

An investigation into the impact of childhood maltreatment on brain structure.

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A thesis submitted for the degree of Doctor of Philosophy

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Declaration

I, Philip Kelly, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

A handwritten signature in black ink, appearing to read 'Philip Kelly', written in a cursive style.

Abstract

Childhood maltreatment remains a major public health concern and has been shown to significantly elevate the risk of developing a psychiatric disorder. However, there is limited understanding of the underlying mechanisms by which maltreatment heightens risk of psychiatric outcomes. By investigating cortical structural abnormalities associated with maltreatment in childhood we hope to learn more about the possible pathways that lead from abuse to psychopathology.

This thesis sets out to systematically investigate two main questions within one of the largest community samples of maltreated adolescents studied to date. First, the way in which maltreatment experience impacts on brain structure. In Chapter 2, novel surface-based neuroimaging analysis techniques are used to investigate the impact of maltreatment on discrete structural indices, including cortical thickness, surface area and local gyrification. Chapter 3 explores how dimensions of maltreatment, comprising severity, subtype and duration of abuse, influence the impact of childhood maltreatment on cortical volume. Chapter 4 extends this investigation into the impact of maltreatment characteristics on cortical structure using surface-based methods of structural analysis.

Second, this thesis aims to investigate sex differences in how maltreatment experience impacts brain structure, given that males and females are observed to exhibit differing behavioural and psychopathological outcomes associated with the experience of childhood maltreatment. Chapter 5 explores the sexually dimorphic impact of maltreatment on cortical volume, and this investigation is replicated in Chapter 6 in relation to distinct cortical indices using surface-based methods.

Finally, Chapter 7 summarises the implications of these empirical studies, and considers the hypothesis that such cortical differences may constitute biological markers of vulnerability, increasing risk for psychiatric disorders across the lifespan.

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Publications

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CHAPTER 1: General Introduction.

Childhood maltreatment

Child maltreatment remains a major public-health and social-welfare concern in industrialised countries (Gilbert, Widom, et al., 2009). In 2012 referrals regarding maltreatment were made in relation to 6.3 million children in the USA alone; of these 686,000 cases were substantiated (US DHHS, 2013). Within the United Kingdom, recent estimates have suggested that three children die each week as a result of child abuse and neglect (OFSTED, 2010) and at least 16% of the population will have experienced some form of serious maltreatment during their childhood (May-Chahal & Cawson, 2005). Deaths related to childhood maltreatment have been estimated as constituting one tenth of all injury related child fatalities worldwide (Butchart, Harvey, Mian, & Furniss, 2006). The children who survive maltreatment are at a greater risk of developing physical and psychological disorders across their lifetime (Cicchetti & Toth, 2005; Danese & Tan, 2014; Lansford et al., 2002). Associated outcomes range from cardiovascular and metabolic conditions, such as heart disease and obesity (Wegman & Stetler, 2009), to internalising and externalising disorders, such as depression or conduct disorder (Cicchetti & Toth, 2005; Gilbert, Widom, et al., 2009). The emergence of many of these disorders can be protracted and problems may only arise well into an individual's adult years (Pechtel & Pizzagalli, 2011). At an economic level, maltreatment has an enduring negative impact both at an individual and societal level with maltreated individuals obtaining lower levels of education, employment and assets compared to their peers (Currie & Widom, 2010). These factors highlight the salience of child maltreatment as a social concern and the importance of understanding the developmental impact of maltreatment in adolescence and adulthood.

Despite the considerable progress within the field of maltreatment there is a still limited understanding as to how maltreatment exposure may impact neurodevelopmental pathways and heighten developmental vulnerability to these negative behavioural and cognitive outcomes. Neurobiological models that attempt to bridge the gap between maltreatment and psychiatric disorders have improved with recent advancements in neuroimaging and the increased precision by which cortical properties can be measured, but this work is only in its infancy. A more detailed understanding of the neurobiological impact of maltreatment will not only help us better understand the emergence of psychopathology but has the potential to lead to the generation of novel methods of intervention.

This introductory chapter is divided into five sections. First, maltreatment is defined and the difficulties in operationalising maltreatment and current prevalence estimates are outlined. Second, the impact of childhood maltreatment on social and economic functioning and the associations between maltreatment and psychopathology are outlined and examined. Third, the putative mechanisms that link maltreatment and mental health are detailed. Fourth, the evidence for altered neurobiological structure in maltreated individuals is discussed. Finally, five outstanding research questions are proposed which form the basis for the empirical investigation of this thesis.

1.1. Historical context

To understand the emergence of the current definitions of maltreatment subtypes, it is helpful to provide a concise historical background of important stages in maltreatment research and its presence as a social issue. A prominent catalyst for the inception of child maltreatment as a social concern was the severe neglect, starvation and physical abuse of 9-year old Mary Ellen Wilson at the hands of her foster parents in the late 1800's. The plight of Wilson was brought to the attention of the founder of the American Society for the Prevention of Cruelty to Animals, Henry Bergh. His astonishment that there was no society to protect children, just as there was one to protect animals, led Bergh and his legal counsel, Elbridge Thomas Gerry, to make a pledge to create one. On April 27, 1875 the New York Society for the Prevention of Cruelty to Children (NYPCC) was established, quickly becoming an integral part of the legal system in child abuse cases in New York. The National Society for the Prevention of Cruelty to Children (NSPCC) was established in the United Kingdom a few years later in 1889 and represented a consolidation of smaller and distinct localised organisations that had preceded it. The creation of the NSPCC also coincided with the passing of the first UK law committed to the protection of children from abuse and neglect. This period marked a turning point in the public's perception of child welfare issues and an increased awareness of childhood maltreatment.

The 1960's is also noted as a notable period in the field of childhood maltreatment as a result of the work of two American paediatricians, Dr Kempe and Dr Steele. Their paper titled "*The battered child syndrome*" presented radiological evidence of physical injuries resulting from abuse and significantly increased public

recognition and identification of child abuse within the medical community (Kempe, Silverman, Steele, Droegemueller, & Silver, 1962).

The 1980's represented a period of significant expansion in attention towards childhood maltreatment within the research community and the development of clinical prevention and intervention strategies (Cohn & Daro, 1987). Importantly, the United Nations Convention on the Rights of the Child was adopted on 20th November 1989 signalling the first international treaty to provide a framework for the appropriate protection of children's rights. The convention was important in setting out protocols by which the state will act in the best interest of the child and the rights of protection, participation in decisions regarding themselves and access to education were upheld (Macpherson, 1989).

1.2. Current understanding in definitions childhood maltreatment

To adequately examine the dimensions of maltreatment, it is important to have a sufficiently accurate vocabulary to describe the experience of maltreatment (English, Bangdiwala, & Runyan, 2005). Some have argued that the progress in our knowledge on the effects of abuse and neglect have been hampered by a lack of consensus on the operationalisation of the construct of child maltreatment (Barnett, Manly, & Cicchetti, 1993; Cicchetti & Manly, 2001). A clear operational definition of childhood maltreatment is important in a number of areas. First, accurate calculation of rates of childhood victimisation are dependent on the ability to categorise experiences of abuse (Radford et al., 2011). Second, it is necessary for effective and directed preventative strategies by appropriately identifying abusive behaviours (Butchart et al., 2006). Finally, it is vital in providing the basis for a legal framework that recognizes and responds appropriately to instances of maltreatment.

The World Health Organisation states that childhood maltreatment encompasses "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" (Krug, Dahlberg, Mercy, Zwi, & Lozano, 2002). Maltreatment can be broadly divided into acts of commission and acts of omission. Acts of commission are "*words or overt actions that cause harm, potential harm or threat of harm to a child. These acts are deliberate and intentional*"

(Leeb, Paulozzi, Melanson, Simon, & Arias, 2008). Acts of Omission are those where the caregiver “*fails to provide for the child’s basic physical, emotional, or educational needs or to protect a child from harm or potential harm*” (Leeb et al., 2008). With both acts of omission and commission the harm to the child may or may not be the intended consequence.

Harm in the context of child maltreatment is the “*acute disruption caused by the threatened or actual acts of commission or omissions to a child’s physical, cognitive or emotional development*” (Leeb et al., 2008). Threatened harm occurs when a caregiver expresses the intention or gives signs through the use of words, gestures or weapons to indicate to the child the likelihood of harm. These can be both implicit, such a breaking a plate in an act of aggression, or explicit, like raising a fist towards the child (Leeb et al., 2008).

The perpetrator of the abuse is typically divided into two categories, the primary caregiver or a substitute caregiver. The primary caregiver is the individual who lives with the child, stated as being an individual from birth through 17 years of age (18 years old;(Leeb et al., 2008), at least part of the time and can include relations or step and foster parents. Substitute caregivers may or may not live with the child and can include figures such as babysitters, teachers, community leaders or any others who are entrusted either implicitly or explicitly with the child’s care (Leeb et al., 2008). The setting in which instances can occur vary and can be found in family, institutional or community settings (UK Department for Education, 2010).

1.3. Definitions

Four types of maltreatment are persistently identified: physical abuse, emotional abuse, sexual abuse and neglect (Cicchetti & Toth, 2005). Witnessing intimate partner violence is increasingly seen as a form of maltreatment, however it is commonly categorised within emotional abuse. The definitions below are set out by the DCSF ‘Working together to safeguard children’ (UK Department for Education, 2010) and are provided as guidance by the UK government and used as reference for prevalence statistics within the NSPCC’s 2011 ‘Child Abuse and Neglect in the UK today ’ (Radford et al., 2011). Additional resources are used for clarity.

Physical abuse

Physical abuse is described as “aggressive episodes that can include acts such as hitting, kicking, baby-shaking or other physical aggression likely to hurt or cause significant harm to the child” (UK Department for Education, 2010). The Centre for Disease Control and Prevention (Leeb et al., 2008) also provides a broad definition which states that physical abuse is the “intentional use of physical force against a child that results in, or has the potential to result in physical injury”. These acts may involve hitting, shaking, throwing, poisoning, burning or scalding, suffocating, or otherwise causing harm to a child. Other instances of abuse can include where a parent deliberately causes illness within their child, also known as Munchausen by proxy syndrome (UK Department for Education, 2010). Abuse can also be the result of discipline or punishment (US DHHS, 2002) and a large number of European countries include corporal punishment in their definitions of physical abuse. However, physical injuries caused by attempted or completed sexual abuse are not constituted as physical abuse but rather sexual abuse (Leeb et al., 2008).

Emotional abuse

Emotional abuse is defined as an act of commission that causes severe and persistent adverse effects on the child’s emotional development (UK Department for Education, 2010). Emotional abuse incorporates a wide range of acts which include “blaming, belittling, degrading, intimidating, terrorizing, isolating, restraining, confining, corrupting, exploiting, spurning or otherwise behaviour that is harmful, potentially harmful, or insensitive to the child’s developmental needs which have potential to damage the child’s psychological or emotional needs” (Barnett, Manly, & Cicchetti, 1991; Leeb et al., 2008; McGee & Wolfe, 1991). Furthermore, it may involve “conveying to the child that they are worthless or unloved, or valued insofar as to meet the needs of another person”. (UK Department for Education, 2013). These acts may also feature “age and developmentally inappropriate expectations of the child as well as an overprotection and limitation of exploration and learning, or preventing the child in participating in normal social interaction” (UK Department for Education, 2010). It may involve serious instances of bullying (including cyber-bullying), causing children frequently to feel frightened or in danger, or the exploitation or corruption of children. Furthermore, Intimate partner violence is increasingly noted as a form of child maltreatment and is included as an example of emotional abuse within England, Canada and the USA (Munro, Brown, Sempik, Ward, & Owen, 2011). Intimate partner violence may take the form of hearing or

seeing ill treatment inflicted to others within the family context. Some level of emotional abuse is involved in all types of maltreatment of a child, although it may occur alone.

Sexual abuse

Sexual abuse involves “forcing or enticing a child or a young person to take part in sexual activities, not necessarily involving a high level of violence, whether or not the child is aware of what is happening” (UK Department for Education, 2010). Specifically these activities may involve physical contact, including assault by penetration (for example rape or oral sex) or non-penetrative acts such as masturbation, kissing, rubbing and touching outside of clothing. They may also include non-contact activities, such as involving children “looking at, or in the production of, sexual images, watching sexual activities, encouraging children to behave in sexually inappropriate ways, or grooming children in preparation for abuse” (UK Department for Education, 2010). The definition of sexual abuse extends to instances of prostitution and sexual exploitation of a child for financial or commercial gain (Leeb et al., 2008). The perpetrators of sexual abuse can be adult males and females and other children, however certain instances of sexualised behaviour between preadolescent children may constitute sexual play (Johnson, 2004).

Neglect

Neglect is the “persistent failure to meet a child’s basic physical and/or developmental needs, likely to result in the serious impairment of the child’s health or development” (UK Department for Education, 2010). Specifically, “it is a state of omission where, regardless of intention, carers fail to provide health, education, emotional development, nutrition, shelter or safety for the child” (Leeb et al., 2008). Neglect is sometimes divided into its constituent domains which include physical neglect, emotional neglect, medical neglect and educational neglect (Barnett et al., 1993). Specifically, physical neglect encompasses situations where there is a failure to provide appropriate nutrition, hygiene or shelter. Whereas emotional neglect can include instances where the caretaker ignores the child or denies emotional responsiveness. Additionally, there are instances of failure to supervise where the caregiver fails to take appropriate measures to protect the child from “pervasive violence within the home, neighbourhood or community” (Kairys & Johnson, 2002). Neglect can also occur prenatally in cases where the mother

doesn't provide basic conditions essential for healthy development, such as inadequate nutrition and substance abuse during pregnancy.

Challenges in defining maltreatment

While there has been progress in recognizing the occurrence of child maltreatment, there have been and remain a number of issues that present significant challenges in how we conceptualize such a diverse array of adverse experiences. Several researchers have stated that the overall progress of childhood maltreatment research has been hindered due to a lack of consensus on the operationalisation of the construct of child maltreatment (Barnett et al., 1993). Others have suggested that this conceptual ambiguity has also compromised the ability to develop prevention and intervention policies in child abuse and neglect (Dubowitz, Black, Starr, & Zuravin, 1993). One challenge has been to reach agreement on the distinction between normative parental practices and maltreatment (Cicchetti & Rogosch, 2001). Maltreatment researcher, Susan Zuravin, identified four principles that one should consider when approaching a definition of maltreatment (Zuravin, 1991). First, due to the large amount of heterogeneity between maltreatment subtypes there is a need for clear distinctions across categories. Second, when developing conceptual and operational definitions of maltreatment, consideration of the objectives that the definitions must serve is needed, such as the differing intentions of definitions within research, medical or legal settings. The third principle suggested the need for clarity in the conceptual definition of maltreatment, and fourth, the measurability of operational translations (Zuravin, 1991). To date there is still a relative paucity of standardized measures of maltreatment experiences.

