicating that rsFC completely mediates the relationship of structural connectivity probability and grey matter covariance within the SCN. In contrast, a small unique association between structural connectivity probability and grey matter covariance was evident in the maltreated group while controlling for rsFC ($\beta=0.07$, se=0.020, $t=3.42$, $p=0.008$). This pattern of results appeared to be specific to the SCN, as structural connectivity probability significantly predicted grey matter covariance in the DMN, fronto-parietal network and whole brain in both groups, after controlling for rsFC.

Table 2: Cross-modal correspondence within structural covariance network, default mode network, fronto-parietal network and the whole brain

	Path	NoCM (n=31)	CM (n=31)
SCN	a	$\beta=0.13$, se=0.016, $t=6.45$, $p<0.001$	$\beta=0.13$, se=0.018, $t=8.01$, $p<0.001$
	b	$\beta=0.39$, se=0.006, $t=8.09$, $p<0.001$	$\beta=0.43$, se=0.046, $t=9.33$, $p<0.001$
	c *	**$\beta=0.09$, se=0.021, $t=4.37$, $p<0.001$**	**$\beta=0.13$, se=0.019, $t=6.87$, $p<0.001$**
	c' *	**$\beta=0.03$, se=0.022, $t=1.24$, $p=0.215$**	**$\beta=0.07$, se=0.020, $t=3.42$, $p=0.008$**
DMN	A	$\beta=0.12$, se=0.006, $t=20.03$, $p<0.001$	$\beta=0.11$, se=0.006, $t=20.79$, $p<0.001$
	B	$\beta=0.28$ se=0.025, $t=11.33$, $p<0.001$	$\beta=0.28$, se=0.025, $t=11.93$, $p<0.001$
	C	$\beta=0.07$, se=0.007, $t=10.24$, $p<0.001$	$\beta=0.07$, se=0.007, $t=10.29$, $p<0.001$
	c'	$\beta=0.05$, se=0.008, $t=6.09$, $p<0.001$	$\beta=0.04$, se=0.009, $t=4.68$, $p<0.001$
Fronto-parietal	A	$\beta=0.07$, se=0.010, $t=6.91$, $p<0.001$	$\beta=0.07$, se=0.012, $t=5.69$, $p<0.001$
	B	$\beta=0.28$, se=0.067, $t=4.25$, $p<0.001$	$\beta=0.23$, se=0.074, $t=3.14$, $p=0.002$
	C	$\beta=0.07$, se=0.012, $t=5.85$, $p<0.001$	$\beta=0.06$, se=0.016, $t=4.02$, $p<0.001$
	c'	$\beta=0.06$, se=0.013, $t=4.38$, $p=0.001$	$\beta=0.06$, se=0.017, $t=3.27$, $p<0.001$
Whole brain	A	$\beta=0.06$, se=0.001, $t=53.20$, $p<0.001$	$\beta=0.06$, se=0.001, $t=55.29$, $p<0.001$
	B	$\beta=0.18$, se=0.007, $t=24.22$, $p<0.001$	$\beta=0.15$, se=0.008, $t=20.02$, $p<0.001$
	c *	**$\beta=0.03$, se=0.002, $t=19.96$, $p<0.001$**	**$\beta=0.03$, se=0.002, $t=17.50$, $p<0.001$**
	c' *	**$\beta=0.02$, se=0.002, $t=12.00$, $p<0.001$**	**$\beta=0.02$, se=0.002, $t=10.46$, $p<0.001$**

Significant group differences in the regression coefficient are signified with an * and emboldened text. Path a: rsFC ~ structural connectivity probability. Path b: grey matter covariance ~ rsFC. Path c: grey matter covariance ~ structural connectivity probability. Path c': grey matter covariance ~ structural connectivity probability, controlling for rsFC.

Cross-modal convergence in binary networks

Childhood maltreatment was associated with significantly enhanced convergence of rsFC with structural connectivity probability in the study-specific SCN ($p<0.05$, Figure 4). This effect was driven by convergence of rsFC and structural connectivity probability in the inferior temporal gyrus amongst the maltreated group (Supplementary Figure 3). Convergence of grey matter covariance and rsFC within the study-specific SCN ranged from 32-47% in the maltreated group and from 30%-58% in the non-maltreated group (Figure 4). The groups did not significantly differ in grey matter covariance-rsFC convergence within the SCN, but childhood maltreatment was related to significantly reduced grey matter covariance-rsFC convergence in the DMN ($p<0.05$, Figure 4, Supplementary Figure 4). Childhood maltreatment was not associated with abnormal convergence of grey matter covariance and structural connectivity, which ranged from 33-41% in the maltreated group and from 27%-45% in the non-maltreated group in the study-specific SCN (Figure 4).

5.6 DISCUSSION

The present study is the first cross-modal analysis of a network disrupted by childhood maltreatment. Childhood maltreatment was linked to blunted age-related decreases in grey matter across a SCN, which encompassed default mode and fronto-parietal areas. Grey matter covariance across this network was moderately correlated with rsFC, and rsFC mediated the relationship between grey matter covariance and structural connectivity in the non-maltreated group. Individuals with a history of childhood maltreatment exhibited a unique association of grey matter covariance with structural connectivity. These findings were specific to a study-derived SCN, and further research is necessary to understand the spatial pattern of cross-modal correspondence across the whole brain.

Grey matter follows regionally distinct, inverted U-shaped developmental trajectories (Gogtay *et al.*, 2004; Giedd *et al.*, 2014). In the current study, grey matter in SCNs was found to linearly decrease through youth. Grey matter loss in two SCNs was significantly less amongst individuals with a history of childhood maltreatment. The present results suggest childhood maltreatment induces flattened development, precocious peaking or early accelerated decline of grey matter. In support of the former, longitudinal studies have shown childhood maltreatment is related to reduced left amygdala growth from 12-16 years (Whittle *et al.*, 2013) and reduced right hippocampal growth from 14-28 years (Paquola et al. 2017). Preclinical studies have begun to elucidate epigenetic pathways that may link early life stress to reduced grey matter growth. Increased DNA [cytosine-5-]-methyltransferase (DNMT1) and decreased retinoic acid receptor-a following maternal separation have been shown to

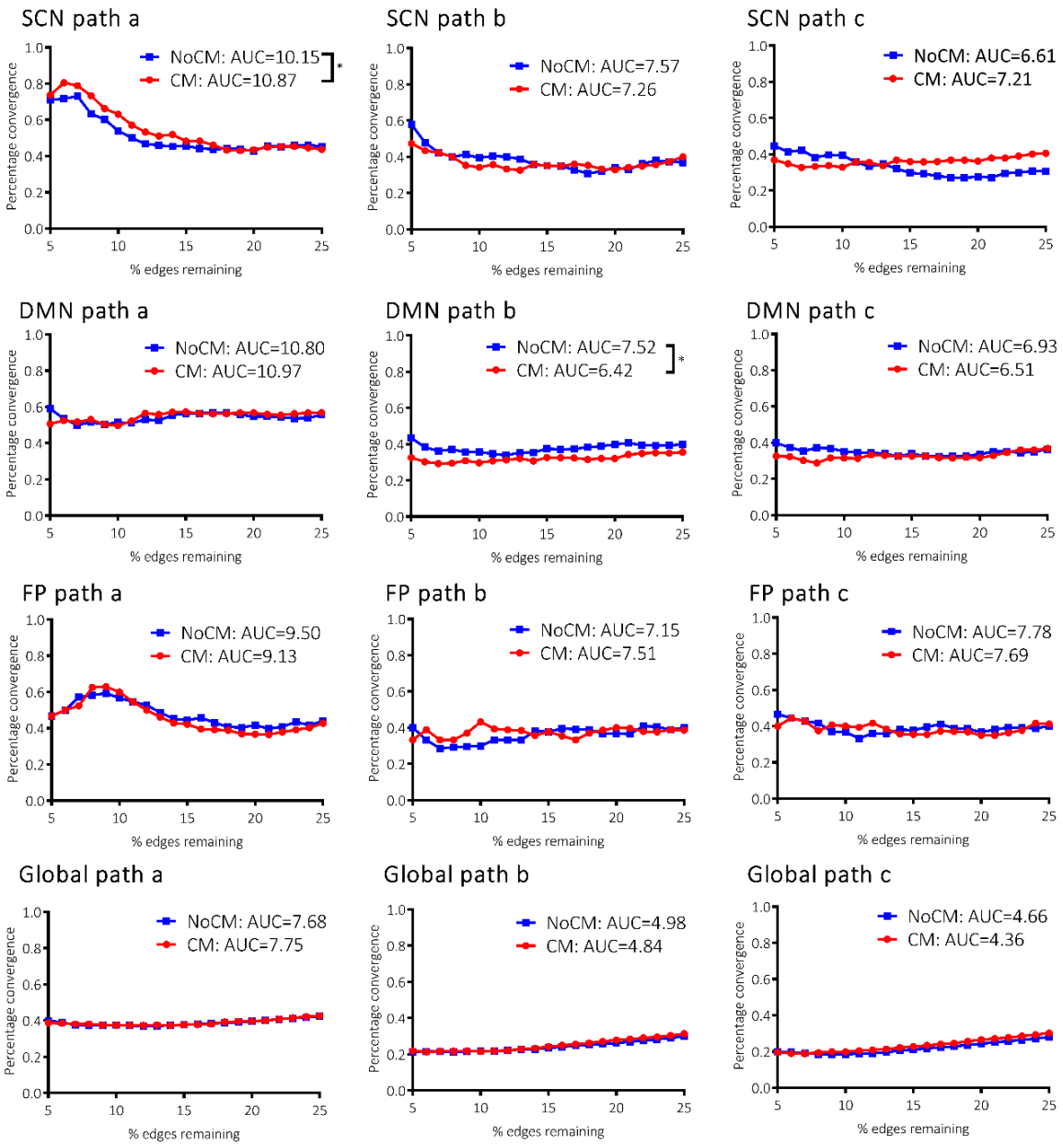

Figure 4: Distribution of cross-modal convergence as function of network sparsity across four levels, namely the SCN, default mode network (DMN), frontoparietal network (FP) and whole brain. Path a: rsFC ~ structural connectivity probability. Path b: grey matter covariance ~ rsFC. Path c: grey matter covariance ~ structural connectivity probability. * signifies a significant group difference in the area under the curve (AUC).

mediate the reduced capacity of adult progenitor cells to differentiate in the dentate gyrus of adolescent rats (Boku *et al.*, 2015). In combination with the present results, this evidence suggests childhood maltreatment could lead to a flattened trajectory of grey matter development in certain regions, with reduced growth prior to the peak and reduced loss after the peak.

The regions implicated in the present study overlap with the default mode network (precuneus, posterior parietal lobules, lateral temporal cortex) (Raichle, 2015) and the fronto-parietal network (rostrolateral prefrontal cortex, precuneus, anterior inferior parietal lobule) (Vincent *et al.*, 2008). The default mode network is involved in self-referential activity, and functional coupling of the default mode network with the fronto-parietal network supports autobiographical planning (Spreng *et al.*, 2010; Gerlach *et al.*, 2014). Findings on the long term effects of childhood maltreatment on grey matter and functional connectivity across these regions are mixed (Paquola, Bennett, and Lagopoulos 2016; van der Werff et al. 2013; Philip et al. 2013). The effect of childhood maltreatment on SCN grey matter, but not SCN expression, observed here is suggestive of a widespread network-level effect of childhood maltreatment. The widespread effects of childhood maltreatment may result from initial insults to hub regions, such as the precuneus. Brain regions at the core of a network have the strongest probability of influencing other regions (Kitsak *et al.*, 2010). Hubs also appear to be disproportionately affected in brain disorders (Crossley *et al.*, 2014). High susceptibility of hubs to neurological insult may be due to a high proportion of shortest paths between brain regions passing through hubs (van den Heuvel et al. 2012) and high baseline activity of hubs conferring enhanced vulnerability to metabolic stress (Fornito, Zalesky and Breakspear, 2015).

The present study is the first to explicitly investigate how rsFC mediates the relationship of structural connectivity to grey matter covariance in brain networks. Alongside the strong independent relationship of rsFC to grey matter covariance, partial mediation of the structural connectivity-grey matter covariance relationship by rsFC provides further support for functional coactivation driving SCN development. Decreased default mode network activity, as has been observed in women with PTSD subsequent to childhood maltreatment (Bluhm *et al.*, 2009), may therefore contribute to resultant reduced grey matter across the default mode SCN. This assertion is further supported by significantly reduced convergence of grey matter covariance and rsFC in the DMN of maltreated individuals. While structural connectivity was not related to grey matter covariance beyond the indirect influence of rsFC in the non-maltreated group, a unique association of structural connectivity with grey matter covariance was discovered within the maltreated group. Previous research has shown that structural connections are on average weaker in adults with a history of childhood maltreatment (Ohashi *et al.*, 2017). Childhood maltreatment may therefore engender greater dependence of synchronous grey matter growth on structural connectedness, but weak structural connections may lead to reduced grey matter growth. Alternatively, childhood maltreatment may independently impact grey matter and white matter growth. Increased grey matter covariance-structural connectivity coupling observed here may be symptomatic of the common trophic effect of early life stress. Longitudinal studies mapping the changes

in structural and functional connectivity and their alignment with grey matter covariance are essential to elucidate the validity of these preliminary hypotheses

This study also raises some important considerations. A data-driven approach was employed in the present study in defining whole brain SCNs, whereas previous studies have focused on a single cortical thickness covariance network or seed-based SCNs. We found that the effect of childhood maltreatment on the grey matter density extended from the study-specific SCN to the DMN and fronto-parietal network, however group differences in cross-modal correspondence were specific to the study-specific SCN. Further research into the construction of SCNs and their relationship to intrinsic connectivity networks may shed light on how local differences in grey matter translate to alterations at a network-level, as well as the evident influence of node definition. The cross-sectional nature of this study limited our ability to directly observe neurodevelopmental effects and establish causal relations. Finally, the psychiatric heterogeneity of this cohort is reflective of the clinical service from which participants were recruited (Scott *et al.*, 2012). Group differences in severity of mental illness may contribute to the findings, however childhood maltreatment is related to worse clinical severity (Simon *et al.*, 2009; Dovran *et al.*, 2016) and selecting participants based on clinical severity would introduce additional bias. Replication in other psychiatric cohorts and healthy cohorts is essential to validate the generalisability of these findings.

For the first time, the present study expounds the relationship of grey matter covariance to both structural connectivity and rsFC. Cross-modal relationships were found to be sensitive to childhood maltreatment. From these comparisons, reduced grey matter following childhood maltreatment was suggested to arise from deficient functional activity or heightened dependence on structural connections for coordinated grey matter growth. The widespread perturbation of grey matter development across the default mode and fronto-parietal networks following childhood maltreatment may have significant implications for mental well-being, given the networks' roles in self-referential activity. Future studies should aim to replicate these findings in healthy and psychiatric cohorts to determine whether abnormal neurodevelopment confers enhanced psychiatric risk.

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CHAPTER VI

Childhood maltreatment represents a major global health burden. Childhood abuse or neglect is retrospectively reported by up to 40% of adults (Stoltenborgh, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2015) and contributes to 59% of cases of depression and anxiety (Li, D'Arcy, & Meng, 2016). Given the strong influence of the early life environment on grey matter development, childhood maltreatment has been theorised to increase psychiatric risk via alterations to brain structure. Previous research has demonstrated that childhood maltreatment is associated with abnormal grey matter volume in numerous clinical and healthy adult cohorts, however the generalisation of these findings to naturalistic clinical cohorts remains unknown. This thesis examines the impact of childhood maltreatment in a young heterogenous psychiatric cohort. The findings link early life stress, neurodevelopment and psychiatric illness in a naturalistic clinical sample, and can form the basis of biologically informed prevention and treatment efforts.

Few empirical studies have previously investigated how childhood maltreatment affects brain development and how grey matter changes relate to structural and functional connectivity in the brain. The preceding chapters employed advanced neuroimaging techniques to determine regional sensitivity to childhood maltreatment, the temporal profile of childhood maltreatment-related effects and the functional abnormalities that accompany grey matter changes.

6.1 BRIEF SUMMARY OF FINDINGS

Chapter II sought to quantify and localise the long-term effect of childhood maltreatment on brain structure. A meta-analysis of extant literature revealed that adults with a history of childhood maltreatment commonly exhibit reduced grey matter in the hippocampus, amygdala and right dorsolateral prefrontal cortex, compared to non-maltreated adults. Sub-group meta-analyses revealed that the study effect sizes were related to the psychiatric health of the cohort. Childhood maltreatment related reductions in hippocampal volume were consistently identified amongst individuals with mood disorders or borderline personality disorder, and to lesser extent amongst psychiatrically healthy cohorts. Moreover, childhood maltreatment was also associated with reduced amygdala volume in psychiatric cohorts, whereas no significant association of amygdala volume with childhood maltreatment was evident in the healthy cohorts. Finally, childhood maltreatment was more strongly related to reduced amygdala volume in older cohorts.

Chapter III mapped the effect of childhood maltreatment throughout youth. Longitudinal and cross-sectional estimations of hippocampal and amygdala volume of 123 young people were combined

in a linear mixed-effect model. Hippocampal and amygdala volumes increased linearly with age, as expected in late adolescence and early adulthood. However, childhood maltreatment appeared to stunt growth of the right hippocampus**.** This study bridged the gap between decades of child and adult research to explicitly show for the first time that childhood maltreatment alters the developmental trajectory of the hippocampus, and this effect persists into young adulthood. Notably, aberrant hippocampal growth following childhood maltreatment was not directly related to current severity of psychopathology.

Recent trauma can also impact grey matter volume (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012), and individuals exposed to childhood maltreatment tend to experience more adverse events throughout life (Min, Minnes, Kim, & Singer, 2013). Chapter IV aimed to disentangle the enduring impact of childhood abuse from the influence of recent stressful events by examining the utility of the cumulative stress and mismatch hypotheses. Given childhood sexual and physical abuse appeared to have the strongest effect on hippocampal and amygdala volume, Chapter IV specifically compared sexual and/or physical abuse to those individuals without any history of childhood maltreatment. Childhood abuse interacted with recent stress in two distinct ways. Mismatched levels of childhood and recent stress were associated with significantly reduced hippocampal volume, as well as perturbed prefrontal and hippocampal functional connectivity. In contrast, childhood abuse appeared to enhance vulnerability to stress-induced reductions in the anterior cingulate cortex. Furthermore, cumulative stress predicted worse psychiatric symptoms.

Chapter V utilised structural covariance networks to explore the effect of childhood maltreatment on distributed grey matter. Childhood maltreatment was associated with reduced grey matter across a structural covariance network that overlapped with the default mode and fronto-parietal networks. Development of a novel framework for examining correspondence of structural covariance with structural connectivity and functional connectivity provided new insights into the biological processes that underpin reduced grey matter following childhood maltreatment. Structural covariance was uniquely associated with functional connectivity in the network, which in concert with extant literature, suggests structural covariance is driven by functional connectivity. Therefore, reductions in default mode/fronto-parietal grey matter following childhood maltreatment likely arises from deceased functional coactivation.

6.2 REGIONAL SENSITIVITY TO CHILDHOOD MALTREATMENT

The present work highlights the sensitivity of the hippocampus and prefrontal cortex to childhood maltreatment. The hippocampus has emerged as the region most consistently affected by childhood maltreatment, however the findings are asymmetric. Specifically, childhood maltreatment

was associated with stunted right hippocampal growth, while childhood abuse and low levels of recent stress were linked to reduced left hippocampal volume. This discrepancy may be explained by a key difference in the studies, namely the type of childhood maltreatment experienced. Subgroup meta-analyses revealed that the right hippocampus is more sensitive to general early life stress, whereas the left hippocampus is more sensitive to specific types of maltreatment, namely sexual or physical abuse. In line with these findings, general childhood maltreatment stunted right hippocampal growth and childhood abuse impacted stress-related changes in left hippocampal volume. The asymmetrical effects of childhood maltreatment types may reflect the hemisphere-specific development, connectivity and function of the hippocampi. A higher density of mineralocorticoid receptors in the right hippocampus engenders greater sensitivity to stress (Neveu, Liège, & Sarrieau, 1998; Zach, Mrzílková, Řezáčová, Stuchlík, & Valeš, 2010). The right hippocampus reaches peak volume earlier than the left hippocampus (Dennison et al., 2013; Uematsu et al., 2012). Both hippocampi are part of the fronto-limbic circuitry via functional relationships with left inferior frontal gyrus, left insula and the cingulate (Robinson, Salibi, & Deshpande, 2016). However, the right hippocampus is more functionally and structurally connected to contralateral sub-lobar and temporal regions, whereas the left hippocampus is more functionally related to ipsilateral limbic regions (Robinson et al., 2016). The observed hippocampal asymmetry may underpin the hemisphere-specific effects of certain types of childhood maltreatment, however future studies with larger samples should endeavour to delineate the type-specific effects of childhood maltreatment with advanced statistical models, such as partial least squares path modelling. Additionally, the hippocampi also exhibit functional and structural differentiation along the anterior-posterior axis (Chase et al., 2015). To date, anterior-posterior hippocampal sensitivity to stress has not been investigated.