1.4. Maltreatment prevalence

Accurately capturing the extent of child maltreatment remains a major concern world-wide. While there is a considerable amount of data estimating the prevalence of child maltreatment, it has been suggested that there is "*agreement only in that the true extent of child maltreatment is unknown*" (Fallon et al., 2010). This can be largely explained by two factors.

First, there is a substantial disparity between estimated prevalence rates of maltreatment, with some studies identifying ten-fold higher rates than others (Fallon et al., 2010). In a systematic review of 28 studies, the extent of the variation between prevalence estimates indicated lifetime estimates of physical violence

ranging from 1.8% to 34%, sexual abuse estimates varied from 1.1% to 32%, emotional abuse estimates ranged from 5.4% to 37.5%, neglect estimates ranged from 6% to 41.5% and lastly domestic violence ranged from 9.8% to 28% (Radford et al., 2011). While the authors considered that these significant variations may reflect the diversity in child maltreatment experience across studies and countries, it seems more likely that they arise from conceptual and methodological differences in identification and measurement (Radford et al., 2011). The accurate identification and measurement of childhood maltreatment is not straightforward and many issues and inconsistencies have been recognised across existing studies.

Second, many cases of child maltreatment are never exposed because they are either, never reported, investigated or pursued by child protection services (Fallon et al., 2010). Estimates suggest that only 1 in 30 children who are abused by caregivers are investigated by child welfare services (Woodman et al., 2008). Reasons for insufficient investigation can range from an inability to clearly identify a perpetrator, inability of the child to provide sufficiently detailed information or limited and overburdened child welfare services (Cicchetti & Toth, 2005). The source of these variations and discrepancies in prevalence estimates will be explored before detailing current prevalence estimates.

Official prevalence estimates

Within the US, official reports indicate that 4.78% of children were identified and investigated on suspicion of being subject to abuse and neglect in 2008 (US DHHS, 2008). In 2012, child protection services across the United States received an estimated 3.4 million referrals relating to 6.3 million children. Of these, 686,000 unique cases were substantiated, representing an 8.3% increase since figures published in 2008 (US DHHS, 2013). Furthermore, serious instances of maltreatment resulting in the death of a child were estimated at 1,640 nationally (US DHHS, 2013). In the United Kingdom, referrals for abuse stand at a very similar rate of 4.96% of children per year (UK Department for Education, 2010). In terms of number of individuals, recent estimates indicate that 39,100 children and young people were the subject of a child protection plan in 2010 due to abuse (UK Department for Education, 2010) increasing to 52,700 in 2013 (UK Department for Education, 2013). Of 39,100 reports detailed in 2010, 3,000 of these involved multiple occurrences of abuse (UK Department for Education, 2010). Of the referrals brought to the child protection services within the US, neglect represented the most prominent form of maltreatment (75%) with physical abuse (15%) sexual

abuse (10%) representing the least common (US DHHS, 2012). This pattern of maltreatment subtype prevalence is consistent with estimates across western industrialised countries (Gilbert, Widom, et al., 2009).

Community prevalence estimates

As stated previously, the estimates derived from community studies indicate that the prevalence of abuse and neglect is greater than estimates from official data of substantiated reports. The NSPCC employed one of the largest community studies in the UK to date in order to understand the extent of current and past experiences of child maltreatment. Employing a random probability community sample of parents and young children, young people and young adults in the UK, the collective finding was that almost one in five young people were found to have experienced some form of abuse during childhood (Radford et al., 2011). Furthermore, almost 1 in 5 (18.6%) of 11-17 year olds, 1 in 4 (25.3%) 18-24 year olds and 1 in 7 (5.9%) of under 11 year olds will have experienced severe maltreatment during childhood (Radford et al., 2011), indicating how far the magnitude of maltreatment extends beyond statistics based on substantiated cases of abuse and neglect

Prevalence estimates of maltreatment subtypes

Estimates from official reports and community studies both indicate that certain maltreatment subtypes are more prevalent than others. Data based on child protection plan showed that neglect was the most prevalent form of abuse with 17,200 substantiated cases (UK Department for Education, 2010). Emotional abuse followed in prevalence, with sexual abuse representing the least prevalent form of abuse (UK Department for Education, 2010, 2013). Importantly, multiple instances of maltreatment experience were recorded in 10.8% of child protection plans (UK Department for Education, 2013). Consistent evidence from several studies suggests that children who are exposed to one type of maltreatment are at a high risk of other types of maltreatment and repeated exposure (Finkelhor, Vanderminde, Turner, Hamby, & Shattuck, 2014; Gilbert, Widom, et al., 2009; Radford et al., 2011). In particular, children are two to three times more likely to also experience other forms of abuse and also experience abuse by different perpetrators (Radford et al., 2011). Co-occurrence of maltreatment subtypes is not an uncommon phenomenon with a recent review indicating that between 36-91% of emotional maltreatment cases are reported with another form of maltreatment, with emotional abuse rarely occurring alone (Lau et al., 2005). To incorporate a

comprehensive range of maltreatment experiences and environmental risk factors is vital to understand the prevalence and impact of child maltreatment.

As stated previously, neglect represents the most common form of maltreatment, although several caveats should be considered in this context. First, many aspects of neglect are present or overlap with other forms of abuse and variability in prevalence estimates may relate to methodological discrepancies between studies (Runyan et al., 2005). Second, measurement of neglect in the community is difficult, partly because it is a broad conceptual term and captures a large range of behaviours (Barnett et al., 1993; Radford et al., 2011). Last, many outcomes and behaviours related to neglect may not be visually apparent compared to physical and sexual abuse. Consideration and exploration of multi-type abuse and the particular contributions of subtypes in maltreatment may provide a richer understanding to the heterogeneity in an individual's response and adaptation to adverse childhood experiences than investigating subtypes of maltreatment discretely.

Prevalence estimates and sex differences

Overall, the number of officially assigned child protection plans in the UK appear not to differ substantially between males and females, with current official statistics indicating that 50.3% of child protection plans relate to males and 47.6% to females (2.1% unknown/unborn; UK Department for Education, 2013). Some researchers assert that there is "gender symmetry" in maltreatment where both males and females are at similarly likely to abuse and to be abused (Straus, 2011) and official statistics can go some way to support this view (UK Department for Education, 2013). However one limitation of these statistics is that they fail to identify sex differences by maltreatment subtype, which are proposed to vary in experience and prevalence by sex (May-Chahal & Cawson, 2005). In a recent study there were no sex differences found in cases of neglect, emotional maltreatment and a relatively small sex difference relating to physical abuse (15% boys and 12% girls), however substantial sex differences were observed for sexual abuse, with 6% boys and 15% girls reporting such experiences (May-Chahal & Cawson, 2005). This clear variation based on sex within sexual abuse prevalence estimates is mirrored elsewhere (Andrews, Corry, Slade, ISSAKiDiS, & Swanston, 2004; US DHHS, 2008, 2012). However, variations across studies are still evident and a current review identified that between 5-10% of girls and 1-5% of boys are exposed to penetrative sexual

abuse during childhood (Gilbert, Widom, et al., 2009). These statistics have prompted other researchers to suggest that females are 2.5 to 11 times more likely to experience childhood sexual abuse than males (Fergusson, Lynskey, & Horwood, 1996; Finkelhor, 1994; Silverman, Reinherz, & Giaconia, 1996).

1.5. The impact of maltreatment: Economic, health, and social functioning and mental health.

The deleterious impact of childhood maltreatment has been relatively well documented and is thought to have a far-reaching impact past the immediate physical health risks that abuse and neglect pose, extending across multiple domains of functioning (Gilbert, Widom, et al., 2009). As highlighted in the previous section, maltreatment is a complex and multi-faceted term that captures a number of adverse experiences that can negatively impact on the child. It is perhaps therefore unsurprising that the outcomes associated with maltreatment are equally varied. This section will review these outcomes associated with maltreatment across a number of domains, including economic functioning, physical health, cognitive, social and affective processing and mental health. Consideration will then be made for sex differences and the influence of maltreatment subtypes in the developmental sequelae of maltreatment.

Economic functioning

Researchers have attempted to estimate the financial cost of child maltreatment across health and human services at both the individual and societal level. Early estimates calculated the economic cost of childhood maltreatment within the United States at approximately \$7 billion (Miller, Cohen, & Wiersema, 1996), while recent figures suggest that the current cost of childhood maltreatment is closer to an annual cost of \$103.7 billion and indirect costs totalling \$70.6 billion in 2007 (Wang, Holton, & America, 2007) and approximately \$124 billion in 2008 (Fang, Brown, Florence, & Mercy, 2012). At an individual level, maltreatment is associated with enduring consequences in personal financial and economic domains. Using a prospective cohort design, 807 individuals who had experienced substantiated cases of physical and sexual abuse and neglect were followed into adulthood to examine the consequences for adult economic outcomes (Currie & Widom, 2010). It was observed that adults with documented histories of childhood abuse/neglect have lower levels of education, employment, earnings and fewer assets as adults

compared to the non-maltreated individuals (Currie & Widom, 2010). However, it should be considered that cases of abuse and neglect are more prevalent in families of lower socioeconomic status and enduring economic consequences may be influenced by differences in socioeconomic status early on in life (Paxson & Waldfogel, 2002).

Physical health

Maltreatment can put the child at risk of physical harm directly, or indirectly through a failure to meet basic physical needs. However studies have shown that maltreatment may also be associated with prospective risk of physical health problems in later life (Danese & Tan, 2014; Wegman & Stetler, 2009; Whitaker, Phillips, Orzol, & Burdette, 2007). A recent meta-analysis of 24 studies exploring the prospective risk of physical health problems later in life of maltreated individual found that neurological and musculoskeletal problems yielded the largest effects sizes followed by respiratory problem, cardiovascular disease, gastrointestinal and metabolic disorders (Wegman & Stetler, 2009). Obesity and eating disorders in childhood and adulthood have been found to be robustly associated with histories of childhood maltreatment (Danese & Tan, 2014; Whitaker et al., 2007). Maltreated individuals have also been reported as displaying greater amount of risky behaviour which can, in many cases, lead to negative health outcomes. In particular, risky sexual behaviour has been linked to a twofold risk of HIV infection (Wilson & Widom, 2008) and higher rates of teenage pregnancies in maltreated compared to non-maltreated individuals (Senn, Carey, Venable, Coury-Doniger, & Urban, 2007).

Cognitive functioning

The experience of maltreatment has been robustly associated with atypical cognitive functioning. Several studies have reported that maltreated children are at an increased risk of lower levels of educational achievement and intellectual performance as well as higher rates of repetition of school years (Boden, Horwood, & Fergusson, 2007; Jonson-Reid, Drake, Kim, Porterfield, & Han, 2004; Lansford et al., 2002; Leiter, 2007; Perez & Widom, 1994). Children maltreated across multiple developmental periods display lower IQ scores than children maltreated in one discrete developmental time period (Jaffee & Maikovich-Fong, 2011), suggesting there may be a dose response relationship between maltreatment experience and its impact on cognitive development.

Executive function encapsulates a variety of different domains vital for higher order cognitive functions such as planning, task switching, and problem solving. It has been reported that maltreated adolescents have significantly lower performance than non-maltreated adolescents on tasks assessing executive functions, such as working memory, verbal fluency and inhibition (Kirke-Smith, Henry, & Messer, 2014). However there are inconsistencies in findings related to executive function, and while particular deficits in domains such as working memory and attention have been reported in adults with histories of maltreatment (Bos, Fox, Zeanah, & Nelson, 2009; Majer, Nater, Lin, Capuron, & Reeves, 2010; Raine et al., 2001) others have reported weak or non-significant associations (Pederson et al., 2004; Twamley, Hami, & Stein, 2004).

Impairments in both short and long term memory have also been associated with childhood maltreatment in youths (Beers & De Bellis, 2002; Samuelson, Krueger, Burnett, & Wilson, 2010; Yasik, Saigh, Oberfield, & Halamandaris, 2007) and adults (Bremner et al., 2004; Majer et al., 2010; Navalta, Polcari, Webster, Boghossian, & Teicher, 2014). Relatedly, maltreated children's autobiographical memories have been found to be more over-general and contain more negative self-representations than those of non-maltreated children (Valentino, Toth, & Cicchetti, 2009).

Social and affective functioning

A large body of evidence has documented the impact of child maltreatment on social and affective functioning and deficits are noticeable in a number of domains. Primarily, childhood maltreatment is considered to be one of the most prevailing causes for disorganised attachment during infancy (Cicchetti, Rogosch, & Toth, 2006; Crittenden & Ainsworth, 1989; George, 1996). As trauma-related symptoms have been associated with disorganised/unresolved attachment (Joubert, Webster, & Hackett, 2012), deficits in attachment have been suggested one factor associated with the emergence of adult psychopathology (Muller, Thornback, & Bedi, 2012).

Affective processing difficulties within maltreated children have been widely investigated and there is a suggestion that these difficulties drive many internalising and externalising disorders associated with maltreatment exposure (Kim & Cicchetti, 2010). Specifically, young children perceive emotional expression based upon common perceptual categories, however abused children, who had experienced

frequent displays of extreme hostility, display broader perceptual categories of anger relative to non-maltreated children (Pollak & Kistler, 2002). Furthermore, physically abused children have been found to accurately identify facial displays of anger on the basis of less sensory information than non-maltreated peers (Pollak & Sinha, 2002). This atypical processing of negative affect can equally be considered as an adaptation to environmental threat that confers functional advantages. Specifically, the apparent superior perceptual sensitivity may facilitate the efficient coding of salient features of the social environment, therefore calibrating these affective processes (i.e. emotional perception) to threatening stimuli (Leist & Dadds, 2009). While this adaptation may be beneficial to the child in the context of an abusive environment, it may become maladaptive in normative social situations (Pollak, 2008).

Mental health

Numerous epidemiological studies have detailed associations between maltreatment and a greater risk of developing a range of mental health problems in adolescence and adulthood (Cicchetti & Toth, 2005; Collishaw et al., 2007; Kearney, Wechsler, Kaur, & Lemos-Miller, 2010; Lansford et al., 2002), most notably anxiety, depression and post-traumatic stress disorder (Keyes et al., 2012). Moreover, the onset of psychiatric disorders across the life course is proposed to be attributable in nearly a third of cases to adverse childhood experiences (Kessler et al., 2010; McLaughlin et al., 2011). In particular, predicted attribution rates for maltreatment-related psychiatric disorders range from 22% to 32% among women and 20% to 24% for men (Afifi et al., 2008). While there is a robust group level association between maltreatment and various psychiatric disorders, it is important to keep in mind that there are a considerable proportion of children who experience maltreatment but who do not develop mental health difficulties in either adolescence or adulthood (Cicchetti, 2013). For example, in one study, 48% of children with histories of abuse or neglect did not meet criteria for adult psychiatric diagnosis including depression, anxiety and PTSD (McGloin & Widom, 2001).