These findings reinforce prior evidence concerning the targeted negative effect of childhood maltreatment on the hippocampus. Connectivity of the hippocampus with the HPA axis engenders sensitivity to early life stress (de Kloet, Fitzsimons, Datson, Meijer, & Vreugdenhil, 2009). Mineralocorticoid and glucocorticoid receptors are abundant in the hippocampus (Patel et al., 2000), where glucocorticoid-induced activation of mineralocorticoid and glucocorticoid receptors alters the expression of 203 genes (Datson, van der Perk, de Kloet, & Vreugdenhil, 2001). The glucocorticoid-responsiveness of genes coding for brain derived neurotrophic factor (BDNF) and fibroblast growth factors indicates the importance of stress in moderating structural development in the hippocampus (Hansson et al., 2006; Mocchetti, Spiga, Hayes, Isackson, & Colangelo, 1996). In addition, early life stress downregulates neurofilament, cytoskeletal, synaptic and myelin related proteins, resulting in fewer mature dendritic spines in the hippocampus (Wei et al., 2015).

The lateral areas of the prefrontal cortex are also sensitive to childhood maltreatment. The dorsolateral prefrontal cortex influences attention through top-down control over sensory processing (Gazzaley & Nobre, 2012). This control is impaired during stressful conditions, when noradrenaline

and dopamine, triggered by the amygdala, down regulate prefrontal cortex activity (Arnsten, 2009). To our knowledge, preclinical research has not broached the effect of early life stress on the lateral prefrontal cortex. The unbiased exploratory approach of Chapter V revealed distributed loss of prefrontal grey matter in the maltreated group, which is consistent with the extant literature reporting reduced grey matter in varied prefrontal regions following childhood maltreatment (Cohen et al., 2006; Dannlowski et al., 2012; Fonzo et al., 2013; Kumari et al., 2014; Sheffield, Williams, Woodward, & Heckers, 2013; Thomaes et al., 2010; Tomoda et al., 2009). Precise spatial localisation of the effect of childhood maltreatment on the prefrontal cortex may be hindered by large individual variability in functional subregions. A repeat-measurement functional MRI study recently showed that the spatial location of the fronto-parietal network is most varied across individuals, relative to other functional networks (Mueller et al., 2013). Functional connectivity of the lateral prefrontal cortex, in particular, exhibited the greatest inter-individual variability. Given the observed functional basis for maltreatment related changes across the fronto-parietal network, individual variation in the functional delineation of the prefrontal cortex may contribute to variability in findings concerning the prefrontal subregions affected by childhood maltreatment.

Based on review and analysis of the existing literature, the volume of the amygdala was found to be reduced following childhood maltreatment. However, in the present cohort, childhood maltreatment did not appear to directly impact amygdala grey matter. Despite this apparent discrepancy, the absence of an association between childhood maltreatment and amygdala volume in the present young cohort aligns with the meta-analysis, where childhood maltreatment was reportedly associated with reduced amygdala volume in older individuals. Although amygdala volume continues to increase into early adulthood, most structural development of the amygdala is complete by preadolescence (Gilmore et al., 2012; Ulfig, Setzer, & Bohl, 2003). The early structural integrity of the amygdala may render resilience to the effects of early life stress. Instead, childhood maltreatment alters the functional responsiveness of the amygdala. Consistent evidence indicates that childhood maltreatment increases the reactivity of the amygdala during emotional tasks (Dannlowski et al., 2012, 2013; Fonzo et al., 2016; Hentze et al., 2016; McCrory et al., 2013)

The present work highlights that the hippocampus and distributed areas of the prefrontal cortex are adversely affected by childhood maltreatment. Extensive research has focused upon the consequence of childhood maltreatment on the adult hippocampus and prefrontal cortex, but little is known concerning how childhood maltreatment shapes grey matter development.

6.3 DEVELOPMENTAL IMPACT OF CHILDHOOD MALTREATMENT

The preceding chapters support the hypothesis that childhood maltreatment alters the developmental trajectory of grey matter. Abused children do not present with reduced hippocampal volume, compared to non-abused children (Carrion et al., 2001; De Bellis et al., 1999; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001), but as discussed above, childhood maltreatment is associated with significantly reduced hippocampal volume in adulthood. Chapter III explicated the discrepancy between child and adult studies and provided the first empirical evidence that the effect of childhood maltreatment on hippocampal volume becomes apparent during young adulthood. This finding aligns with the time-course of synaptophysin expression in rats exposed to maternal separation (Andersen & Teicher, 2004). Non-stressed rats exhibit peak hippocampal synaptophysin at post-natal day 60; corresponding to the typical period of synaptic overproduction in young adulthood. Stressed rats exhibited normal synaptophysin levels at post-natal days 20 and 40, but significantly reduced synaptophysin at post-natal day 60. Stress-related differences in synaptophysin time-course were not evident in the amygdala or prefrontal cortex, which aligns with the absence of differences in amygdala development. Additionally, childhood maltreatment was associated with reduced age-related decreases across the default mode and fronto-parietal networks. In concert, these findings suggest childhood maltreatment affects growth and decline of grey matter.

The pervasive effect of childhood maltreatment on grey matter is underpinned by heightened neuroplasticity in youth. Shifting proportions of protein kinases and glutamate receptor subunits throughout the lifespan imbue a developmental sequence of heightened neuroplasticity followed by synaptic stabilisation. Early in life, abundant GluN2B isoforms in N-methyl-D-aspartate (NMDA) receptors prevent the formation of functional synapses when synaptic activity is not tightly correlated (Gray et al., 2011). GluN2B's role in preventing spurious formation of functional synapses is thought to facilitate activity-dependent synaptic pruning. Later in development, activity-dependent switches from GluN2B to GluN2A and the deposition of peri-neuronal nets dampen plasticity (Carstens, Phillips, Pozzo-Miller, Weinberg, & Dudek, 2016; Gray et al., 2011). Concurrently, control of long term potentiation induction switches from high to low affinity calcium-dependent triggers, which increases long term potentiation thresholds (Yasuda, Barth, Stellwagen, & Malenka, 2002). As these changes occur and synapses become more stable near the end of development, early life insults are solidified in brain networks.

The insidious nature of childhood maltreatment is also related to epigenetic modifications. DNA methylation, the most studied form of epigenetic modification, involves the transfer of a methyl group onto the 5^{th} carbon of a cytosine (Moore, Le, & Fan, 2013). Methylation typically represses the expression of the respective gene, but recent research has demonstrated DNA methylation in the gene body can also increase transcription (Hellman & Chess, 2007; Rauch, Wu, Zhong, Riggs, & Pfeifer,

2009). DNA methylation is catalysed by DNA methyltransferases (DNMTs). Conditional knockout models of DMNT demonstrate that methylation is critical to neuronal differentiation and maturation during development (Fan et al., 2001). Boku et al. (2015) highlighted the relationship of early life stress to epigenetic modifications and delayed perturbations in grey matter development. They found that early life stress increased DMNT expression, which in turn increased DNA methylation of retinoic acid receptor α. Resultant decreases in retinoic acid receptor α led to reduced capacity of adult progenitor cells to differentiate in the dentate gyrus of late adolescent rats. In humans, post-mortem examination of the hippocampal tissue of suicide completers revealed childhood abuse was associated with increased methylation and decreased expression of neuron-specific glucocorticoid receptor, NR3C1 (McGowan et al., 2009; Suderman et al., 2012). Cross-species analyses also identified early life stress related methylation at promoters of protocadherins; proteins involved in synaptogenesis and dendrite formation (Keeler, Molumby, & Weiner, 2015). Outside the hippocampus, early life stress elicits lasting increases in DNA methylation of BDNF in the prefrontal cortex (Roth, Lubin, Funk, & Sweatt, 2009). Given BDNF supports neuronal survival (Karpova, 2014), reduced BDNF gene expression following childhood maltreatment may underpin abnormal development of prefrontal grey matter.

The emergence of observable effects of childhood maltreatment on grey matter during late adolescence and young adulthood coincides with a critical shift from grey matter growth to grey matter decline. During this period, cortical thinning is driven by synaptic pruning and intra-cortical myelination (Gogtay et al., 2004; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986; Whitaker et al., 2016). Chapter V indicated that childhood maltreatment leads to blunted age-related decreases in grey matter across frontal, parietal and temporal regions. Down regulation of lipopolysaccharide binding protein following early life stress, as observed in the mouse hippocampus, may slow synaptic pruning (Wei, Simen, Mane, & Kaffman, 2012). Lipopolysaccharide binding protein recruits microglia (Zweigner, Schumann, & Weber, 2006), which then engulf synaptic material (Paolicelli et al., 2011). This theory is supported by the observation that peak lipopolysaccharide binding protein expression coincides with microglia recruitment and intense synaptic pruning in the hippocampus (Dalmau, Finsen, Zimmer, Gonzlez, & Castellano, 1998; Faulkner, Low, & Cheng, 2007; Wei, Simen, Mane, & Kaffman, 2012). The complementary roles of lipopolysaccharide binding protein and microglia in the cortex requires investigation.

Alternatively, the growing influence of stress hormones in late adolescence and young adulthood may give rise to the observable effects of childhood maltreatment. Post-mortem quantification of glucocorticoid receptor mRNA and protein expression revealed that glucocorticoid receptor expression in the dorsolateral prefrontal cortex peaks during late adolescence (Sinclair, Webster, Wong, & Weickert, 2011). The abundance of glucocorticoid receptors and their increasing expression on pyramidal neurons during this period is thought to amplify glucocorticoid-induced genomic changes and connotes enhanced stress-responsivity. Decreased glucocorticoid receptor expression following

childhood maltreatment, via increased DNA methylation of NR3C1 (McGowan et al., 2009; Suderman et al., 2012), may further enhance sensitivity to stress during adolescence. Chronic stress, via glucocorticoid action, induces dendritic retraction in the medial prefrontal cortex (Radley et al., 2004, 2011). No studies have investigated the structural effects of stress on the dorsolateral prefrontal cortex, however in line with this reasoning, Chapter IV showed that enhanced vulnerability to stress-related reductions in anterior cingulate cortex thickness amongst individuals exposed to childhood abuse. Childhood maltreatment may further enhance stress-responsivity during late adolescence and young adulthood, thus increasing stress-induced dendrite retraction within the medial prefrontal cortex. The translation of these findings between the subregions of the prefrontal cortex is impeded by an absence of preclinical research completed in both regions.

Evidently, childhood maltreatment alters brain development through immediate synaptic alterations, which are solidified with brain maturation, and lasting epigenetic modifications, which continue to shape grey matter into adulthood. The observable effects of childhood maltreatment on grey matter appear to emerge during late adolescence and young adulthood, owing to the critical shift from growth to decline and the heightened influence of stress hormones in this age period.

6.4 Relation of Grey Matter Changes to Brain Connectivity

Throughout the twentieth century the field of neuroscience expounded the functional specialisation of distinct brain regions. From lesion studies to region of interest neuroimaging analyses, researchers attempted to locate the specific brain regions responsible for psychological processes or neurological disorders. The rapidly growing field of connectomics models neural complexity by combining knowledge of functional specialisation with estimates of brain connectivity. The structural and functional connectivity of brain regions can inform efficiency and effectiveness of neural communication. Furthermore, connectivity analyses can aid understanding of the propagation of disease processes. Understanding how the impact of childhood maltreatment on grey matter development translates to altered brain function is essential to understanding how these changes affect behaviour and health.

In Chapter IV, reduced left hippocampal volume amongst individuals exposed to childhood abuse and low recent stress was accompanied by enhanced functional connectivity of the left hippocampus with bilateral rostral anterior cingulate cortices. The hippocampus and rostral anterior cingulate are structurally connected by the cingulum, which is further subdivided into a posterior hippocampal portion and an anterior cingulate portion (Beckmann, Johansen-Berg, & Rushworth, 2009). Diffusion tensor imaging studies demonstrate that childhood maltreatment is associated with reduced fractional anisotropy in the cingulum bundle, particularly in the posterior hippocampal portion (Choi, Jeong,

Rohan, Polcari, & Teicher, 2009; Huang, Gundapuneedi, & Rao, 2012). While highlighting the nonlinearity of structure-function relationships, these findings also demonstrate that the impact of childhood maltreatment extends beyond reduced hippocampal volume to altered structural and functional connectivity of the hippocampus with the anterior cingulate cortex. The hippocampus and rostral anterior cingulate subserve contextual fear generalisation (Cullen, Gilman, Winiecki, Riccio, & Jasnow, 2015). Alterations to hippocampal-anterior cingulate connectivity following childhood maltreatment may underlie observed increases in fear generalisation amongst maltreated children (McLaughlin et al., 2016).

Extensive preclinical evidence demonstrates that early life stress impacts hippocampal grey matter through synaptic and dendritic changes. The neuroimaging literature suggests that cortical grey matter differences may be driven by altered functional connectivity, a finding that was observed in Chapter V (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Zielinski, Gennatas, Zhou, & Seeley, 2010). Two key findings illustrate the functional basis of reduced grey matter in cortical regions. Firstly, childhood maltreatment-related grey matter reductions were evident across a structural covariance network that substantially overlaps with intrinsic connectivity networks, namely the default mode and fronto-parietal networks. Secondly, grey matter covariance within the SCN was found to uniquely correspond to functional connectivity, which aligns with previous research in healthy participants (Alexander-Bloch et al., 2013; Reid et al., 2016). The directionality of this relationship was recently elucidated in a longitudinal study of infants, where resting state functional connectivity preceded the emergence of grey matter covariance (Geng et al., 2017). Given childhood maltreatment is associated with reduced functional connectivity within the default mode network (Bluhm et al., 2009; Philip et al., 2013), deficient functional coactivation across the distributed frontal, temporal and parietal cortical areas may underpin reduced grey matter following childhood maltreatment.

The multi-modal approaches employed in this thesis provided new insight into the networks affected by childhood maltreatment. In particular, the complementary volumetric and connectivity techniques shed new light on the behavioural consequences and physiological origins of grey matter differences following childhood maltreatment.

6.5 CHILDHOOD MALTREATMENT TO ADULT MENTAL ILLNESS

Henry Kempe and colleagues offered the first epidemiological and clinical evidence of child physical abuse with "*The Battered-Child Syndrome"* (Kempe, Silverman, Steele, Droegemueller, & Silver, 1962). This seminal work prompted a paradigmatic shift in the medial and societal handling of childhood maltreatment. Many developed states introduced child protection laws in the 1970's (Gilbert et al., 2012), including in New South Wales, where the present research was conducted (Ombudsmen Act 1974). Increased responsiveness to childhood maltreatment and the expansion of childhood

maltreatment definitions to include emotional aspects led to an inflation in official reports of childhood maltreatment (Mansell, 2006). Despite increased reporting and the implementation of child protection services, the rate of childhood maltreatment does not appear to be decreasing in developed nations (Gilbert et al., 2012). A recent meta-analysis estimated global prevalence of childhood maltreatment at 40% (Stoltenborgh et al., 2015).

The largest contribution of childhood maltreatment to public health pertains to the disproportionately high level of mental illness amongst adults with a history of childhood maltreatment (Moore et al., 2015). Childhood maltreatment also predicts an unfavourable course of mental illness. Combining data across sixteen epidemiological studies and ten clinical trials, Nanni, Uher, & Danese (2012) found that adults with a history of childhood maltreatment had 224%, 234% and 140% higher odds of depressive episode recurrence, persistence of depressive episodes and treatment resistance compared to non-maltreated individuals, respectively. These findings were independent of age, even though childhood maltreatment is also related to earlier age of illness onset (Scott, McLaughlin, Smith, & Ellis, 2012). Understanding the neurobiological basis of enhanced psychiatric risk and clinical differentiation is essential to effective, biologically informed interventions for individuals with a history of childhood maltreatment.

In line with this aim, the present work followed the National Institute of Mental Health's Research Domain Criteria (RDoC) framework for organising research. Towards the ultimate goal of precision medicine in psychiatry, the RDoC initiative recommends that research be conducted across several traditional diagnostic categories (Insel, 2014). In theory, transdiagnostic research will enable biologically informed individualised treatment options; improving upon highly variable treatment response within the current symptom-based classifications (Cuthbert & Insel, 2013). Furthermore, the transdiagnostic approach accommodates high co-morbidity and within-disorder heterogeneity in young people (Kessler et al., 2012). The knowledge garnered from researching childhood maltreatment in a transdiagnostic cohort offers greater potential for generalisability than diagnosis-specific research and will facilitate individualised treatment amongst a cohort typified by an unfavourable illness course.

This thesis supports the assertion that maltreated individuals represent a neurobiologically distinct subgroup of individuals with mental illness (Teicher & Samson, 2013). In particular, stunted right hippocampal growth and blunted default mode/fronto-parietal grey matter decline during late adolescence and young adulthood distinguish maltreated individuals from other young people with emerging mental illness. These findings depict late adolescence and young adulthood as crucial periods for effective interventions. The hippocampus represents an important target for treatment of childhood-maltreatment related psychiatric illness. Preliminary preclinical research suggests that the rapid anti-depressant effect of ketamine, an NMDA receptor antagonist, operates via up regulation of the mammalian target of rapamycin and BDNF in the hippocampus and medial prefrontal cortex (Zhou et

al., 2014). Important clinical insight will come from exploring the differential impacts of treatments on brain structures, and tailoring treatment programs towards individuals' specific deficits.

Atypical neurodevelopment following childhood maltreatment may cause psychiatric disorder, as posited by neurodevelopmental theories of psychopathology (Rapoport, Addington, Frangou, & Psych, 2005). Contrary to expectations, the observed brain differences between maltreated and non-maltreated individuals did not account for clinical differences, however. Cumulative childhood and recent stress were associated with worse psychiatric symptom severity whereas the mismatch hypothesis predicted brain differences. Symptom severity may not capture clinical differentiation stemming from maltreatment related brain changes. Instead, grey matter reductions following childhood maltreatment may confer risk of developing a psychiatric disorder. Rao et al., (2010) reported that childhood maltreatment-related reductions in the hippocampus partially mediated the relationship of childhood maltreatment with the first episode of depression within the next five years (Rao et al., 2010). Additionally, enhanced sensitivity of the anterior cingulate to later stress may confer vulnerability to post-traumatic stress disorder. Reduced rostral anterior cingulate grey matter following adulthood trauma represents a risk factor for post-traumatic stress disorder (Admon et al., 2013).

Advances in multivariate statistical methods may improve our understanding of how childhood maltreatment-related alterations to brain development confer psychiatric risk. The present thesis modelled one-to-one relationships between CTQ scores, brain structure/function and symptom severity. Multivariate methods may improve our understanding of how multiple features of a brain network predict multiple features of mental functioning. For example, canonical correlation analysis estimates linear relationships between two high dimensional datasets (Witten, Tibshirani, & Hastie, 2009). The resultant canonical variates can depict links between sets of neuroimaging metrics and sets of clinical variables (Smith et al., 2015). In a recent study of 663 youths, a sparse canonical correlation analysis was used to reveal relationships of functional connectivity patterns to general and specific dimensions of psychopathology (Xia et al., 2017). A similar approach could be applied to determine the specific aspects of the biological phenotype engendered by childhood maltreatment that are associated with distinct combinations of psychiatric symptoms.

Given the steady rate of childhood maltreatment, intervention following childhood maltreatment is essential to reducing the burden of childhood maltreatment on the individual and society. The present thesis characterised the biological phenotype of childhood maltreatment-related psychiatric illness. Understanding this phenotype will aid precision psychiatry and help overcome high levels of treatment resistance amongst individuals with a history of childhood maltreatment. Moving forward clinical studies need to assess the effectiveness of early intervention programs on neurodevelopment and the effectiveness of treatments targeted towards specific brain deficits.

6.6 METHODOLOGICAL CONSIDERATIONS

Beyond the limitations of each individual experiment described in the preceding chapters, there are general methodological considerations that require mention. As part of a larger project on youth mental health, recruitment was conducted through a mental health clinic, which specialises in care for young people. Unfortunately, this sole recruitment approach precluded the involvement of healthy young people. In the present work, the absence of healthy participants limited potential research questions, such as exploring resilience and vulnerability following childhood maltreatment. Emerging research suggests certain individuals may be genetically predisposed to develop a psychiatric illness following childhood maltreatment. In particular, Caspi et al (2003) implemented a prospective longitudinal design to investigate the relationship of early life stress with adulthood depression and the serotonin transporter gene, 5-HTTLPR. They found that childhood maltreatment significantly predicted a diagnosis of major depressive disorder exclusively in individuals with a short allele of 5-HTTLPR. Meta-analysis of Caspi et al (2003) and nine additional studies strongly supports a two-hit effect of childhood maltreatment and a short allele of 5-HTTLPR on increased risk of depression (Karg, Burmeister, Shedden, & Sen, 2011). The present sample may represent a specific genetic profile that is psychiatrically sensitive to childhood maltreatment. Although the findings have a high clinical relevance due to the naturalistic sampling, it is difficult to quantify the generalisability of the findings to healthy individuals.

The breadth of possible research questions was also hindered by some limitations with respect to the available clinical information. For example, the CTQ does not incorporate details of the timing of maltreatment. The timing of maltreatment is critical to developing a holistic understanding of the effects of childhood maltreatment as sensitivity to stress varies throughout early life (Khan et al., 2015; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Additionally, the only clinical characteristic reliably assessed across participants was symptom severity.