Internalising disorders

Maltreated children have an increased risk of developing depressive disorders. A quarter to a third of maltreated children meet the criteria for major depression by adulthood (Fergusson, Boden, & Horwood, 2008; Green et al., 2010; Widom, DuMont, & Czaja, 2007) with the onset of depression emerging in childhood for

many maltreated children (Thornberry, Ireland, & Smith, 2001). For instance, the odds ratio for risk of depression in adolescents and adults with childhood experiences of abuse has been estimated to increase from 1.3 to 2.4, representing a moderate increase compared to peers (Lansford et al., 2002). Post-traumatic stress disorder (PTSD) occurs after an experience of a traumatic event and, expectedly, higher rates of post-traumatic stress symptomatology has been observed in samples of maltreated children (Banyard, Williams, & Siegel, 2001; Brewin, Andrews, & Valentine, 2000; Lansford et al., 2002; Widom, 1999). Specifically, incident rates of PTSD are found to be highest within individuals who have experienced sexual abuse, followed by physical abuse and neglect (Widom et al., 2007). Furthermore, dose response relationship between sexual abuse and PTSD has been observed in a meta-analysis of studies exploring the link between sexual abuse and subsequent psychiatric disorders (Andrews et al., 2004). However, even when maltreatment does not give rise to diagnosable disorders, elevated internalising symptoms, including anxiety and depression, have been robustly associated with maltreatment experience (Cicchetti & Toth, 2005; Kearney et al., 2010).

Externalising disorders

Children who have been abused are at greater risk of being diagnosed a range of externalising disorders, such as oppositional defiant, attentional and conduct disorders (Burke, Loeber, & Birmaher, 2002; Green et al., 2010) as well as antisocial personality disorder and substance misuse disorders (Fergusson et al., 2008; Spatz Widom, Marmorstein, & Raskin White, 2006). Furthermore, although the evidence is currently mixed, a number of studies have suggested that maltreatment is associated with elevated levels of callous-unemotional traits, a core affective personality feature of psychopathy (Graham, Kimonis, Wasserman, & Kline, 2012; Kimonis, Cross, Howard, & Donoghue, 2013; Koivisto & Haapasalo, 1996; Viding & McCrory, 2012). As with internalising problems, even when maltreated children do not present with diagnosable disorders they may show elevated sub-threshold symptoms compared to non-maltreated peers (Cicchetti & Toth, 2005; Kearney et al., 2010; Manly, Cicchetti, & Barnett, 1994; Stewart, Livingston, & Dennison, 2008). The development of behavioural problems seems to be partly moderated by the chronicity of the abuse with earlier experiences presenting with greater association of behavioural problems in childhood and adolescence (Kotch et al., 2008; Manly, Kim, Rogosch, & Cicchetti, 2001; Thornberry et al., 2001).

The link between childhood maltreatment and offending is well established, with an increased likelihood of arrest as a juvenile (31% compared to 19% of community matched peers) and as an adult (48% compared to 36%) with increased risk of violent behaviour and delinquency (Fang & Corso, 2007; Maxfield & Widom, 1996; Widom, 1989). Prospective studies of adolescents and adults with documented abuse histories show that both men and women are more likely to be arrested and convicted, especially for violent crimes (Rivera & Widom, 1990; Smith, Ireland, & Thornberry, 2005).

One pervasive limitation in much of the current research is the tendency to focus on a single diagnostic outcome of child maltreatment, with the exception of one investigation, which found that maltreatment is associated with a broad range of mental health outcomes and the more severe the maltreatment exposure, the greater the number and severity of the outcomes (Cecil, Viding, Barker, Guiney, & McCrory, 2014). As maltreatment is linked to a greater prevalence of comorbid mental health disorders (Oswald, Heil, & Goldbeck, 2010), the underlying structure of psychopathology should be accounted for (Chapman et al., 2004; Kendler, Kuhn, & Prescott, 2004; Stein et al., 2010; Widom, 1999; Zachar & Kendler, 2010). Furthermore, psychopathology is often presented as a dichotomous diagnosis; as stated previously even when maltreatment does not lead to the defined diagnosis of a clinical disorder it has been robustly associated with elevated symptoms of internalising disorders (Cicchetti & Toth, 2005; Kearney et al., 2010).

However, an important consideration when exploring the developmental sequelae of child maltreatment is the suggestion that the nature of psychiatric disorders in maltreated individuals may be distinct to those without histories of maltreatment. Maltreated individuals with depressive, anxiety and substance use disorders have an earlier age at onset, greater symptom severity, greater comorbidity, and greater risk of suicide, and poorer treatment response than non-maltreated with the same diagnoses (Teicher & Samson, 2013). Phenotypic expression of psychopathology may be strongly influenced by exposure to maltreatment, leading to a constellation of ecophenotypes; phenotypic variation resulting from environmental factors. While these ecophenotypes fit within conventional diagnostic boundaries, they likely represent distinct subtypes (Teicher & Samson, 2013).

Sex differences in the association between maltreatment and psychopathology

As with the prevalence of certain forms of abuse, the sequelae of child maltreatment is found to be influenced by sex. Generally, females have been noted as experiencing more negative consequences or to be at greater risk for some health problems after the experience of child maltreatment compared to males (Lansford et al., 2002; Thompson, Kingree, & Desai, 2004). Epidemiological studies of mental disorders consistently report that sex differences exist in prevalence estimates for many psychiatric disorders (Eaton et al., 2012). Sex differences in prevalence data were systematic such that females show higher rates of mood and anxiety disorders and generally in internalising symptomatology, while males display higher rates of antisocial personality and substance use disorders and externalising symptomatology (Eaton et al., 2012).

Sex differences in maltreatment related psychopathology are similarly prevalent. For instance, physical abuse has been found to show associations with externalising symptom in men, but only with internalising symptom in women (Keyes et al., 2012). For example, females with a history of physical abuse show a greater preponderance of lifetime rates of major depression and illicit drug abuse/dependence than their maltreated male counterparts (MacMillan et al., 2001). Generally, lifetime psychopathology associated with childhood maltreatment was further illustrated to vary significantly between the sexes, except in the case of anxiety disorders (MacMillan et al., 2001).

Furthermore, early institutional care, a commonly recognised form of neglect, shows a similar sexually divergent association with psychiatric symptomatology, displaying a male weighted vulnerability to externalising symptoms while the majority of internalising symptoms are exhibited in females (Bos et al., 2011). However, it's noted that males are as likely to express externalising symptoms regardless of history of institutional care (Bos et al., 2011). Maltreatment also represents an increased risk of suicidal ideation and attempts on one's own life, although women are believed to contribute more to these associations, particularly in suicidal attempts (Afifi et al., 2008; Johnson et al., 2002; Swannell et al., 2012).

The influence of maltreatment characteristics on the association between maltreatment and psychopathology

Subtypes of maltreatment or abuse have been hypothesised to exert differential effects on developmental outcomes. However, there are still mixed views regarding the occurrence of specific rather than common effects of maltreatment subtypes (Petrenko, Friend, Garrido, Taussig, & Culhane, 2012). I will briefly highlight the distinct and varied associations between subtypes of abuse and behavioural developmental outcomes, considering the vital recognition of poly-victimisation in research.

Physical abuse, out of all abuse subtypes is thought to be the strongest predictor of externalising problems (Litrownik et al., 2005), elevated levels of aggression and violence (Herrenkohl, Egolf, & Herrenkohl, 1997; Kaufman & Cicchetti, 1989; Loeber et al., 2005; Smith et al., 2005; Widom, 1989), and delinquent behaviours (Taussig, 2002). Specifically, physical abuse in girls is closely related to youth violence over other forms of maltreatment (Maas, Herrenkohl, & Sousa, 2008). However, both physical abuse and sexual abuse are associated with a doubling of the risk of attempted suicide for young people who are followed up into early adulthood (Fergusson et al., 2008). For physical and sexual abuse these effects persist after adjustment for confounding family and individual variables (Fergusson et al., 2008). Sexual abuse alone is related to increases in both internalising and externalising behaviour problems as well as difficulties with socialisation over and above other maltreatment types (Litrownik et al., 2005). Sexual abuse and neglect are commonly associated with more internalising problems, especially among children who experienced both these maltreatment types (Bolger & Patterson, 2001; Litrownik et al., 2005). Children who are severely neglected show greater difficulties in verbal comprehension, greater cognitive deficits in the form of learning disabilities or poor academic achievement compared to those exposed to physical abuse (Augoustinos, 1987; Eckenrode, Laird, & Doris, 1993; Kendall-Tackett, 1997; Law & Conway, 1992; Wodarski, Kurtz, Gaudin, & Howing, 1990). Other researchers have suggested that physical neglect is associated with lower intellectual functioning (Kaufman, Jones, Stieglitz, Vitulano, & Mannarino, 1994). These varied associations with negative behavioural outcomes further underline the heterogeneity in response to maltreatment during childhood, potentially influenced by the specific experience or pattern of experiences of abuse and neglect.

The occurrence of childhood maltreatment increases the likelihood of future experiences of abuse and neglect (Duncan, 1999). As a result, maltreated children are predicted to experience multiple forms of abuse and neglect in their lifetimes (Finkelhor, Ormrod, Turner, & Hamby, 2005; Finkelhor, Ormrod, & Turner, 2007; Moylan et al., 2010). As stated previously, emotional abuse is hypothesised to feature within all forms of maltreatment and estimates of co-occurrence with other subtypes range between 36-91% (Behl, Conyngham, & May, 2003; Butchart et al., 2006; Lau et al., 2005). The greater number of abuse subtypes that occur together, the greater the child's risk of poor developmental outcomes, reflecting a dose-response relationship (Anda et al., 2006; Pechtel & Pizzagalli, 2011; Radford et al., 2011). Collectively, these findings suggest that the examination of multiple forms of maltreatment concurrently is crucial so as to investigate the separable impact of subtypes as well as the cumulative effects of co-occurring forms of maltreatment.

Maltreatment experienced over multiple and distinct developmental periods also represents an important contributory factor to associated behavioural and psychiatric outcomes. Maltreatment spanning over multiple developmental periods has shown to increase the risk of externalising and internalising problems compared to maltreatment experienced within a discrete developmental period (Jaffee & Maikovich-Fong, 2011). This chronic maltreatment has also been associated with higher rates of juvenile offending (Stewart et al., 2008), poorer peer relations (Bolger & Patterson, 2001), and increasing levels of anxious and depressed behaviours, particularly PTSD and depression symptoms, over time than those with more transitional maltreatment (English, Bangdiwala, et al., 2005; Éthier, Lemelin, & Lacharité, 2004; Jaffee & Maikovich-Fong, 2011). Age of abuse onset also represents a vital instrumental factor in development, as the sequelae of abuse has been found to vary depending on the developmental stage of the child when the abuse occurred (Margolin & Gordis, 2000). For example, severity of emotional maltreatment was particularly important in the infancy-toddler period, and physical abuse during the preschool period, in predicting externalising behaviour and aggression (Manly et al., 2001). The chronicity of abuse in its multiple dimensions therefore represents a vital aspect to consider in research when conceptualising the pathways from abuse to psychiatric outcomes.

1.6. Putative mechanisms linking maltreatment and mental health

There are a number of proposed putative mechanisms via which maltreatment confers a risk of developing mental health problems both in adolescence and adulthood. I will overview the current understanding of the proposed psychological and neurobiological mechanisms that may be impacted as a consequence of maltreatment, and confer risk for subsequent mental ill health.

Psychological mechanisms

Affective processing, specifically emotion recognition and emotional responsivity – in particular to perceived threat - have been commonly and consistently found to be disrupted in maltreated individuals (Camras, Sachs-Alter, & Ribordy, 1996; Cicchetti & Toth, 2005; Hennessy, Rabideau, Cicchetti, & Cummings, 1994; Maughan & Cicchetti, 2002; Pollak & Kistler, 2002; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003). Atypical emotion regulation profiles have been found to mediate the link between maltreatment and the child's symptoms of anxiety (Maughan & Cicchetti, 2002) and it is proposed that perturbations in emotional regulation may represent a candidate mechanism for conferring risk to the development of psychopathology in maltreated individuals (Cicchetti & Toth, 2005).

Alexithymia is a psychosomatic disorder in which an individual is unable to identify and differentiate emotional responses. Maltreated adolescents have been found to exhibit greater difficulties identifying their own emotional states and distinguishing them from bodily sensations signalling arousal, commonly characterised by alexithymia symptoms (Aust, Härtwig, Heuser, & Bajbouj, 2013; Cohen, Brown, & Smailes, 2001). The ability to effectively identify and regulate one's own emotion is vital for the normative development of affective processing and disturbances to this trajectory may alter an individual's path leading them towards psychiatric disorders characterised by abnormal affect (Pollak, 2008).

Positive attachment plays an important role in social and affective development and attachment with the primary caregiver develops during the first year of life (Cicchetti & Toth, 2005). Attachment theory suggest that a secure attachment provides a foundation on which exploration and integration of cognitive, affective and behavioural abilities are built, and which influence ongoing and novel

relationships and an individual's understanding of the self (Sroufe, 1979). Maltreatment in childhood is seen as a considerable threat to the capacity to develop a secure attachment and research has suggested that maltreated children are more likely to exhibit insecure attachment styles with prevalence rates estimated as high as 95% (Cicchetti, Rogosch, & Toth, 1994; Cummings, 1994; Stronach et al., 2011; Toth, Manly, & Cicchetti, 1992). As insecure attachment style has been found to be a risk factor for depression in adulthood and a number of authors have suggested it represents one important route by which the experience of maltreatment may confer risk of the emergence of psychiatric disorders in later life (Carnelley, Pietromonaco, & Jaffe, 1994; Hankin, 2006; Hankin, Kassel, & Abela, 2005; Roberts, Gotlib, & Kassel, 1996).

Over general memory (OGM) represents the difficulty or inability to retrieve specific autobiographical memories. Adults with histories of childhood trauma have been found to show specific difficulties within this domain (Henderson, Hargreaves, Gregory, & Williams, 2002; Kuyken & Brewin, 1995). Furthermore, neglected children describe more negative self-representations as well as overgeneral memories in autobiographical memory tasks compared to non-maltreated peers (Valentino et al., 2009). Adult research has found a clear association between depression and OGM (Williams et al., 2007), with overgeneral memory predicating delayed recovery from episodes of affective disorders (Dalgleish, Spinks, Yiend, & Kuyken, 2001). Hence, it has been proposed OGM may link maltreatment with the risk for the emergence of depressive symptoms in later life (Stange, Hamlat, Hamilton, Abramson, & Alloy, 2013; Valentino et al., 2009).