Neuroimaging analyses were carried out in line with established protocols, however, no gold standards exist. Neuroimaging preprocessing is an area of active research. In particular, intense debate surrounds the minimisation of non-neural signal in functional imaging (Murphy & Fox, 2017). Non-neural noise may be minimised by regressing the average time series of all brain voxels, namely the global signal. However, this approach also removes neural signal and mathematically mandates artefactual anti-correlations (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Murphy & Fox, 2017). In Chapters IV and V, non-neural noise was minimised with a component-based method, CompCor (Behzadi, Restom, Liau, & Liu, 2007). CompCor operates via removal of principal components derived from the BOLD signal of white matter and cerebrospinal fluid (Behzadi et al., 2007). Relative to the global signal regression method, CompCor reduces anticorrelations and increases the specificity and sensitivity of positive correlations (Chai, Castañán, Öngür, & Whitfield-Gabrieli,

2012). However, whether the post-processed timeseries represent a 'truer' version of brain connectivity is impossible to assert at this point.

6.7 FUTURE DIRECTIONS

The delay in observable effects of childhood maltreatment on hippocampal volume to late adolescence and young adulthood suggests the likelihood that early intervention programs may be of benefit. Intervention programs may mitigate the negative impact childhood maltreatment by exploiting protracted neurodevelopment. This assertion is bolstered by findings from the Bucharest Early Intervention Program where physical and emotional neglect during infancy was found to be associated with significantly reduced fractional anisotropy in white matter tracts at ten years of age (Bick et al., 2015). However, deficits in fractional anisotropy were smaller and less widespread amongst children that were placed into foster care at two years of age, relative to those that stayed in institutional care. The efficacy of early intervention programs for normalising grey matter development after childhood maltreatment is yet to be evaluated.

Ultra-high field MRI is opening new avenues in subcortical research. Signal to noise and contrast to noise ratios increase with higher field strengths, which in turn enable higher resolution imaging (Balchandani & Naidich, 2015). This approach has important implications for studying hippocampal subfields and amygdala nuclei. A preliminary effort to capture differential sensitivity of hippocampal subfields to childhood maltreatment with a 3T scanner demonstrated similar effects in CA2/CA3 and CA4/dentate gyrus (Frodl et al., 2014). The study was restricted to examination of CA2/CA3 and CA4/dentate gyrus due to poor correspondence of automatic and manual segmentation of the CA1. Ultra-high field MRI can overcome this issue and, in addition, allow interrogation of anterior-posterior axis differentiation (Robinson et al., 2016). Ultra-high field protocols have also been devised to delineate the amygdala into subregions that reflect histologically defined amygdala subnuclei (Entis, Doerga, Barrett, & Dickerson, 2012). The amygdala subnuclei exhibit qualitatively different responses to early life stress (Padival, Blume, Vantrease, & Rosenkranz, 2015; Rau, Chappell, Butler, Ariwodola, & Weiner, 2015). Examination of the specific effects of childhood maltreatment on amygdala subregions may shed light on the inconsistent findings in the field.

Multi-modal imaging and increased availability of post-mortem human histological data open new lines of inquiry for understanding brain development. Chapter V and previous studies already provided novel insight into the development of brain networks by demonstrating the functional basis of coordinated maturation and subsequent emergence of structural covariance networks (Alexander-Bloch et al., 2013). Cortical shrinkage during adolescence was recently shown to be related to intra-cortical myelination (Whitaker et al., 2016). Neuroanatomically precise transcription distribution maps further

supported this finding, as myelination and cortical shrinkage were coupled with expression of myelin basic protein. Improved utilisation of human data is essential for biological interpretations of neuroimaging findings and to reduce animal harm and sacrifice in scientific practice.

6.8 CONCLUSION

Childhood maltreatment is an intriguing natural model for understanding the profound impact of the early life environment on brain development and the serious consequences this has on an individual's mental function. Interpretation of this thesis in a wider conceptual model provides insight into environmental control over neurodevelopment. Early life events can have a significant impact on brain development, the consequences of which may only become readily observable during later periods of dynamic change. Environmentally induced alterations to neurodevelopment produce phenotypic differences in adult mental health and illness. Each specification of this conceptual model, accompanied by advances in human neuroimaging, enhances our understanding of how the early life environment sculpts an individual's brain and mental functions.

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APPENDIX

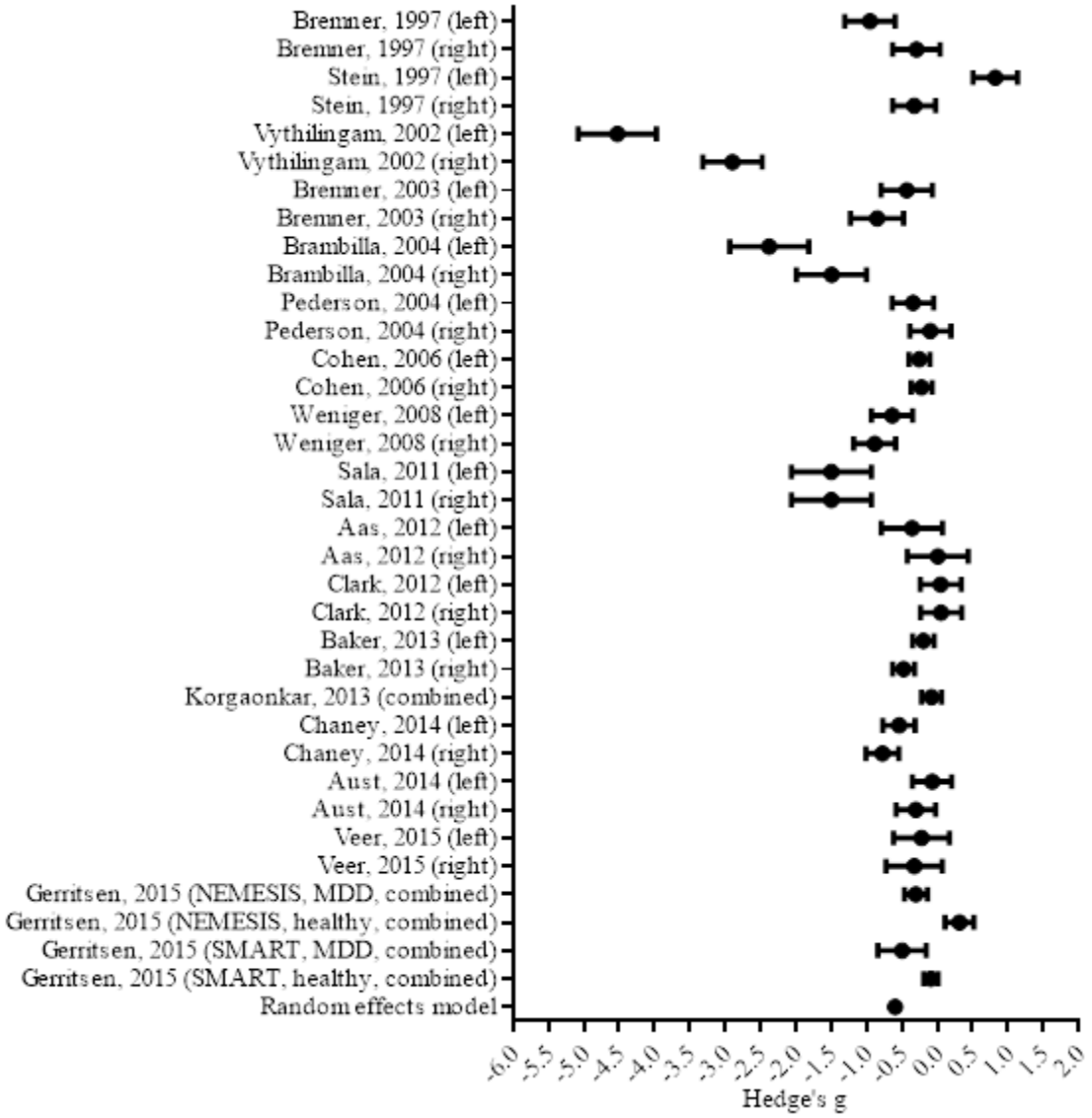
SUPPLEMENT TO CHAPTER II

Supplementary Table 1: Inclusion of studies in hippocampus meta-analysis tests.

	Main meta-analysis	Hemisphere specific	Age	Gender	No medication	Diagnosis matched controls	Diagnostic group	CM type	Multiple traumas
Bremner, 1997	X	X	X	X			P	4	
Stein, 1997	X	X	X	X			P	4	
Vythilingam, 2002	X	X	X	X	X			5	
Vythilingam, 2002 (MDD only)						X	M		
Bremner, 2003	X	X	X	X	X	X	P	5	
Brambilla, 2004	X	X	X	X	X		M/B	4	
Pederson, 2004	X	X	X	X		X	P	3	
Cohen, 2006	X	X	X	X	X	X	H	1	
Weniger, 2008	X	X	X	X			B	4	X
Sala, 2011	X	X	X	X		X	B	4	
Aas, 2012	X	X	X	X		X		1	
Clark, 2012	X	X	X	X	X	X	H	1	X
Baker, 2013	X	X	X	X	X	X	H	1	
Korgaonkar, 2013	X			X		X	H	1	X
Chaney, 2014	X	X	X	X		X	M	1	
Aust, 2014	X	X	X	X	X	X	H	1	
Veer, 2015	X	X	X	X			P	2	
Gerritsen, 2015 (NEMESIS, MDD)	X		X	X		X	M	2	
Gerritsen, 2015 (NEMESIS, healthy)	X		X	X	X	X	H	2	
Gerritsen, 2015 (SMART, MDD)	X		X	X		X	M	2	
Gerritsen, 2015 (SMART, healthy)	X		X	X	X	X	H	2	

Diagnostic groupings: P=PTSD group, H=healthy group, M=mood disorder group, B=borderline personality disorder group
Childhood maltreatment (CM) types: 1=any severely stressful event, 2=abuse or neglect, 3=abuse, 4=physical or sexual abuse, 5=sexual abuse.