Neurobiological mechanisms

Childhood maltreatment represents considerable stress to the individual. The reaction to this environment stress involves a number of interconnected areas of the brain and the release of specific hormones so that the individual is effectively prepared to respond to events that may threaten their well-being. The functioning of these stress systems has been the subject to a great amount of research in the domain of child maltreatment.

The hypothalamic-pituitary-adrenal (HPA) axis represents the body's slower and more protracted response to stress, in contrast to the initial rapid response provided by the autonomic nervous system (ANS). The HPA axis consists of

hormonal cascades and feedback mechanisms which necessitates multiple physiological changes to adequately deal with the demands the environmental stress provides, such as vigilance to threat and alertness to defend oneself (Sapolsky, Uno, Rebert, & Finch, 1990). Cortisol is a vital hormone in this system in that it promotes the mobilisation of stored glucose and lipid stores which allow for the stress related physiological changes. Feedback loops at several levels of the neurochemical cascade allow for a homeostatic response to the present threat and the return to normative levels once the threat has gone. This response is critical as elevated levels of cortisol can have deleterious effects on health (Lupien, McEwen, Gunnar, & Heim, 2009; Sapolsky, Romero, & Munck, 2000). Importantly, the feedback loops are provided with regulatory input from several regions of the brain including the hippocampus (Sapolsky et al., 2000), prefrontal cortex and the amygdala (Herman et al., 2003).

Animal studies have been able to provide a rich understanding of the impact of prolonged exposure to environmental stress. Particularly, the deleterious impact of chronic stress on HPA function across the lifespan (Meaney & Szyf, 2005) and to the structure of localised regions of the brain (Harvey, Brand, Jeeva, & Stein, 2006). Within humans, many authors suggest that chronic or prolonged stress may lead to a similar protracted and ongoing dysregulation of the HPA axis, subsequently increasing vulnerability to psychiatric symptomatology in later life (Cicchetti & Toth, 2005; McCrory, De Brito, & Viding, 2010). Maltreated children have consistently been found to have atypical cortisol functioning however the precise nature and direction of the impact remains unclear, and may relate to the timing, type and duration of maltreatment (McCrory et al., 2010). While some studies have shown that maltreated children exhibit higher basal circulating cortisol levels and more blunted response cortisol level in threatening situations (Cicchetti & Rogosch, 2001; Danese & McEwen, 2012), others have shown that physically and sexually abused children display hypercortisolism and physically abused children display hypocortisolism (Cicchetti & Rogosch, 2001). While such adaptation may be functional in the short term, in the long run it may prove to be maladaptive in other, more normative contexts. It has been suggested that alterations to HPA functioning may serve to predispose and individual to psychiatric vulnerability in later life (Essex et al., 2011; Pechtel & Pizzagalli, 2011; Van Goozen & Fairchild, 2006; van Goozen, Fairchild, & Harold, 2008).

Genetics of vulnerability and epigenetic mechanisms

As noted in the previous sections, not all children who experience maltreatment go on to develop psychiatric disorders (Cicchetti, 2013). It has been proposed that heterogeneity in response to maltreatment may be attributable, in part, to genetic influences (Caspi & Moffitt, 2006; Moffitt, Caspi, & Rutter, 2006). Gene environment studies have shown that environmental stressors, such as maltreatment, can interact with specific gene variants and polymorphisms to increase or decrease biological vulnerability of stress to maladaptive outcomes (Caspi & Moffitt, 2006; Kim-Cohen et al., 2006). Certainly, while some genetic polymorphisms may confer risk to the emergence of psychiatric disorders (e.g. Monoamine oxidase A; (Caspi et al., 2002), other may promote resilience in the wake of maltreatment (e.g. Brain-derived neurotrophic factor (BDNF) gene and corticotrophin-releasing hormone receptor (CRHR1) gene (Bradley et al., 2008; Kaufman et al., 2006; Polanczyk et al., 2009). One must also consider the fact that there are not specific genes that are responsible for separable psychiatric disorders, rather there are genetic variants which add small variations to the probability that someone may develop, or similarly be protected from developing a psychiatric disorder (Plomin, Owen, & McGuffin, 1994). Furthermore evidence is emerging that maltreatment may have long-lasting impacts on physiological function through changes to gene expression; epigenetics (Champagne, 2010; McGowan et al., 2009).

1.7. Evidence for altered neurobiological structure in MT individuals

Childhood maltreatment has been associated with a cascade of neurochemical, psychological and hormonal changes that can have a prolonged and lasting impact on brain structure and function (Teicher et al., 2003). By investigating the cortical deviations within individuals who have experienced maltreatment we can attempt to uncover the neuro-developmental pathways that lead from abuse to psychopathology.

Early animal models of stress have been able to establish a causal relationship between early stressful caregiving and structural deficits in the brain (Arnsten, 2009; Hill, Hillard, & McEwen, 2011), providing a useful basis for human research into the neural impact of maltreatment. These animals models have found that aberrant maternal caregiving is associated with later alterations in HPA

functioning (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Nishi, Horii-Hayashi, & Sasagawa, 2014) global structure differences (Oomen et al., 2011) and atypical levels of neurotrophins, which support neurogenesis (Roceri et al., 2004). Specifically, hippocampal structure has been consistently shown to be vulnerable to early stress, displaying structural deficits such as abnormalities in synaptic formation (Andersen & Teicher, 2004; Sanchez, Ladd, & Plotsky, 2001). I will briefly specify the limited functional imaging studies of maltreatment before focussing on the extensive literature regarding structural studies of maltreatment.

Functional studies

Standing in contrast to the numerous literature exploring the structural impact of maltreatment, the investigation into the functional impact of childhood maltreatment is still in its infancy. Using fMRI, PET and EEG neuroimaging techniques¹, the majority of these studies have been conducted in adults with a relative scarcity focusing on functional processing in children. Adult studies have encompassed investigations into a number of different faculties including reward processing, affective processing, low-level sensory processing and memory. I will briefly consider a number of these studies to highlight the current understanding of the functional differences of maltreated populations.

Adult studies

Affective processing has received the most attention in imaging studies in adults with histories of maltreatment. Particular focus has been paid to the amygdala, which has been found to show distinct neural activity differences during passive viewing of emotional faces (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011) and fear acquisition paradigms in maltreated individuals with concurrent psychiatric disorders (Bremner et al., 2005). Increased amygdala response during threat-related facial expression viewing is also found to have a strong association with self-report trauma scores in maltreated adults free of psychiatric diagnosis (Dannlowski et al., 2012). These studies advocate the view that maltreatment may be associated with atypical neural affective processing profiles, characterised by increased localised activation compared to non-maltreated peers (Bremner et al., 2005; Dannlowski et al., 2012; Grant et al., 2011). A number of PET studies have been conducted on women survivors of childhood sexual abuse which have assessed a

¹ fMRI = Functional magnetic resonance imaging; PET = Positron emission tomography; EEG = Electroencephalography.

variety of faculties such as fear processing during a traumatic script task (Bremner et al., 1999; Schmahl, Vermetten, Elzinga, & Bremner, 2004; Shin, Rauch, & Pitman, 2006), emotional control of attention using an stroop task (Bremner et al., 2004) and verbal declarative memory (Bremner et al., 2003) all present a consistent finding of atypical neural processing in the maltreated individuals, characterised by increased neural activation.

Child studies

As mentioned previously, there is a relative scarcity of functional studies on maltreated children. Selectively, maltreated youth have been found to display neural activity differences characterised by increased anterior cingulate cortex (ACC) activation during reward processing task (Carrion, Garrett, Menon, Weems, & Reiss, 2008; Mueller et al., 2010). This atypical neural profile was viewed as impaired cognitive control due to increased reactivity to negative affect (Mueller et al., 2010). Maltreatment has also been associated with reduced activation the right hippocampus during memory retrieval and, importantly, symptom severity correlated with left hippocampal activation during retrieval (Carrion, Haas, Garrett, Song, & Reiss, 2010).

Two studies exploring the impact of early severe deprivation in post-institutionalised children on emotion processing found that the post-institutionalised children displayed increased amygdala response to threatening facial cues (Maheu et al., 2010; Tottenham et al., 2011). Atypical processing of emotional faces in maltreated children has also been reported in a sample free from current psychiatric diagnoses of psychopathology; identifying increased bilateral anterior insula activation to angry faces compared to controls (McCrory et al., 2011). Elevated amygdala activation was also observed in response to angry faces (McCrory et al., 2011), even when these stimuli were presented outside of conscious awareness (McCrory et al., 2013).

The structural impact of maltreatment

Within this section I will review the current literature on the regional impacts of maltreatment on brain structure, considering both adult and child literature and discrepancies between them where apparent. Lastly, and importantly, the limitations to both the structural and functional studies will be discussed to accurately frame the current findings. A core assumption within the structural literature is that cortical

structure informs function and thus observed structural deficits may be related to current or future variations in behaviour.

Global structural differences

Prior to examining regional effects of maltreatment, I will briefly consider global structural differences. A number of studies have observed smaller intracranial and cerebral volumes in samples of maltreated children with and without PTSD compared to healthy individuals (Carrion et al., 2001; De Bellis, Keshavan, et al., 1999; De Bellis et al., 2002). Two studies have observed increased ventricular volume within maltreated samples (De Bellis, Keshavan, et al., 1999; De Bellis et al., 2002); as well as showing a positive correlation between lateral ventricle volume and duration of abuse (De Bellis, Keshavan, et al., 1999). Hemispheric laterality refers to the dominance of one hemisphere over the other and a number of studies have noted a lack of volumetric hemispheric laterality within maltreated samples compared to controls (Carrion et al., 2001; Ito, Teicher, Glod, & Ackerman, 1998; Saltzman, Weems, & Carrion, 2006; Teicher et al., 1997).

The prefrontal cortex

The prefrontal cortex is a vast region (Figure 1.1) that encompasses many diverse cortical structures that vary in cytoarchitecture and functional role. Among these roles, the prefrontal cortex regulates our thoughts, actions and emotions through extensive connections with other cortical and sub-cortical regions (Arnsten, 2009). Importantly the prefrontal cortex is a regulatory hub for a range of behaviours, cognitions and affect (Davidson, Putnam, & Larson, 2000; Fuster, 1997; Miller & Cohen, 2001; Ochsner & Gross, 2005). It is a key area for inhibiting inappropriate responses and actions and promotes task-relevant attention (Aron, Robbins, & Poldrack, 2004; Buschman & Miller, 2007; Gazzaley et al., 2007; Thompson-Schill et al., 2002). These roles are key in promoting our ability to flexibly adapt to new environments and novel contingencies and demands.

The prefrontal cortex plays a vital role in the brains response to environmental stressors. Through its connections to subcortical areas it acts to limit the response to stress and exerts inhibitory feedback on the hypothalamic-pituitary-adrenal (HPA) axis (Diorio, Viau, & Meaney, 1993). As with many areas involved in the brains stress response, the prefrontal cortex has a high density high density of glucocorticoid receptors (Diorio et al., 1993). However, prolonged cortisol levels

within areas of high glucocorticoid receptors can cause neurotoxic effects such as accelerated loss and metabolism of neurons (Lupien et al., 2009; Sapolsky et al., 1990). In animal studies prolonged stress has been shown to have adverse alterations on the prefrontal cortex, specifically, reduced dendritic length, branching, spine density and neurogenesis (Arnsten, 2009; Lupien et al., 2009; Sapolsky et al., 1990).

The experience of childhood maltreatment in humans represents severe and prolonged environmental stress and thus promotes the continued exposure to elevated levels of cortisol within the prefrontal cortex. As the prefrontal cortex develops towards maturity, the response to stress becomes more restrictive as the PFC exerts a greater inhibitory control on other stress-related regions in typical development (Arnsten, 2009). Major projections to the prefrontal cortex myelinate primarily between adolescence and the third decade of life (Weinberger, 1987). This prolonged window of development means that the PFC is particularly responsive to environmental input over a sustained period of time and makes it a prime target of the maladaptive effects of extensive periods of stress. The impact of these environmental stressors could manifest, like in animal studies, in gross morphology as well as fine structure alterations (Fuster, 2002).

Structural studies in children who have experienced maltreatment have produced diverse findings. While Initial studies reported an absence of structural differences within the prefrontal cortex of maltreated participants (De Bellis et al., 1999), subsequent studies from De Bellis and colleagues observed smaller grey and white matter volume within the prefrontal cortex (De Bellis & Keshavan, 2003; De Bellis et al., 2002). A number of more recent studies have noted volumetric increases in middle inferior and ventral regions of the PFC (Carrion et al., 2009; Richert, Carrion, Karchemskiy, & Reiss, 2006). However, Carrion and colleague's sample presented with extensive psychiatric comorbidity proving it difficult to tease apart the influence of maltreatment on cortical structure from the presence of a psychiatric disorder, which have been consistently associated with local brain alterations (Nutt & Malizia, 2004). In addition to the increases in volume within the ventral regions of the PFC, both of the studies reported local reductions in volume in the dorsal areas of the PFC (Carrion et al., 2009; Richert et al., 2006). These divergent frontal findings may suggest that the prefrontal cortex should be explored on a finer scale which better reflects its regional functional distinctions. As such, two

regions, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) will be discussed separately within the following sub-sections.

Adult samples have also been characterised by an inconsistent pattern of findings in relation to the prefrontal cortex. In a study of depressed and anxious patients reporting childhood emotional maltreatment, the left medial prefrontal cortex displayed a significantly reduced volume associated with the experience of emotional maltreatment (van Harmelen et al., 2010). Moreover, this pattern of reduced medial prefrontal cortex and dorsolateral PFC was found to be evident in a non-clinical samples of maltreated individuals with mixed and specific histories of maltreatment (Andersen et al., 2008; Dannlowski et al., 2012; Tomoda, Suzuki, et al., 2009). Dannlowski and colleagues (2012) hypothesised that the structural deficits were indicative of inhibition of cortical development that could be associated with enduring deficits in the region's functions of emotion processing and regulation. The multiple experiences of abuse subtype within these studies suggest that a common underlying experiential mechanism impacts prefrontal structures.

Orbitofrontal cortex

The orbitofrontal cortex (OFC; Figure 1.1) is central to social and emotional regulation and is vital in adapting to changing environmental demands by controlling and regulating emotional and motivational states (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Ochsner & Gross, 2005; Rempel-Clower, 2007). The OFC has direct connections with the amygdala, anterior cingulate and medial sensory regions (Öngür & Price, 2000), allowing for the functional integration and modulation of sensory and visceral motor information, critical in emotion processing (Rolls, 2000). As with all of the prefrontal cortex, the OFC has a protracted development with cortical maturity seen well into the 20's (Toga, Thompson, & Sowell, 2014). However, dysfunction of the OFC may only become apparent until early adolescence or adulthood when it starts to reach cortical maturation (Bachevalier & Loveland, 2006). Maltreated children and adolescents without concurrent psychiatric diagnoses, have been found to show localised reductions in GMV within the OFC, with atypical structure argued represent difficulties in the individual's social functioning and ability to adapt to varying social environments (De Brito et al., 2013; Hanson et al., 2010).

Anterior cingulate cortex

The anterior cingulate cortex (ACC) sits medially in the frontal cortex (Figure 1.1). The ACC is functionally connected to a diverse set of cortical, limbic and paralimbic regions, including possessing strong interconnections with frontal regions, the amygdala and anterior insula (Devinsky, Morrell, & Vogt, 1995). Recent investigations have sought to functionally divide the ACC into regions of affective and cognitive processing (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Bush, Luu, & Posner, 2000; Paus, Castro-Alamancos, & Petrides, 2001). While some have suggested at its role in a host of cognitive functions (Posner & DiGirolamo, 1998), others have associated it with transient mood states (Mayberg et al., 1999), the emergence of depression and anxiety disorders (Brody et al., 2001; Mayberg et al., 2000), and the perception of pain (Rainville, Duncan, Price, Carrier, & Bushnell, 1997).

Whole brain studies have been inconclusive in reporting grey matter reductions in samples of maltreated children (Hanson et al., 2010). Conversely region of interest (ROI) studies in adult populations have indicated local decreases in volume (Cohen et al., 2006; Kitayama, Quinn, & Bremner, 2006; Treadway et al., 2009). In one study rostral ACC volume was inversely correlated with childhood trauma levels and also cortisol levels within a clinical sample of major depressive disorder (MDD) sufferers (Treadway et al., 2009). The elevated cortisol levels were interpreted as a possible mechanism by which the structural deficits occur (Treadway et al., 2009). However similar volumetric deficits were observed in a sample of PTSD sufferers that had not experienced inter-personal trauma, which may suggest that such structural deficits are not specific to childhood maltreatment but rather a common underlying mechanism in trauma (Yamasue et al., 2003). The lack of consistency regarding structural findings in child and adult samples could be interpreted as a delayed structural response to childhood trauma that only becomes perceivable once in adulthood. Alternatively, the methodology employed to investigate cortical structure, in this case volumetric approaches, may not be sensitive to subtle cortical reorganisation during adolescence (Hutton, Draganski, Ashburner, & Weiskopf, 2009).

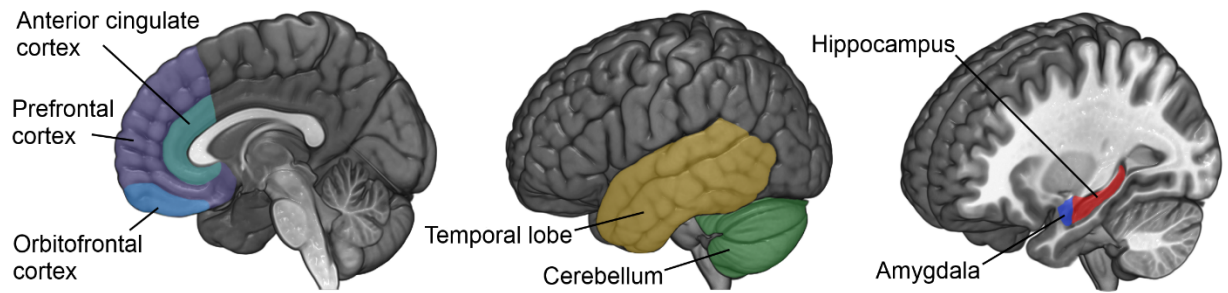


Figure 1.1. Illustration of the approximate location of cortical regions impacted by the experience of childhood maltreatment.

Cerebellum

The traditional view of the cerebellum's (Figure 1.1) role has been within motor control and coordination of motor behaviour (Glickstein, 2006), however there is increasing evidence that it plays a part in cognition, behaviour and the development of psychiatric illnesses (Rapoport, van Reekum, & Mayberg, 2000). Specifically, due to its extensive connections with limbic structures and the HPA axis, it has been associated in attentional functions as well as regulating fearful responses (Wolf, Rapoport, & Schweizer, 2008). Furthermore its associations with the fronto-cerebellar network have led to the hypothesis that the cerebellum aids in the fine grained modulation of behaviour (Arnsten & Rubia, 2012) and executive functioning (Schmahmann, Weilburg, & Sherman, 2007), functions that have been shown to be impaired in maltreated children (Beers & De Bellis, 2002). The cerebellum, like many other areas affected by traumatic experiences, undergoes a protracted development which may allow for an extended window of vulnerability to environmental stressors (De Bellis & Kuchibhatla, 2006).

Within the structural literature, there is a consistent finding of reduced cerebellar volume within maltreated samples (Bauer, Hanson, Pierson, Davidson, & Pollak, 2009; Carrion et al., 2001; De Bellis & Kuchibhatla, 2006). Furthermore De Bellis and Kuchibhatla found that cerebellar volume within the maltreated children was positively correlated with age of onset of the trauma and negatively correlated with the duration of the trauma (De Bellis & Kuchibhatla, 2006). Such findings illustrate the influence that dimensions of maltreatment, such as chronicity, have on atypical structure associated with childhood abuse and neglect.

Temporal regions

The middle temporal gyrus (Figure 1.1) has been hypothesised as playing a vital role in autobiographical memory function (Holland, Addis, & Kensinger, 2011).

Autobiographical memory is found to be affected in a number of psychiatric disorders such as PTSD and is often reported as being over-general in maltreated children (Kleim & Ehlers, 2008; Valentino et al., 2009). Animal studies have established a causal relationship between experiences of early stress and reduced grey matter in temporal regions (Jackowski et al., 2011). Early human studies identified temporal lobe abnormalities alongside a number of other areas that were structurally affected by the experiences of maltreatment (De Bellis et al., 2002). However, it has also been found that maltreated young adults display increased superior temporal gyrus (STG) volumes (Tomoda et al., 2011). Interestingly, STG volume was strongly correlated with levels of parental aggression and inversely associated with parental education (Tomoda et al., 2011). The researchers proposed that that these findings were the result of parental verbal abuse attenuating neuronal pruning and delaying its development, which would usually see a grey matter volume decline with age (Tomoda et al., 2011). Longitudinal studies would be needed to test this hypothesis.

Two studies within maltreated children have shown decreases in volume of the temporal regions (De Brito et al., 2013; Hanson et al., 2010), albeit in left and right hemispheres respectively. These findings were hypothesised to reflect an impaired memory function and reflect a latent neurobiological vulnerability for the future psychopathology (De Brito et al., 2013). Within De Brito and colleagues study, the sample were free of psychiatric diagnoses, while the study by Hanson and colleagues included a small proportion of participants with psychiatric diagnoses. The psychiatrically “healthy” samples in both studies afforded the authors to confidently associate the structural findings with the experience of childhood maltreatment rather than a confounding influence of psychopathology.

Amygdala

The complex structure of the amygdala (Figure 1.1) has long been associated with a central role in emotion processing (Gallagher & Chiba, 1996). Specifically, the amygdala has been implicated in fear processing and the learning of the emotional significance of environmental stimuli (Davis & Whalen, 2001). Animal studies have provided the basis for this understanding with both rodents and primates, demonstrating the homologous amygdala’s role in responding to negatively and positively valenced stimuli alike (Breiter et al., 1996; Hennenlotter et al., 2005; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004). In humans, the amygdala’s extensive connections with the HPA axis have established its vital role

in regulating response to cognitive-emotional challenges and threats in the environment (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009).

However, findings of atypical structure in animal models have not generally transferred to human adolescent and child investigations with numerous studies finding that amygdala volume did not differ in maltreated children compared to controls (De Bellis, Baum, et al., 1999; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Woon & Hedges, 2008). Nevertheless two recent structural studies, which were undertaken in the context of early institutionalisation and deprivation, found indications of increased amygdala volumes following early life trauma (Mehta et al., 2009; Tottenham et al., 2010). While the amygdala volume being sensitive to duration spent in care and time of adoption (Mehta et al., 2009; Tottenham et al., 2010). A proposed theory for volumetric increases in the amygdala is that smaller amygdala volumes act as a protective factor against the emergence of post-traumatic symptoms by attenuating responsivity to environmental threat (Teicher et al., 2003).

Hippocampus

The hippocampus is a major component of the limbic system and is located under the cerebral cortex (Figure 1.1). The hippocampus plays a functional role in memory processing, and specifically in the formation of memories about experienced events (Mizomuri, Smith, & Puryear, 2007; Squire, 2004). Its anatomic location within the limbic system, projections to the HPA axis, and a high level of glucocorticoid receptors make it a prime target for research into stress response (MacQueen & Frodl, 2011; Patel et al., 2000). Animal models have provided a causal link between early-life stress and later hippocampal atrophy (Sanchez et al., 2001; Welberg, Seckl, & Holmes, 2001).

Child studies have generally not uncovered structural differences within the hippocampus (Carrion et al., 2001; Jackowski, De Araújo, De Lacerda, De Jesus Mari, & Kaufman, 2009; Mehta et al., 2009). Adult studies on the other hand have consistently displayed decreased hippocampal volume associated with maltreatment (Bremner et al., 1997; Kasai et al., 2008; Stein et al., 1997; Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006; Vythilingam et al., 2002; Woon & Hedges, 2008). These studies have recruited diverse samples such as mixed sex survivors of physical and sexual abuse (Bremner et al., 1997; Stein et al., 1997; Vythilingam et al., 2002), survivors of multiple abuse subtypes and

concurrent borderline personality disorders (Driessen et al., 2000) and maltreatment related depression (MacQueen & Frodl, 2011). Finer grained analysis of the hippocampus, differentiating between functionally separable sub-fields, has also indicated that maltreatment exerts an impact on particular regions of the hippocampus, specifically left CA2-CA3 fields and CA4-Dentate gyrus (Teicher, Anderson, & Polcari, 2012). Only one adult study has noted an absence of hippocampal volume reduction in adults with experience of childhood maltreatment (Pederson et al., 2004). Moreover, studies involving combat veterans who were exposed to stress that may not be classed as inter-personal trauma have noted smaller hippocampal volumes within those with PTSD (Gurvits et al., 1996; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005).

Longitudinally, decreases in hippocampal volume have been associated with the emergence of PTSD in maltreated adolescents, structural response related to cortisol levels was only noticeable a year or longer after the cessation of abuse (Carrion, Weems, & Reiss, 2007). The prevailing hypothesis is that childhood trauma exerts a gradual effect on hippocampal morphology such that discernible differences emerge in late adolescent and adulthood. The 'neurotoxicity hypothesis' proposes that stress-induced prolonged exposure to glucocorticoids leads to a reduction in cell complexity and cell death (apoptosis; (Gould & Tanapat, 1999). Within humans this prolonged stress may span years or decades leading to distal changes in hippocampal volume much later in life. Alternatively, the 'vulnerability hypothesis' posits that smaller hippocampal volume that may predate stress exposure, represents a neural risk factor for the psychopathology (Gilbertson et al., 2002; Rao et al., 2010). Longitudinal studies are required to fully understand the discrepancies between findings in adult and child samples and to provide evidence towards the proposed theories of hippocampal response to prolonged stress.

Cortical development, maltreatment characteristics and sex differences

Cortical development

Grey and white matter follow markedly different trajectories across adolescence. Grey matter volume peaks during childhood and follows a decrease in adolescence and into adulthood, whereas white matter increases in a linear fashion into young adulthood (Groeschel, Vollmer, King, & Connelly, 2010). However, regional differences are apparent in these developmental trajectories, including the prefrontal

cortex which develops slower than other cerebral areas with considerable developmental changes during adolescence (Andersen et al., 2008; Giedd et al., 2009; Lenroot & Giedd, 2006; Marsh, Gerber, & Peterson, 2008). While many frontal regions generally follow a cubic developmental trajectory, even within orbitofrontal cortex there is variation in the slope of the neurodevelopmental trajectory (Shaw et al., 2008).

It is well known from developmental neuroscience that there are periods of increased neuronal plasticity, which consists of synaptic proliferation and a reduction of synapses and the number of axons (Andersen et al., 2008; Heim & Binder, 2012). During these periods, environmental experiences have a profound impact on the organisation and programming of the cortex (Andersen et al., 2008). Many regions vital in the neural response to stress have a protracted maturation, which can allow for greater windows of vulnerability or periods when the impact of stress is maximal (Andersen & Teicher, 2004; Andersen et al., 2008; Teicher et al., 2004). The hippocampus and the amygdala represent two such regions that are particularly sensitive to variations in the chronicity of abusive experiences (Andersen et al., 2008). Certainly, while maltreatment across multiple developmental periods is associated with an increased risk towards a range of negative outcomes (English, Bangdiwala, et al., 2005; Éthier et al., 2004; Jaffee & Maikovich-Fong, 2011), the impact of abuse experienced during one developmental period may be associated with atypical cortical structure but not be manifest in behaviour until the individual navigates the demands of subsequent developmental milestones, consistent with the theory of latent vulnerability (McCrorry & Viding, *in press*). Developmental timing constitutes an important factor in the investigation of the impact of maltreatment on cortical structure and warrants further systematic investigation.

Maltreatment characteristics

As previously discussed, behavioural studies have illustrated the importance of the dimensions that characterise maltreatment in understanding the heterogeneity in an individual's behavioural and cognitive outcome (e.g. English, Bangdiwala, et al., 2005; Litrownik et al., 2005; Petrenko et al., 2012). Consistent with behavioural literature, the relatively sparse research within structural imaging of maltreatment has shown that dimensions of maltreatment exert differential associations with cortical structure. To date, very few studies have investigated the impact of maltreatment severity and subtype on cortical structure, let alone investigating

potential associations with externalising and internalising symptoms.

Problematically, a number of existing studies recruiting paediatric and adult samples have measured only one form of abuse (Bauer et al., 2009; Hanson et al., 2010) or recruit samples who have experienced just one or two forms of maltreatment (Andersen et al., 2008; Bremner et al., 1997; van Harmelen et al., 2010). Some researchers have suggested that certain forms of abuse exert greater impact on brain structure, such as sexual abuse, which could account for heterogeneity in structural findings (Teicher et al., 2004). Based on previous studies, one could suggest that the pattern of co-occurrence between subtypes or similarly the interaction between them contributes to separable differences in atypical structure (Edmiston et al., 2011). However, a systematic investigation of the variation of occurrence across subtypes on cortical structures constrained by appropriate analyses is currently lacking from the existing literature.