Supplementary Figure 1: Pooled studies investigating hippocampal volumes, presented with Hedge's g and standard errors

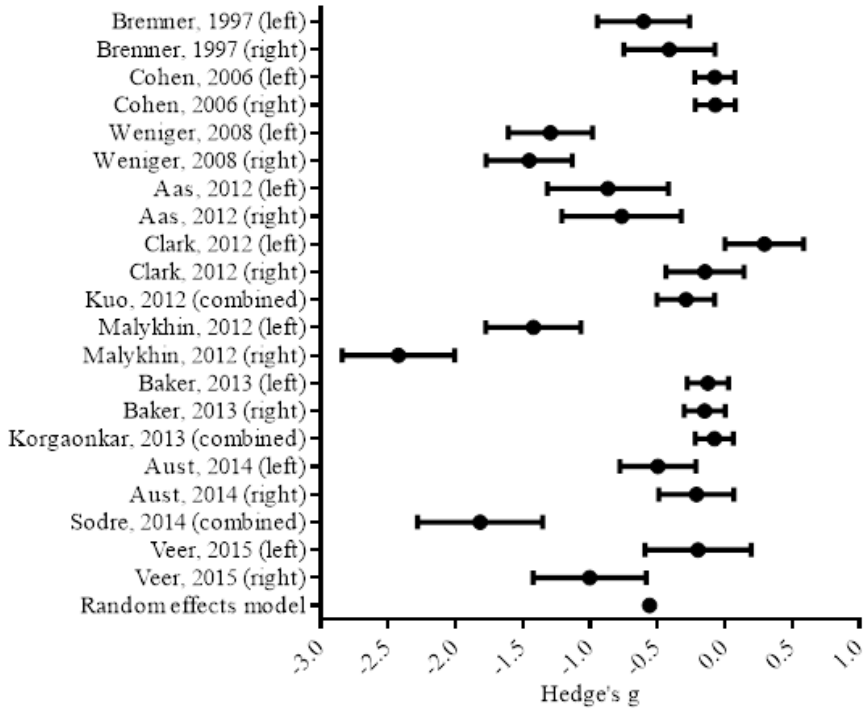


Supplementary Table 2: Inclusion of studies in amygdala meta-analysis tests

	Hemisphere specific	Age	Gender	Healthy	Diagnosis matched controls	CM type	Multiple traumas
Bremner, 1997	X	X	X			3	
Cohen, 2006	X	X	X	X	X	1	X
Weniger, 2008	X	X	X			3	X
Aas, 2012	X	X	X		X	1	X
Clark, 2012	X	X	X	X	X	1	X
Kuo, 2012		X	X		X	1	
Malykhin, 2012	X	X	X		X	3	
Baker, 2013	X	X	X		X	1	
Korgaonkar, 2013			X	X	X	1	X
Aust, 2014	X	X	X	X	X	1	
Sodre, 2014			X	X	X	-	
Veer, 2015	X	X	X			2	

Childhood maltreatment (CM) types: 1=any severely stressful event, 2=abuse or neglect, 3=abuse, 4=physical or sexual abuse, 5=sexual abuse.

Supplementary Figure 2: Pooled studies investigating amygdala volumes, presented with Hedge's g and 95% standard errors.



Supplementary Table 3: Chi-square test for heterogeneity

		No. of studies	Q	d.f.	I^2	p value
Hippocampus	Left	15	96.770	14	85.533	<0.001
	Right	15	55.554	14	74.799	<0.001
	Combined	35	176.585	34	80.746	<0.001
Amygdala	Left	9	30.819	8	74.042	<0.001
	Right	9	45.795	8	82.531	<0.001
	Combined	21	90.388	20	77.873	<0.001

Supplementary Table 4: Egger's test for publication bias

		No. of studies	t	d.f.	p value
Hippocampus	Left	15	2.15	13	0.051
	Right	15	1.68	13	0.117
	Combined	35	3.44	33	0.001
Amygdala	Left	9	1.98	7	0.088
	Right	9	2.77	7	0.028
	Combined	21	4.41	19	<0.001

Supplementary Table 5: Contributing effect sizes of each study to significant clusters in VBM meta-analysis

Author, year	Right dorsolateral prefrontal cortex	Right hippocampus	Right postcentral
Soloff, 2008	0	-0.133859	0
Tomoda, 2009	-0.003541	0	0
Tomoda, 2009	0	0	0
Thomaes, 2011	-0.024525	-0.132921	0
Tomoda, 2011	0	0	0
Tomoda, 2012	0	0	0
Benedetti, 2012	0	0	0
Carballedo, 2012	0	0	0
Carballedo, 2012	0	0	0
Dannlowski, 2012	-0.013547	-0.017788	-0.129695
Fonzo, 2013	-0.075133	0	-0.004554
Kumari, 2013	0	0	0
Labudda, 2013	0	0	0
Lu, 2013	0	0	0
Sheffield, 2013	0	0	0
Walsh, 2014	0	0	0
Van Dam, 2014	0	0	0
Chaney, 2014	0.019988	-0.096628	0
Cancel, 2015	-0.002166	0	0
Opel, 2015	-0.040491	-0.109655	0

Supplementary Table 6: Meta-regressions and subgroup contrasts

Region	Test	Peak voxel	No. of voxels	SDM value	p value
Right dorsolateral prefrontal cortex	A. Age regression	ns			
	B. Gender regression	ns			
	C1. Healthy cohort	28,36,30	142	-1.777	0.000350952
	C2. Psychiatric cohort	ns			
	Difference between C1 and C2	24,40,30	87	-1.479	0.000139356
	D1. Unmedicated cohort	22,36,32	127	-2.060	0.000103235
	D2. Medicated cohort	ns			
	Difference between D1 and D2	ns			
	E1. Groups matched for diagnoses	28,38,34	188	-2.011	0.000067115
	E2. Groups not matched for diagnoses	ns			
	Difference between E1 and E2	ns			
	F1. Any stressor	ns			
	Difference between F1 and not F1	24,38,32	172	1.349	0.000061929
	F2. Abuse or neglect	24,36,32	196	-2.315	0.000030994
	Difference between F2 and not F2	26,40,32	249	-2.821	0.000005186
	F3. Abuse	ns			
	Difference between F3 and not F3	26,40,32	204	1.255	0.000165164
	F4. Physical or sexual abuse	ns			
	Difference between F4 and not F4	ns			
	F5. Sexual abuse	ns			
	Difference between F5 and not F5	ns			
Right hippocampus	A. Age regression	30,-36,-6	323	-1.507	0.000030994
	B. Gender regression	30,-30,-12	243	-1.614	0.000459313
	C1. Healthy cohort	42,-10,-10	135	-1.763	0.000366390
	C2. Psychiatric cohort	30,-28,-14	86	-1.360	0.001703084
	Difference between C1 and C2	42,-12,-12	105	-1.401	0.000304461
	D1. Unmedicated cohort	42,-10,-14	76	-1.918	0.000335455
	D2. Medicated cohort	32,-34,-12	310	-1.374	0.000319958
	Difference between D1 and D2	ns			
	E1. Groups matched for diagnoses	42,-12,-12	64	-1.810	0.000474811
	E2. Groups not matched for diagnoses	36,-26,-14	150	-1.188	0.000583172
	Difference between E1 and E2	30,-28,-10	32	1.290	0.003220320
	F1. Any stressor	ns			
	Difference between F1 and not F1	42,-10,-10	72	1.167	0.000619292
	F2. Abuse or neglect	42,-12,-12	86	-2.091	0.000325143
	Difference between F2 and not F2	42,-12,-12	122	-2.454	0.000123858
	F3. Abuse	26,-24,-12	290	-1.620	0.000738025
	Difference between F3 and not F3	42,-12,-12	81	1.093	0.000639915
	F4. Physical or sexual abuse	30,-28,-14	175	-1.586	0.000490248
	Difference between F4 and not F4	30,-30, -10	128	-3.001	0.001119912
	F5. Sexual abuse	ns			
	Difference between F5 and not F5	ns			

Region	Test	Peak voxel	No. of voxels	SDM value	p value
Right postcentral gyrus	A. Age regression	ns			
	B. Gender regression	ns			
	C1. Healthy cohort	58,-20,24	77	-1.509	0.002735257
	C2. Psychiatric cohort	ns			
	Difference between C1 and C2	62,-22,30	157	-1.258	0.000815392
	D1. Unmedicated cohort	58,-20,36	179	-1.782	0.000815392
	D2. Medicated cohort				
	Difference between D1 and D2	ns			
	E1. Groups matched for diagnoses	60,-22,34	188	-2.011	0.000067115
	E2. Groups not matched for diagnoses	ns			
	Difference between E1 and E2	ns			
	F1. Any stressor	ns			
	Difference between F1 and not F1	62,-22,30	73	1.048	0.001584351
	F2. Abuse or neglect	58,-22,34	127	-1.827	0.001450181
	Difference between F2 and not F2	62,-22,32	209	-2.821	0.000381887
	F3. Abuse	ns			
	Difference between F3 and not F3	60,-22,32	192	1.054	0.000882506
	F4. Physical or sexual abuse	ns			
	Difference between F4 and not F4	ns			
	F5. Sexual abuse	ns			
	Difference between F5 and not F5	ns			

ns=not significant. Peak voxel given in MNI coordinates.
Note: SDM value represents difference in grey matter, with negative scores indicating reduced grey matter density in the maltreated group relative to the non-maltreated group.

SUPPLEMENT TO CHAPTER III

Supplementary Table 1: Demographic and clinical characteristics of participants at each time point

	Wave 1 (n=123)	Wave 2 (n=52)	Wave 3 (n=21)	Wave 4 (n=13)	Wave 5 (n=6)
Age, years	19.9 ± 3.3	21.1 ± 3.6	20.3 ± 3.3	19.7 ± 3.3	19.6 ± 3.5
Female	79 (64.2%)	33 (63.5%)	11 (52.4%)	7 (53.8%)	3 (50%)
Time since last scan, months	-	14.0 ± 9.6	5.9 ± 5.9	3.7 ± 1.9	4.9 ± 4.1
Childhood maltreatment group	68 (55.3%)	34 (65.4%)	12 (57.1%)	9 (69.2%)	5 (83.3%)
HDRS[1]	14.0 ± 6.7 (n=109)	9.5 ± 6.9 (n=29)	10.2 ± 4.4 (n=6)	7.5 ± 10.6 (n=2)	11.5 ± 9.5 (n=4)
BPRS[1]	42.7 ± 9.4 (n=111)	34.9 ± 8.1 (n=29)	33.8 ± 5.9 (n=6)	29.0 ± 5.7 (n=2)	38.5 ± 13.0 (n=4)
SOFAS[1]	61.7 ± 13.0 (n=100)	68.8 ± 10.2 (n=22)	66.8 ± 8.8 (n=6)	85.0 ± 7.1 (n==2)	66.5 ± 18.0 (n=4)
Medication use[1]	76.5% (n=102)	72.3% (n=47)	68.8% (n=16)	66.7% (n=9)	75% (n=4)

Mean ± standard deviation or n (percentage of cohort) for each wave are given where appropriate. HDRS: Hamilton Depression Rating Scale. BPRS: Brief Psychiatric Rating Scale. SOFAS: Social and Occupational Functioning Assessment Scale. [1] Clinical interviews were conducted with a subset of individuals at each time point, n provided for each time point in brackets.