Constructs of maltreatment that encode for severity of abuse have been incorporated into a number of structural studies (Edmiston et al., 2011; Teicher et al., 2012). Commonly these measures have been used to define group allocation rather than as a dimensional measure exploring the association between severity and cortical deficits. Nevertheless, in one study a whole brain analysis of maltreated adolescences found that the severity of childhood trauma scores were negatively correlated with GMV across a number of cortical regions, including the prefrontal cortex, striatum, amygdala, cerebellum and sensory association cortices (Edmiston et al., 2011). Such findings suggest that severity may have a dose-response relationship with grey matter volume (GMV) alterations across a number of cortical areas. Moreover, the findings suggest that different forms of maltreatment are associated with distinctive patterns of atypical GMV (Edmiston et al., 2011). Specifically, physical abuse was associated with reductions in the insula, an area implicated in personal agency (Farrer & Frith, 2002), whereas emotional neglect was associated with reductions across regions of the frontal cortex, striatum, amygdala and hippocampus; areas reported to serve emotional regulation processes (Sinha, Lacadie, Skudlarski, & Wexler, 2004). Furthermore, a co-occurrence of physical and emotional neglect was negatively correlated with cerebellar grey matter volume (Edmiston et al., 2011). Frustratingly, none of these results were corrected for multiple comparisons, casting doubt on their statistical strength and underlining the importance of appropriate statistical methods in such investigations. Equally, potential associations between GMV and psychiatric

symptomatology was absent from this analysis which may have provided further clarification to the significance of the findings.

Region of interest (ROI) analyses have also provided insights into the contribution of abuse severity to brain structure; bilateral hippocampus has been found to have a negative association with self-reported severity of childhood trauma (Dannlowski et al., 2012) and particular subfields of the hippocampus have shown variable associations with trauma severity (Teicher et al., 2012). It is important to consider that an ROI approach on previously defined regions can, however, promote biased and inappropriately constrained characterisation of anatomy (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). The diverse associations of cortical volume with severity scores within subtype seem to support the suggestions from behavioural literature which proposes characterising abuse severity by subtype, in addition to a cumulative score (Bolger, Patterson, & Kupersmidt, 1998; Litrownik et al., 2005; McGee, Wolfe, Yuen, Wilson, & Carnochan, 1995).

Multi-type abuse is highly prevalent, therefore, assuming that different forms of maltreatment occur independently may lead to potentially inflated effects in the influence one subtype has on variations in cortical structure over and above the influence of other subtypes of abuse (Finkelhor et al., 2007; Herrenkohl & Herrenkohl, 2009). While a number of structural studies have not controlled for multi-type abuse (Hanson et al., 2010; Sheffield, Williams, Woodward, & Heckers, 2013), other investigations have explored associations between cortical structure and cumulative severity scores across subtypes and independent subtype severity scores (Dannlowski et al., 2012; Edmiston et al., 2011; Teicher et al., 2012; Teicher et al., 2004). Patterns of co-occurrence between subtypes may also exert differential impacts on cortical structure, such that physical abuse experienced with another form of abuse has a markedly different effect on the individual than if it occurred alone, reflecting a non-cumulative impact of abuse subtype on brain structure. These considerable limitations therefore advocate a systematic investigation into the way in which maltreatment characteristics impact brain structure within a community sample of adolescents, constrained by appropriate statistical methods and presented within the context of developmental psychiatric symptomatology.

The dimension of chronicity has received a generous amount of attention when the impact of maltreatment on brain structure has been considered. The

cortex and sub-cortex have been found to have regional periods of sensitivity during childhood and into adulthood (Andersen et al., 2008), which may pose a potential mechanism by which duration of abuse engenders differential behavioural and psychological outcomes. Two sub-cortical regions have gained particular focus, the amygdala and the hippocampus due to their association with the HPA axis and stress sensitivity (Herman, Ostrander, Mueller, & Figueiredo, 2005). The amygdala has been found to be sensitive to environmental stress, particularly in the form of maltreatment during the pre-adolescence (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014) and its volume has been found to be negatively correlated with time spent in institutional care, commonly considered to be a form of neglect in many circumstances (Mehta et al., 2009). Similarly, the hippocampus has been found to be negatively associated with duration of abuse (Bremner et al., 1997) and positively associated with age of trauma onset in paediatric participants with PTSD (Tupler & De Bellis, 2006). Whole brain analyses have also found that left and right occipital volumes are negatively associated with duration of sexual abuse before the age of 12 (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009) and the frontal cortex is more sensitive to abuse that has occurred during adolescence (Andersen et al., 2008). However these two studies were performed within adult samples and are insufficient in providing clues to structural deficits that occur during the developmental period of adolescence. Given the distinctive characteristics that define maltreatment and shape outcomes on a behavioural and structural scale, it is of great interest to systematically examine the contributions of these characteristics on cortical structure and psychiatric symptomatology.

Sex differences

The most consistent finding within the neuroscience literature exploring the influence of sex on brain structure, is that males have generally larger brains than females, even when taking into account total body size and total intracranial volume (Allen, Damasio, Grabowski, Bruss, & Zhang, 2003; Cosgrove, Mazure, & Staley, 2007; Kitayama et al., 2007; Luders, Gaser, Narr, & Toga, 2009; Shin et al., 2005). Similarly, the ratio between grey matter and white matter varies between the sexes, with females possessing proportionally more grey matter to white matter volume than males (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999; Luders et al., 2005).

Local grey matter differences, in which males possess greater grey matter volume than females, in subcortical structures, such as the amygdala, thalamus and putamen, and on the cortical surface, including the middle temporal gyrus, left inferior gyrus and right occipital and lingual gyrus (Chen, Sachdev, Wen, & Anstey, 2007; Koolschijn & Crone, 2013; Peper et al., 2009). Conversely, females compared to males have shown comparatively increased GMV within dorsal, anterior, posterior and ventral cingulated cortices and right inferior parietal lobule (Chen et al., 2007). In relation to the functional properties of these cortical regions, authors have suggested that males have increased grey matter within primary visual and visuospatial regions, whereas females show comparatively larger GMV within language related regions, suggesting divergent abilities in each of these domains (Brun et al., 2009; Harasty, Double, Halliday, Kril, & McRitchie, 1997). Hemispheric differences between the sexes have similarly been noted, with the suggestion that females possess greater hemispheric symmetry in grey matter volume compared to males (Gur et al., 1999; Hiscock, Israelian, Inch, Jacek, & Hiscock-kalil, 1995). Substantial sex differences in white matter structures are equally prevalent in the current literature, but are beyond the scope of the current thesis (Gong, He, & Evans, 2011; Yan et al., 2011).

Developmental trajectories of cortical structure have been found to follow sexually divergent routes to maturity, with a 1-2 years earlier peak in subcortical and cortical grey matter trajectories in females than in males (Lenroot & Giedd, 2010). Regionally, areas such as the hippocampus show sexual dimorphism in growth during adolescence (Suzuki et al., 2005). Myelination within the hippocampus, an area rich in sex steroid receptors, occurs more rapidly in girls from age 6 onwards (Benes, Turtle, Khan, & Farol, 1994). Such difference in developmental trajectories could possibly enhance the vulnerability to stress in females during the period when sexual abuse is more likely to occur (Benes et al., 1994). Differing developmental rates of alterations in the ratio of grey to white matter between the two sexes are also significant; males show a more prominent age related grey matter volume decrease and white matter volume increase compared to females (De Bellis, Keshavan, et al., 2001). However, cerebral white matter increases linearly at a faster pace within females than males (Koolschijn & Crone, 2013). Sex differences in grey matter trajectories are also observed at a regional level, showing an earlier grey matter volume peak in the frontal and parietal lobes in females than males (Lenroot et al., 2007), a pattern which has been suggested as being linked to pubertal development. Interestingly, sexually divergent developmental trajectories,

such as within the amygdala and the hippocampus, have been suggested to be related to observed sex differences in the age of onset, prevalence and symptomatology associated with many neuropsychiatric disorders of childhood (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997). There is a considerable paucity of knowledge regarding sexually divergent outcomes of maltreatment on cortical structure; even more so considering the extent of the existing knowledge of differing behavioural outcomes that follow maltreatment for males and females.

1.8. Limitations to existing research

A number of prevailing limitations should be addressed to contextualise the existing literature and to guide future studies so that the understanding of how the experience of maltreatment translates into various behavioural and psychopathological outcomes can be furthered.

The presence of psychiatric disorders, as mentioned throughout this chapter, can confound the interpretation of the structural and functional results. Many psychiatric disorders are characterised themselves by cortical changes and differences, thus it makes it difficult to untangle the influence of maltreatment from psychiatric disorders. Only a handful of studies focusing on maltreatment and brain structure/function have involved samples without a concurrent diagnosis of psychiatric disorders (De Brito et al., 2013; Hanson et al., 2010; McCrory et al., 2013; McCrory et al., 2011).

Additionally, demographic factors that have been associated with differing neuro-developmental trajectories, such as age and IQ (Shaw et al., 2006; Shaw et al., 2008), are routinely neglected when controlling or covarying potentially confounding variables in group analyses comparing children with and without maltreatment exposure. A well-matched control group is imperative if we want to elucidate whether observable structural differences are associated with the experience of maltreatment, rather than some other characteristic that differs between groups.

The size of sample has often been criticised within these structural and functional studies. A well accepted parameter for between subject fMRI studies in research of developmental disorders is a sample size of 20 within the experimental

and control group (Brambilla et al., 2003). Maltreated samples have typically been quite small (Bremner et al., 1997; Carrion et al., 2007; De Bellis, Hall, et al., 2001; Jackowski et al., 2009; Mehta et al., 2009; Treadway et al., 2009) with some as small as 8 participants in the maltreated group (Kitayama et al., 2006). Such small samples represent a limitation for interpretation of the associations and conclusions that we can draw from these studies. While this criticism highlights a fundamental limitation of many structural investigations it also highlights the practical difficulties researchers have when recruiting and testing such samples.

The majority of structural studies have focused on volumetric techniques to quantify structural differences within maltreated samples. While these techniques have been widely used over the past decade and are well validated, it has been suggested that volume is a rather blunt measure of the underlying cortical structure (Hutton et al, 2005). Cortical volume is a cumulative measure of a number of discrete cortical properties, such as cortical thickness, area and gyrification that have differing neurodevelopmental pathways and genetic influences (Panizzon et al., 2009; Schaer et al., 2008). This convincing rationale for diversification of structural indices would allow for a fuller and better characterised picture of the structural impact of maltreatment.

1.9. Summary and aims of the current thesis

This introductory chapter has provided an overview of the far reaching impact of maltreatment; extending across multiple domains of behaviour, cognitive functioning and neurobiology, and its importance as a major public health issue. However, there is still a limited understanding as to how maltreatment exposure might heighten developmental vulnerability to these outcomes through neural pathways.

As shown in the previous section, there is great amount of existing literature detailing the impact of maltreatment on the structure of the brain both in adolescence and adulthood. However there are a number of gaps in our current understanding which are key in characterising the neurodevelopmental sequelae of childhood maltreatment. First, the methodological techniques used to investigate the impact of maltreatment on cortical structure have been limited to the investigation of grey and white matter volume. Recent studies highlighting the importance of other indices of brain structure associated with psychiatric and behavioural problems suggest a considerable gap in our current understanding of maltreatment and the

brain (e.g. (Hyatt, Haney-Caron, & Stevens, 2012; Wallace et al., 2014). Second, specific maltreatment characteristics may pose separable influences on behavioural outcomes (e.g. English, Upadhyaya, et al., 2005). By investigating whether different maltreatment experiences exert specific and/or common effects on brain structure we can start to fully illustrate the pathways from maltreatment to behavioural and psychiatric outcomes through atypical brain structure. Lastly, previous research has highlight sexually divergent behavioural and psychiatric outcomes associated with exposure to childhood maltreatment.

Due to observable sex differences in cortical structure of normative samples, the hormonal stress response and psychiatric disorders associated with maltreatment, there is a considerable rationale to hypothesise that sex differences are also evident within structural outcomes associated with maltreatment, potentially representing divergent neural biomarkers for later risk of specific psychiatric disorders. In the current thesis, we present five empirical chapters that address these gaps in the current understanding of the impact of childhood maltreatment on brain structure.

Chapter 2, the first empirical chapter of this thesis, draws on a dataset of 22 children who had been reported to social services due to experience of childhood maltreatment, matched with a non-maltreated group of 21 children on age, gender, ethnicity, IQ and socio-economic status. Chapters 3 to 6 extended this sample further to 122 children, within the same age range and similarly matched on age, gender, IQ, ethnicity and socio-economic status. This larger sample affords sufficient power to carry out the appropriate analyses to answer questions regarding potential distinct effects of different maltreatment types, as well as sex differences. Both groups were without diagnosis of any psychiatric disorder and hadn't experienced neurological trauma or disease. Across both samples and data collection points, all participants undertook a T1 structural scan on the same MRI scanner and the same scanning sequence was utilised. A large battery of well-validated instruments were administered to measure current psychological, affective, behavioural and interpersonal functioning, and symptomatology of psychiatric disorders. The maltreatment history for the children referred to social services was characterised and substantiated through official reports and rated by the assigned social worker. A subset of these case reports were double rated to ensure consistency. Within the most recent population, both maltreated and non-

maltreated samples were administered a self-rated trauma symptom questionnaire intended to characterise the children's perceptions of their experiences. As a result, these two samples are well suited to address the research questions detailed below.

In **Chapter 2**, we address the impact of maltreatment on distinct indices of brain structure. Existing studies of maltreatment's impact on brain structure have been limited to exploring volumetric indices of grey and white matter. While these studies have provided a wealth of knowledge regarding atypical patterns of grey matter volume; the methods used may not provide a complete representation of the impact of maltreatment. Grey matter volume is determined by a number of distinct neural indices that possess distinct genetic and developmental trajectories (Hutton et al., 2009). One outstanding task is to systematically investigate these properties as independent indices and explore how they may influence previously described volumetric differences. Using surface based methods, we investigated associations between childhood maltreatment and surface area, cortical thickness and local gyrification. This study represented the first investigation to cumulatively examine these cortical indices within a maltreated population. We hypothesised that there would be areas of significant difference between the two groups that would overlap with previously described volumetric studies as well as the identification of novel areas of atypical cortical structure not previously described in either the child or adult literature, but which surface-based methods might be more sensitive in picking up.

In **Chapter 3**, we explored how characteristics of childhood maltreatment may exert distinguishable influences on grey matter volume. Behavioural studies have highlighted the importance of properly characterising the experience of maltreatment as factors of chronicity severity and subtype have been found to be associated with different profiles of behavioural functioning (English, Upadhyaya, et al., 2005; Litrownik et al., 2005; Petrenko et al., 2012). Using substantiated reports of abuse within the full sample of participants (n=122) and self-rated reports of trauma exposure within the recent sample (n=84) we investigated whether chronicity, severity, subtype and occurrence of abuse are associated with dissociable differences on cortical volume.

In **Chapter 4**, we extended the investigation into the characteristics of maltreatment on distinct indices of cortical structure. As noted, cortical thickness, surface area and local gyrification possess distinct developmental trajectories which

may influence the impact of maltreatment experience depending on the severity or subtype experience across these temporal periods.

In **Chapter 5**, we investigated the sexually dimorphic impact of maltreatment on grey matter volume. Epidemiological studies of psychiatric disorders consistently report that sex differences exist in prevalence estimates for many psychiatric disorders (Eaton et al., 2012; Zahn-Waxler, Shirtcliff, & Marceau, 2008). Furthermore, males and females display sexually distinct development of stress-sensitive corticostriatal-limbic regions (Giedd et al., 1997; Lenroot et al., 2007). This information, taken alongside the observation that males and females show divergent structural development across a number cortical regions (Lenroot & Giedd, 2010), suggests that experience of maltreatment may be associated with sexually dimorphic cortical structure profiles.

In **Chapter 6**, we explored how sex differences impact finer grained cortical indices that determine grey matter volume. As stated previously, cortical thickness, surface area and local gyrfication are purported to have distinct genetic and developmental trajectories. The developmental trajectories of cortical structure are suggested to be separable across a number of brain regions and in the emergence of psychiatric disorders (Lenroot & Giedd, 2010; Raznahan et al., 2011). Surface-based measures of cortical structure may therefore help characterise differences in the impact of maltreatment in males and females.

Finally, in **Chapter 7**, we summarise our findings from these five empirical chapters and discuss the potential implications of this research and the possible avenues for further investigations.

CHAPTER 2: Cortical thickness, surface area
and gyrification abnormalities in children
exposed to maltreatment: Neural markers of
vulnerability?

2.1. Introduction

Childhood maltreatment (physical, sexual, emotional abuse or neglect) remains a major public health concern and has a profound impact on the individual, increasing risk of psychiatric problems in adolescence and adulthood, including anxiety, depression and conduct disorder (Gilbert, Widom, et al., 2009). There is limited understanding as to how maltreatment exposure may heighten developmental vulnerability to these outcomes. Extant neuroimaging studies, using volumetric approaches to measure gray matter volume (GMV) have reported atypical brain structure in individuals exposed to childhood adversity (McCrary et al., 2010).

Adults who have experienced childhood maltreatment typically show reduced GMV in the prefrontal cortex, anterior cingulate cortex, hippocampus and cerebellum (Carrion et al., 2007; Kitayama et al., 2006; Tomoda, Suzuki, et al., 2009; Weniger, Lange, Sachsse, & Irle, 2008). Children who have experienced maltreatment or institutionalization show reduced GMV in the prefrontal cortex, middle temporal gyrus and cerebellum (Carrion et al., 2001; Carrion et al., 2009; De Bellis & Kuchibhatla, 2006; De Brito et al., 2013; Hanson et al., 2010). While these studies have typically imaged individuals with concurrent psychiatric disorders (limiting our ability to tease apart the influence of maltreatment from psychopathology), more recent studies have recruited non-clinically defined samples (De Brito et al., 2013; Hanson et al., 2010; Teicher et al., 2012). Extant studies have employed volumetric methods to study structural correlates of maltreatment; however, a finer grained characterisation of atypical structural development associated with maltreatment may be helpful in a number of respects.

Structural determinants of GMV

Volumetric approaches such as voxel and tensor based morphometry (VBM, TBM) are thought to reflect a several structural parameters, including cortical thickness, cortical surface area and gyrification (Hutton et al., 2009; Voets et al., 2008), which capture more discrete features of underlying cortical micro-structure. I will briefly unpack these measures to provide background on how they reflect cortical structure and develop differently across the lifespan.

Cortical thickness provides clues to the underlying grey matter microstructure, including a reflection of cortical layers (Rakic, 1988), density of neurons and their related processes, such as myelination (Paus et al., 1999; Sowell, 2004). Surface area on the other hand, provides a reflection of neuron density (Sisodiya & Free, 1997; Sisodiya, Free, Fish, & Shorvon, 1996) as well as an indication of the number of cortical columns within each region (Rakic, 1988). Cortical thickness integrity has been associated with intellectual ability (Narr et al., 2007; Shaw et al., 2006), memory (Walhovd et al., 2006), personality traits (Wright, Feczko, Dickerson, & Williams, 2007; Wright et al., 2006) and disorders, such as conduct disorder (Hyatt et al., 2012). The association of many of these behavioural and cognitive functions (and dysfunctions) with maltreatment experience (Gilbert, Widom, et al., 2009), provide a motivation to investigate the impact of maltreatment on these independent indices of brain structure

The human brain is highly gyrified compared to that of non-human primates, and this is linked to the evolutionary expansion of the cerebral cortex disproportionate to intracranial volume (Rakic, 1995). Cortical folding has a strong relation to surface area, in that gyrification is the ratio between surface area and convex hull area of the cortex (Van Essen & Drury, 1997). Increases in gyrification are believed to allow for greater surface area within a restricted volume and to increase the number of cortical neurons within a localised region (Mota & Herculano-Houzel, 2012; Welker, 1990; Zilles, Palomero-Gallagher, & Amunts, 2013). Subsequently, researchers propose that the size and surface area of the human brain should be considered critical determinants of human cognitive function (Geschwind & Rakic, 2013). Patterns of atypical cortical gyrification have been observed in a number of disorders such as attention-deficit hyperactivity disorder (Wallace et al., 2014; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009), autism (Jou, Minshew, Keshavan, & Hardan, 2010) and schizophrenia (Palaniyappan & Liddle, 2012b); and in the association with indicators of general intelligence (Luders et al., 2008). These studies have highlighted the relationship between the amplitude of cortical folding and dysfunction and function in mental abilities, thus underlining the importance in considering this structural metric as an important element in the investigation of the impact of childhood maltreatment.

Development and trajectories

Consensus on what drives changes in grey matter volume has not been consistent, with some authors suggesting that volumetric change is primarily driven by cortical thickness (Storsve et al., 2014) and others postulating that surface area is the dominant contributor (Im et al., 2008; Pakkenberg & Gundersen, 1997). However, it seems that cortical thickness, surface area and cortical folding show unique localised variations across the cortex in children and adolescents (White, Su, Schmidt, Kao, & Sapiro, 2010), and inverse relationships between the two indices have been reported in localised regions of the cortex (Hogstrom, Westlye, Walhovd, & Fjell, 2013; Storsve et al., 2014). This negative relationship between surface area and cortical thickness is used by some to support the theory that areal expansion promotes increased connectivity more efficiently than changes in cortical thickness, and synaptic pruning during early developmental periods supports optimal areal expansion (Murre & Sturdy, 1995; Ruppín, Schwartz, & Yeshurun, 1993; White et al., 2010). The unique contributions of surface area and cortical thickness give further credence to the stance that they are driven by distinct mechanisms (Panizzon et al., 2009) and should therefore be considered separate morphometric features of neurodevelopment (Storsve et al., 2014).

Cortical thickness is highly associated with age with regional differences in cortical maturation (Shaw et al., 2008). The developmental trajectory is one of cortical thinning, with lower order regions following a more linear trajectory across childhood to adulthood and areas with higher order function, such as frontal regions, following more complex cubic trajectories (Shaw et al., 2008). In preadolescent children, cortical thinning at a younger age is more apparent in visual and somatosensory regions, and in temporal and frontal regions at older ages (Muftuler et al., 2011). The process of cortical thinning is thought to be influenced by progressive changes in myelination (Yakovlev & Lecours, 1967) and regressive changes, such as synaptic pruning (Huttenlocher & Dabholkar, 1997; Huttenlocher, de Courten, Garey, & Van der Loos, 1982). Collectively these changes are thought to optimise computation of the cortex as frequently used circuits are insulated and rarely used synapses succumb to apoptosis (Sowell, Thompson, & Toga, 2007).

Peak gyrification is reached in early life, approximately around the time of toddlerhood, (Raznahan et al., 2011), which is followed by an subsequent overall decrease in folding during adolescence and into adulthood (Armstrong, Schleicher,

Omran, Curtis, & Zilles, 1995; Raznahan et al., 2011). Locally, cortical folding has been found to show particular decline between 6-29 years of age in frontal and parietal cortices (Mutlu et al., 2013; Su, White, Schmidt, Kao, & Sapiro, 2013). As local gyrification is believed to be formed within the early years of development, environmental stressors, such as child abuse and neglect, may have a more prominent influence on this metric during this period. The distinct genetic influences and differing developmental trajectories of these metrics provide a convincing rationale to investigate these properties as independent indices of brain structure (Panizzon et al., 2009; Raznahan et al., 2011).

The current study

This study investigated the impact of maltreatment on cortical thickness, surface area and local gyrification. We recruited a group of children exposed to documented maltreatment at home and compared them with a group of non-maltreated peers. We predicted that maltreated children would show cortical thickness, surface area and folding differences, as compared with non-maltreated peers, in the prefrontal cortex (e.g. orbitofrontal cortex, OFC) and the middle temporal gyrus, consistent with volumetric studies of GMV in community samples of maltreated children without significant psychopathology (De Brito et al., 2013; Hanson et al., 2010). We were also keen to explore whether previously undetected anatomical differences between maltreated and non-maltreated children would be detected using these more specific structural indices.

2.2. Method

Participants

Two groups of children were recruited from the London area (Table 2.1). Children with documented exposure to maltreatment (n=22) were recruited from a Social Services (SS) department in London following a two-phase strategy. First, the research team met with each SS team who identified potential families in their caseload. Prior to contacting a family (or a foster family), agreement regarding the suitability of a case was reached between the research assistant and the social worker. SS only put forward cases that did not have a diagnosis of learning disability and judged as competent to consent in addition to living within a stable foster or care placement (minimum of 6 months), if the child was not living with biological parents.

In a second phase, the allocated social worker contacted the family or foster family to introduce them to the research. Interested families and foster families were then contacted by a research assistant and a home visit was arranged to describe to the child and the parents the study in more detail, answer any outstanding questions, and to seek consent. For children living with their biological parents assent was obtained from the child and from at least one parent. Where there was shared parental responsibility (such that the child's biological parent is still contactable), consent was obtained from both parties.

Non-maltreated comparison children (n=21) matched on age, self-reported Tanner stage, sex ratio, handedness, cognitive ability and ethnicity (Table 2.1) were recruited from secondary/primary schools and via advertisement in local newspapers and on the Internet. Exclusion criteria included history of abuse, neglect, and/or exposure to domestic violence as reported by the main carer on the Child Bad Experience Questionnaire (Dodge, Bates, & Pettit, 1990) and the Dunedin Abuse Scales (Magdol, Moffitt, Caspi, & Silva, 1998) and previous contact with SS in regards to the child's quality of care or maltreatment. Consent was obtained from the child and their parent(s).

All participants completed a comprehensive battery of psychological measures (see Measures section and Table 2.1). None of the participants reported a history of head trauma, neurological disease, or contraindications for MRI. Note that of the current sample, 17 children in the Maltreated Group and 19 children in the Non-Maltreated Group were common to those recruited for our previous study on cortical volume (De Brito et al., 2013). The study was approved by University College London Ethics Committee (0895/002).

Measures

Maltreatment history

SS case files for the maltreated group were independently rated on Kaufman's four-point scale (Kaufman et al., 1994), which is rated from 0 = 'no abuse present' to 4 = 'evidence of severe abuse' by the child's social worker in relation to neglect (n=19, mean = 2.53, \pm 1.12), physical (n=8; mean = 1.50, \pm 0.54), sexual (n=5; mean = 2.00, \pm 1.87) and emotional abuse (n=18; mean = 2.94, \pm 1.06; See supplementary material for more detail regarding maltreatment exposure). Six of the case files were double rated by a senior social work professional; there was 83% agreement in

relation to the presence of physical abuse, sexual abuse and neglect and 100% agreement in relation to the presence of emotional abuse.

Cognitive Ability

Participants were administered the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) in order to provide an estimated full scale intelligence quotient (FSIQ). None of the participants scored below 70 or above 130 on the WASI.

Socio-economic Status (SES)

The highest level of education attained by the mother or long-term foster mother was taken as an indicator of SES and evaluated on a 5-point scale (from 0=formal qualification, to 5=postgraduate or professional qualification).

Pubertal status

The eight item self-report Puberty development scale (Petersen, Crockett, Richards, & Boxer, 1988) was administered to derive a two-stage indicator of pubertal development based upon Tanner stages.

Psychiatric symptoms

The Trauma symptom checklist for children (Briere, 1996) was used to assess acute and chronic post-traumatic symptomatology in addition to other symptom clusters. The 44 item self-report measure has five clinical scales (Anger, Depression, Anxiety, Post-traumatic stress & Dissociation) and two validity measures.

The Mood and Feelings Questionnaire (Angold, Costello, & Messer, 1996) is a 33-item self-report measure that assesses core depressive symptoms in children. The State Trait Anxiety Inventory for children was used to assess state and trait anxiety (Spielberger, 1973). This 20 item self-report measure provides separate scores for state and trait anxiety and a composite anxiety score.

The Strengths and Difficulties Questionnaire (SDQ)(Goodman, 1997), a 25-item parent report measure, was included to assess general psychological and behavioural functioning. The SDQ includes five behavioural scales (Emotional symptoms, Conduct problems, Hyperactivity, Peer problems & Prosocial behaviour) and a composite score of total difficulties.

Image acquisition

Participants were scanned at the Birkbeck-UCL Neuroimaging Centre using a 1.5 Tesla Siemens (Siemens Medical Systems) Avanto MRI scanner with a 32-channel head coil. A high-resolution, 3D T1-weighted structural scan was acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence. Imaging parameters were: 176 slices; slice thickness=1 mm; gap between slices=0.5 mm; TR=2730 ms; TE=3.57 ms; field of view=256 mm x 256mm²; matrix size=256 x 256; voxel size=1×1×1 mm resolution. The scanning time was 5.5 minutes. To minimize head motion, foam padding was used against the sides and the back of the participant's head. Ear buds were provided to attenuate scanner noise.

MRI analysis

All images were initially manually inspected for any deformations or inconsistencies that may impede its processing such as movement artefacts or structural abnormalities. No participants were excluded due to deformations in the MRI image. All analyses were whole brain performed in the absence of firm a priori hypotheses using these techniques for the first time in a sample of maltreated individuals. The estimated total intracranial volume (eTIV) was calculated within FreeSurfer for each participant. No group differences were observed between the maltreated and non-maltreated groups ($p=0.37$).