Supplementary Methods

The full model for the i^{th} family, j^{th} individual and k^{th} time point, where linear age provided the best fit, e_{ijk} is the normally distributed residual error, β represents the parameter estimate and (1|subject) represents subject as a random factor, was modelled as such:

(1) $Measure_{ijk} = Intercept + d_{ij} + \beta_1(predictor) + \beta_2(age) + \beta_3(predictor*age) + (1|subject) + e_{ijk}$

The analysis was repeated for four "measures" (HDRS, BPRS and SOFAS and medication use) and two "predictors" (CM and CTQ).

(2) $ROI_{ijk} = Intercept + d_{ij} + \beta_1(predictor) + \beta_2(age) + \beta_3(predictor*age + \beta_n(covariates)) + (1|subject) + e_{ijk}$

The analysis was repeated for each ROI and two "predictors" (CM and CTQ). Covariates were entered for each ROI if $p<0.20$ in the univariate feature selection (see Supplementary Table 2).

When the full CM interaction model provided the best fit for ROI development:

(3) $ROI_{ijk} = Intercept + d_{ij} + \beta_1(age) + \beta_2(predictor) + \beta_3(predictor*age) + \beta_4(measure) + \beta_n(covariates) + (1|subject) + e_{ijk}$

The analysis was repeated for each ROI, and each "measure" that was found to be associated with both childhood maltreatment in analysis (1) and ROI volume in the univariate regression analysis.

Supplementary Table 2: Univariate regression for feature selection

Analysis	Measures	Left amygdala	Right amygdala	Left hippocampus	Right hippocampus
Covariate in ROI analysis	Sex	t=-0.063, p=0.950	t=0.785, p=0.433	t=0.689, p=0.481	t=0.466, p=0.642
	Any mood diagnosis	t=-1.297, p=0.196	t=-1.185, p=0.237	t=-2.368, p=0.019	t=-2.887, p=0.004
	Any psychosis diagnosis	t=2.262, p=0.025	t=2.072, p=0.039	t=2.572, p=0.011	t=2.357, p=0.019
	Any anxiety diagnosis	t=2.188, p=0.030	t=2.253, p=0.025	t=1.406, p=0.161	t=1.514, p=0.132
	Period of illness onset	t=0.566, p=0.572	t=1.041, p=0.299	t=-1.261, p=0.209	t=-0.891, p=0.374
	eTIV	t=-1.828, p=0.069	t=0.370, p=0.712	t=-1.507, p=0.133	t=2.445, p=0.015
Mediator analysis	HDRS	t=-1.248, p=0.213	t=-0.311, p=0.756	t=0.938, p=0.350	t=1.351, p=0.179
	BPRS	t=-0.870, p=0.386	t=-0.681, p=0.497	t=1.294, p=0.198	t=0.773, p=0.441
	SOFAS	t=-0.392, p=0.696	t-1.708, p=0.090	t=-0.767, p=0.444	t=-1.327, p=0.187
	Medication use	t=0.541, p=0.589	t=-0.331, p=0.741	t=1.779, p=0.077	t=2.142, p=0.034

Supplementary Table 3: Complex model prediction of ROI volumes by dichotomous and continuous measurements of childhood maltreatment

Region	Intercept	Age	CM	Age × CM	Any mood diagnosis	Any psychosis diagnosis	Any anxiety diagnosis	HDRS	eTIV
Left amygdala	F=23.77 β=2374.94***	ns	ns	ns	ns	ns	ns		ns
Right amygdala	F=13.89 β=1911.33***	ns	ns	ns		ns	ns		
Left hippocampus	F=20.57 β=5425.25***	ns	ns	ns	ns	ns	ns		ns
Right hippocampus	F=59.03 β=4615.16***	F=6.64 β=0.49**	ns	F=4.35 β=3.65*	ns	ns	ns	F=6.80 β=10.01*	ns

Region	Intercept	Age	CTQ	Age × CTQ	Any mood diagnosis	Any psychosis diagnosis	Any anxiety diagnosis	HDRS	eTIV
Left amygdala	F=26.16 β=2402.07***	ns	ns	ns	ns	ns	ns		F=4.31 β=-0.01*
Right amygdala	F=14.97 β=1968.13***	ns	ns	ns		ns	ns		
Left hippocampus	F=21.90 β=5496.25***	ns	ns	ns	ns	ns	ns		ns
Right hippocampus	F=60.44 β=4714.32***	ns	ns	ns	ns	ns	ns	F=7.09 β=10.25*	ns

Empty cells indicate the variable was not included in the model due to the results of univariate feature selection. CM: childhood maltreatment. HDRS: Hamilton Depressive Rating Scale. eTIV: estimated intracranial volume. CTQ: childhood trauma questionnaire. Significance depicted by *:p<0.05, **:p<0.01, ***:p<0.001.

SUPPLEMENT TO CHAPTER V

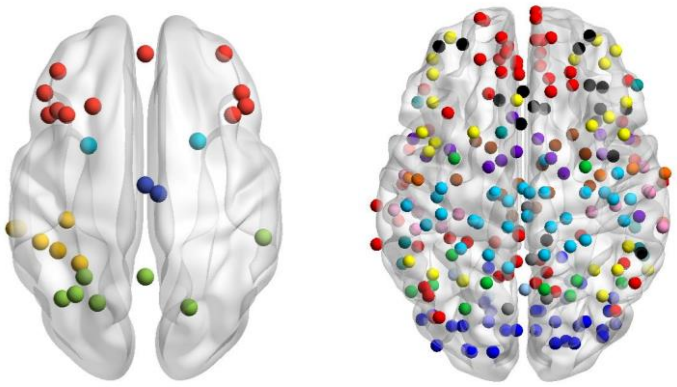
Clinical Assessment

A trained research psychologist conducted a clinical assessment (in a semi-structured interview format) to inform the diagnostic classification and to determine the nature and history of any mental health problems. The assessment included the Hamilton Depression Rating Scale (HDRS, 17-item) to quantify current (over the last seven days) mood symptoms[28], the Brief Psychiatric Rating Scale (BPRS) to quantify current general psychiatric symptoms[29], the Kessler-10 (K-10) to quantify current psychological distress[30,31] and the Overall Anxiety Severity and Impairment Scale (OASIS), to measure of anxiety-related difficulties[32].

Primary diagnoses (as determined by a trained research psychologist via DSM-IV criteria) included depressive disorder (n=58), bipolar disorder (n=36), psychotic disorder (n=12) and anxiety disorder (n=15). 71% of the participants presented with comorbid axis-1 psychiatric diagnoses. To better characterise participants, the presence of any mood disorder, psychosis disorder or anxiety disorder is noted in Table 1. Patients who were treated with psychotropic medications were assessed under 'treatment as usual' conditions, that is, medications were not interrupted in any way. At the time of assessment 29.7% of patients were not taking any psychotropic medications, 51.6% were taking a second-generation antidepressant, 14.1% were taking mood stabilising medication, and 23.4% were taking an atypical antipsychotic medication (Table 1).

Resting state functional MRI analysis

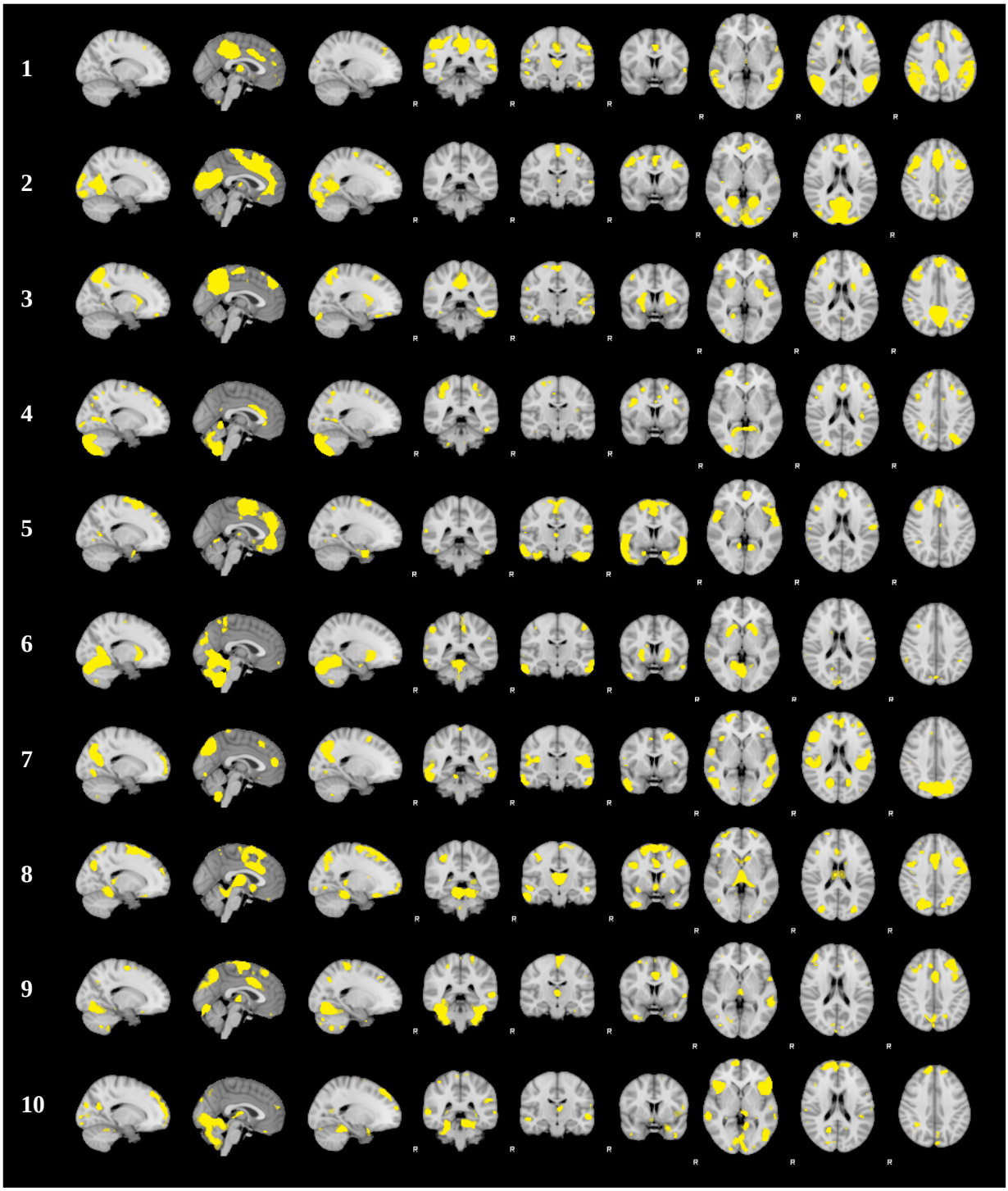
To determine whether motion artifacts may confound group differences, the maximum framewise displacement of each participant was extracted and statistical related to childhood maltreatment and age. Participant movement did not significantly differ between maltreated and non-maltreated groups ($t(60)=0.49$, $p=0.62$) and was not correlated with age ($\beta=-0.001$, $p=0.85$).



Supplementary Figure 1: Network nodes utilised in for multi-modal analyses. (Left) 28 "Study specific nodes" derived from the SCN, for which coordinates are presented in Supplementary Table 2. (Right) 236 "Power nodes" created as 5mm regions of interest around the central coordinates of functional activation in Power et al., (2011), for which red indicates the default mode network and yellow indicates the fronto-parietal network.

Supplementary Table 1: Atlas labels and MNI coordinates (mm) of network nodes

Lobe	Region	x	y	z
Frontal	1. Left frontal pole	-40	40	24
	2. Left inferior frontal gyrus	-46	30	20
	3. Left juxtapositional cortex	0	-12	66
	4. Left middle frontal gyrus	-40	22	36
	5. Left middle frontal gyrus	-44	20	30
	6. Left middle frontal gyrus	-36	20	48
	7. Left superior frontal gyrus	-24	24	52
	8. Medial superior frontal gyrus	0	48	40
	9. Right frontal pole	36	48	16
	10. Right middle frontal gyrus	40	20	40
	11. Right middle frontal gyrus	46	24	38
	12. Right middle frontal gyrus	44	30	32
	13. Right precentral gyrus	6	-16	68
Temporal	14. Left fusiform area	-40	-42	-18
	15. Left fusiform area	-36	-28	-18
	16. Left inferior temporal gyrus	-58	-32	-22
	17. Left inferior temporal gyrus	-48	-38	-22
	18. Left lingual gyrus	-30	-48	-6
	19. Left middle temporal gyrus	-60	-32	-14
Parietal	20. Left lateral occipital cortex	-22	-66	44
	21. Left lateral occipital cortex	-32	-62	54
	22. Left lateral occipital cortex	-38	-64	46
	23. Left superior parietal lobule	-28	-54	58
	24. Medial precuneus	0	-54	42
	25. Right lateral occipital cortex	20	-68	50
	26. Right supramarginal gyrus	54	-36	28
Subcortical	27. Left putamen	-26	6	6
	28. Right putamen	24	8	2



Supplementary Figure 2: Structural covariance networks detected through independent component analysis in 121 youth with emerging mental disorder.

Supplementary Table 2: Estimation of the effect of childhood maltreatment and age on SCNs

SCN	Total variance explained[1]	Average grey matter density					Network expression				
		Intercept	Age	CM	Age*CM	Other	Intercept	Age	CM	Age*CM	Other
1	2.99%	t=17.109	t=-5.462	ns	ns	nil	t=3.814	t=-1.162	ns	ns	nil
2	2.93%	t=13.902	t=-2.799	ns	ns	nil	ns	ns	ns	ns	nil
3	2.82%	t=16.121	t=-5.084	t=-2.653	t=2.505	nil	ns	t=-3.714	ns	ns	nil
4	2.79%	t=12.380	ns	ns	ns	nil	ns	ns	ns	ns	nil
5	2.70%	t=17.929	t=-4.336	t=-3.001	t=2.931	nil	ns	ns	ns	ns	nil
6	2.68%	t=14.312	ns	ns	ns	nil	ns	ns	ns	ns	nil
7	2.67%	t=15.733	t=-2.870	ns	ns	nil	ns	ns	ns	ns	nil
8	2.62%	t=16.304	t=-3.952	ns	ns	nil	ns	ns	ns	ns	nil
9	2.56%	t=15.507	ns	ns	ns	nil	ns	ns	ns	ns	nil
10	2.43%	t=18.237	t=-4.041	ns	ns	nil	ns	ns	ns	ns	nil

t-statistics are presented for tests where $p<0.05$ following FDR correction. "Other" column is used to indicate significant effects of covariates (sex and diagnosis).
[1]: amount of variance in grey matter map explained by component

Relationship of childhood maltreatment to grey matter in functional networks

To assess the applicability of the findings in 3.1 to rsFC networks, we repeated the statistical procedure outlined in 2.5 with grey matter density of Power nodes in the default mode and fronto-parietal networks. Childhood maltreatment was associated with significantly reduced grey matter density in the DMN (β=-0.096, se=0.033, t=-2.85, p=0.005 uncorrected) and a trend level reduction in grey matter density was evident in the fronto-parietal network (β=-0.096, se=0.049, t=-1.953, p=0.053 uncorrected). Grey matter density significantly decreased with greater age in both networks (DMN: β=-0.008, se=0.001, t=-6.151, p<0.001. Fronto-parietal: β=-0.009, se=0.002, t=-4.673, p<0001). Maltreated and non-maltreated groups exhibited significantly different age-related grey matter loss in the DMN (β=0.004, se=0.002, t=-2.549, p=0.012 uncorrected), but not in the fronto-parietal network (β=0.004, se=0.002, t=1.699, p=0.092 uncorrected).

Supplementary Table 3: Estimation of effect of childhood maltreatment and age on mean functional connectivity

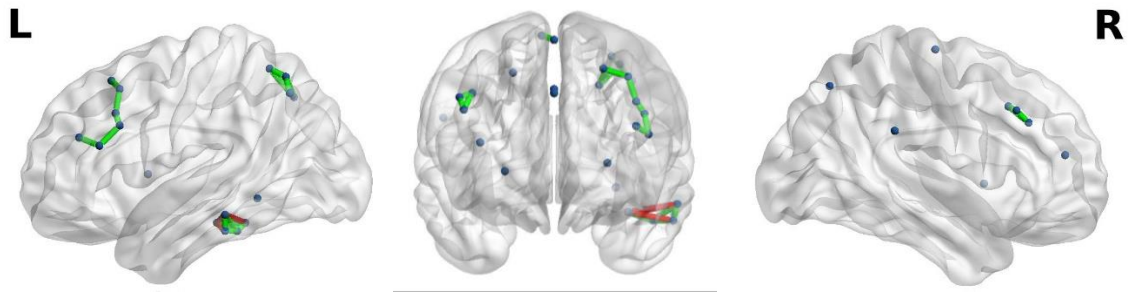
Network	Intercept	Age	CM	Age*CM	Other
SCN	β=0.50, se=0.019, p=0.010	β=-0.010, se=0.008, p=0.218	β=-0.04, se=0.222, p=0.851	β=0.01, se=0.011, p=0.828	nil
DMN	β=0.40, se=0.169, p=0.021	β=0.00, se=0.001, p=0.904	β=0.18, se=0.196, p=0.361	β=0.00, se=0.001, p=0.361	nil
Fronto-parietal	β=0.54, se=0.166, p=0.002	β=0.01, se=0.001, p=0.328	β=0.01, se=0.192, p=0.992	β=0.00, se=0.001, p=0.918	nil

"Other" column is used to indicate significant effects of covariates (sex and diagnosis).

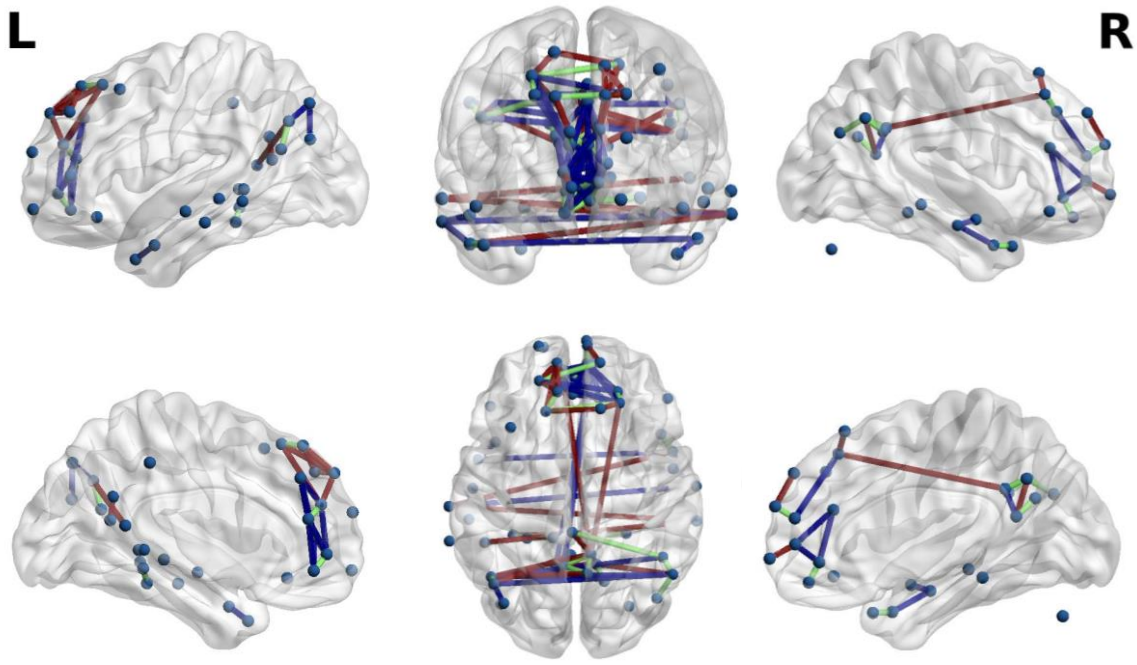
Supplementary Table 4: Estimation of effect of childhood maltreatment and age on mean structural connectivity probability

Network	Intercept	Age	CM	Age*CM	Other
SCN	β=1448, se=786, p=0.071	β=25.2, se=31.9, p=0.434	β=777, se=912, p=0.398	β=-42.5, se=44.6, p=0.346	nil
DMN	β=1448, se=786, p=0.071	β=25.2, se=31.9, p=0.434	β=777, se=912, p=0.398	β=169, se=188, p=0.372	nil
Fronto-parietal	β=23935, se=5420, p<0.001	β=-210, se=220, p=0.344	β=-2209, se=6289, p=0.723	β=-92.8, se=308, p=0.763	Sex: β=2833, se=961, p=0.005

"Other" column is used to indicate significant effects of covariates (sex and diagnosis).



Supplementary Figure 3: Edge-wise convergence of rsFC and structural connectivity in the study-specific SCN, using a threshold of 0.08. Red indicates convergence in the maltreated group only. Green indicates convergence in both groups. No edges were only convergent in the non-maltreated group. The brain is presented in left lateral, frontal and right lateral views.



Supplementary Figure 4: Edge-wise convergence of grey matter covariance and rsFC and structural connectivity in the default mode network, using a threshold of 0.05. Red indicates convergence in the maltreated group only. Green indicates convergence in both groups. Blue indicates convergence in the non-maltreated group only. The top row displays the brain in left lateral, frontal and right lateral views. The bottom row displays the brain in left medial, superior and right medial views.