Cortical thickness and surface area measures

The FreeSurfer surface based pipeline (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl et al., 2004; Fischl, Sereno, & Dale, 1999) was used to process the T1 images into a standard space in which cortical thickness values could be derived on a participant by participant basis. Initial steps in this well-validated (Fischl et al, 1999; Dale et al, 1999; Segonne et al, 2004) surface based morphometric pipeline were as follows. White matter points were defined from estimates of their location based on their position in Talairach space as well as the voxel intensity and local neighbourhood intensities. Skull stripping and classification of white and gray matter was computed automatically on each hemisphere. A two-dimensional tessellated mesh consisting of over 300,000 vertices is constructed over the white matter surface to distinguish the gray-white matter boundary. This mesh is expanded outwards to meet the gray matter and pial surface boundary. The estimated boundaries were manually edited in all cases for any errors and inconsistencies by

visual inspection. Additional control points were added for grey and white matter differentiation where necessary and edits to the brain mask were made when there were inconsistencies in differentiation between the pial surface and other organic matter, including dura and bone. The structural measures were calculated in native space. The native surface of each participant is transformed into a spherical representation which is registered to a common atlas, preserving the vertex identities.

Cortical thickness at each vertex was measured by calculating the shortest distance from the white matter to the pial surface (in millimetres). The surface area was calculated at the pial level and represents the area of vertex on the gray matter surface, calculated as the average of the area of the tessellated triangles touching that vertex. Parcellation of each participant's cortex into gyral regions was based on the Desikan-Killiany atlas (Desikan et al., 2006). The average surface area value for each parcellated region was extracted for all participants.

These measures were estimated in native space, thus giving an un-adjusted estimate of absolute cortical thickness. Each participant's cortex was normalised to the spherical standard curvature template with surface registration using cortical folding patterns to match cortical geometry across subjects. The FreeSurfer surface based analysis pipeline has been described extensively and its validity supported (Dickerson et al., 2008; Han et al., 2006).

Local gyrification index

The local gyrification index (*I*GI) is a supplementary measure incorporated within the FreeSurfer analysis suite. Developed by Schaer and colleagues (Schaer et al., 2008), the *I*GI builds upon the two-dimensional linear gyrification measure developed by Zilles et al (Zilles, Armstrong, Schleicher, & Kretschmann, 1988). An advantage of the local gyrification index is that it takes into account the intrinsic 3D nature of the cortical surface compared with 2D methods which are susceptible to bias from slice orientation and buried sulci. Schaer's method has been employed across a number of psychiatric conditions such as conduct disorder, psychosis and schizophrenia to identify associated abnormal cortical gyrification (Hyatt et al., 2012; Janssen et al., 2009; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011). The *I*GI method uses the pial and white matter surface identification against an additional outer hull layer that tightly wraps the pial surface. The *I*GI value at each

vertex is computed within 25mm circular regions of interest and represents the ratio of pial surface to outer hull surface, an indication of sulcal cortex buried in its locality and thus the extent of cortical folding. See Schaer and colleagues (Schaer et al., 2008) for further details of this analytic approach.

Statistical analysis

Regionally specific between group differences in cortical thickness and IGI were investigated within the QDEC application of FreeSurfer using a two sample t-test models. Cortical thickness measurements were smoothed with a full-width-at-half-maximum kernel of 15mm. Local gyrification index measurements were smoothed at 5mm and 0mm, due to IGI maps being inherently smooth (given that GI is calculated in a radius of 25mm). Excessive smoothing of the IGI data can contribute to the failure in computing Monte-Carlo null-z simulation to correct for multiple comparisons. IGI results are displayed smoothed at 5mm in the results section and without smoothing in the supplementary materials. Between group differences were corrected for multiple comparisons with a Monte Carlo z-field simulation at $p < 0.05$ (two-tailed). Significant clusters were then used as masks to extract mean cortical thickness and local gyrification values for each participant. Cortical thickness, surface area and local gyrification undergo dynamic changes during childhood and adolescence and are known to be influenced by gender and age (Giedd & Rapoport, 2010; Raznahan et al., 2011). Although there were no significant group differences in age and sex, additional group comparisons were conducted within SPSS with age and sex as covariates to fully ensure that these variables did not account for any of the findings.

2.3. Results

Demographic characteristics

There were no statistically significant differences between the maltreated and non-maltreated groups in relation to age, sex ratio, ethnicity, FSIQ, self-reported Tanner stage, SES and handedness (Table 2.1). Measures of depression, anxiety and post-traumatic symptoms were also examined and did not differ across groups. Relative to their peers, children in the maltreated group had higher parent-reported levels of conduct problems and hyperactivity scores on the SDQ.

Cortical thickness

The cortical thickness analysis identified one cluster, in the right hemisphere, that was reduced in the maltreated group compared to the controls (Figure 2.1, cluster 1; Monte Carlo null z simulation corrected $p < 0.05$). Annotation, based on the Desikan-Killiany parcellation Atlas (Desikan et al., 2006), of the group structural data indicated that the peak coordinate fell within the ventral anterior cingulate cortex (ACC) (Table 2.2, cluster 1; $X = 8.3, Y = 37.0, Z = -3.9$) with the cluster extending across the superior frontal gyrus and into anterior aspects of the OFC. No other significant clusters surviving whole brain cluster correction were found within the right or left hemispheres.

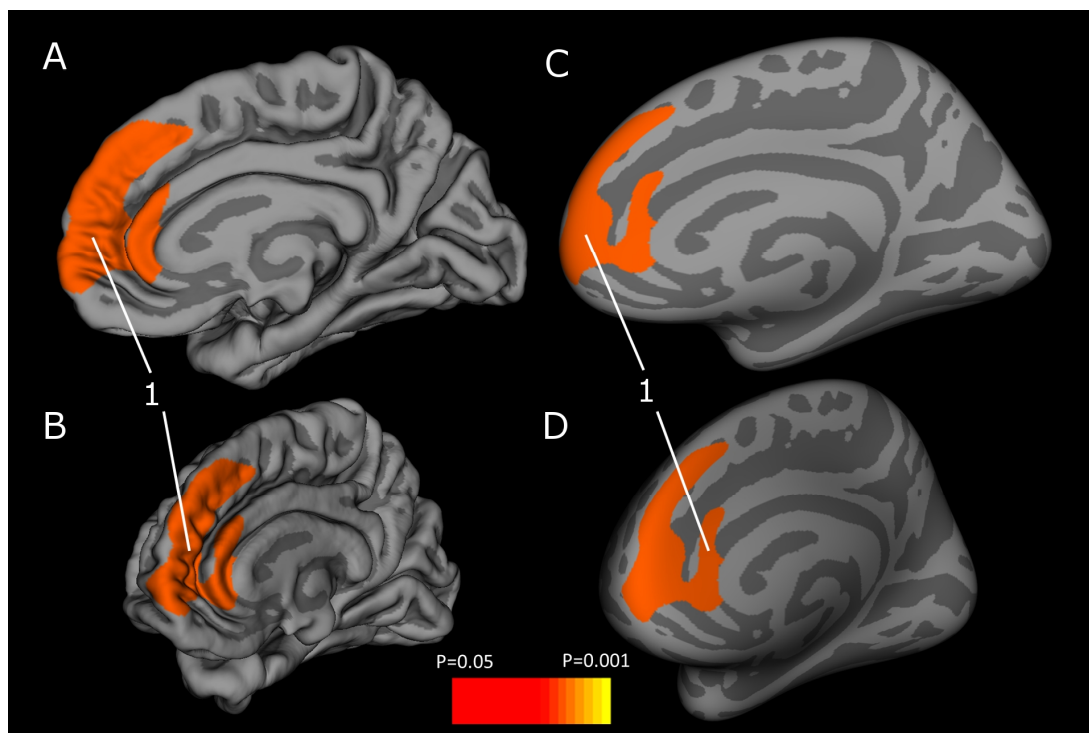


Figure 2.1. Significant clusters of cortical thickness decrease in the maltreated group.

Notes: Significant clusters projected onto the pial and inflated surface of the right hemisphere in (A & C) medial view and a (B & D) tilted frontal medial view. The significant cluster shows decreased cortical thickness within the maltreated group compared to the non-maltreated group and survived cluster correction ($p < 0.05$). Cluster label defined in Table 2.2.

Table 2.1. Background characteristics and questionnaire data for non-maltreated and maltreated children.

Demographics	<i>Control (n = 21)</i>		<i>MT (n = 22)</i>		<i>p</i>
Sex, N of males (%)	10 (47.62)		14 (63.64)		0.36
Ethnicity, N of Caucasian (%)	10 (47.62)		7 (31.82)		0.36
Handedness, N or right handed (%)	19 (90.48)		18 (81.82)		0.26
Tanner stage					
No. of pre/early pubertal (%)	6 (28.57)		7 (31.82)		1.00
No. of mid pubertal (%)	15 (71.43)		15 (68.18)		1.00
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Age (in years)	12.77	1.19	12.27	1.41	0.23
WASI, 2 scale subset	107.48	11.52	102.55	11.57	0.72
SES					
Highest level of education	2.81	1.33	2.27	1.39	0.20
Mood and Feelings Questionnaire					
Total Score	11.90	8.17	10.05	8.94	0.49
TSCC					
Anxiety	47.75	12.25	46.10	12.96	0.68
Depression	45.40	9.55	44.48	11.48	0.78
Anger	44.05	7.81	45.52	10.20	0.61
Post-traumatic Stress	44.25	6.47	47.86	11.64	0.23
Dissociation	47.00	6.70	49.81	10.98	0.33
State/Trait Anxiety Inventory for Children					
Trait	33.33	7.45	32.38	8.44	0.70
State	27.81	4.40	26.29	2.76	0.19
Total	61.14	9.86	59.25	9.41	0.53
SDQ					
Conduct problems	1.29	1.10	3.45	2.67	0.10
Peer problems	1.71	1.49	1.55	1.92	0.75
Emotional problems	2.67	1.46	2.68	1.76	0.98
Prosocial behaviour	8.19	2.29	8.13	2.03	0.92
Hyperactivity	3.15	2.48	5.13	3.11	0.03

a The highest level of education provided by the mother or long-term foster mother was taken as a proxy of socio-economic status and was evaluated on a scale from 1 to 5 (1 = No formal qualifications; 5 = Postgraduate level).

All p values derived from t-tests with the exception of sex, ethnicity, handedness and Tanner stage comparisons which used Fisher's exact test.

Surface area

Surface area values extracted on a gyral level were inputted into SPSS and an independent group analysis was performed to identify if any of the gyral regions differed in their average surface area values. Three regions based on the Desikan-Killiany parcellation atlas were identified to have a significantly reduced average surface area at an uncorrected level in the maltreated sample compared to non-maltreated peers: the right entorhinal region ($p = 0.034$); the left middle temporal gyrus ($p = 0.006$); and the left lingual gyrus ($p = 0.005$). To control for multiple comparisons a step-up FDR correction was applied; only differences in the middle temporal gyrus ($p=0.038$; cluster 5; Figure 2.2) and lingual gyrus ($p=0.038$; cluster 6; Figure 2.2) remained significant. Table 2.3 summarises the significant parcellated region statistics for the surface area analysis.

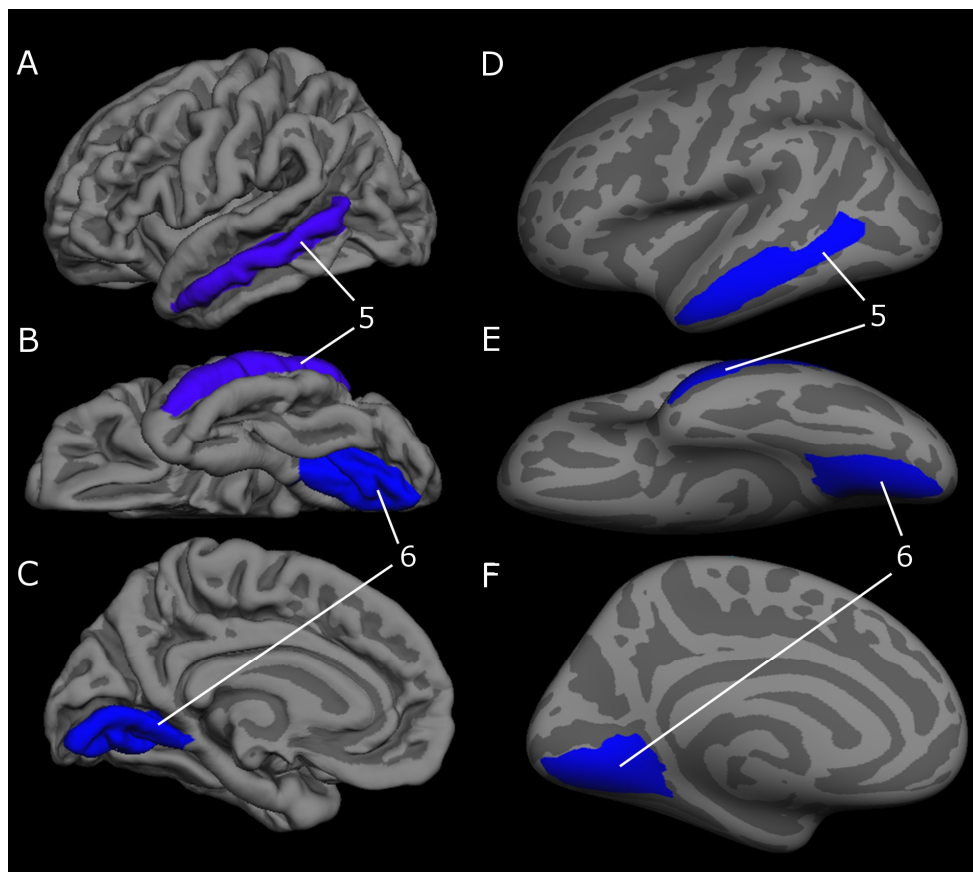


Figure 2.2. Significant gyral regions of reduced surface area in the maltreated group.

*Notes: Clusters shown in the left hemisphere in lateral (A & D), inferior (B & E) and medial (C & F) views. Cluster 5 is the parcellated region of the middle temporal area ($p = 0.006$) and cluster 6 is the lingual gyrus ($p = 0.005$). Cluster labels (numbers) correspond with those given in **Table 2.3**.*

Local gyrification index (IGI)

The local gyrification analysis identified two significant clusters in the left hemisphere, with reduced gyrification within the maltreated group compared to the controls (Figure 2.3, cluster 2 & 3; Monte Carlo null z simulation corrected $p < 0.05$). Automated annotation of the group structural data (Table 2.2, cluster 2 & 3) labelled the first cluster within the lingual gyrus. This cluster survived a more conservative level of Monte Carlo null-z simulation cluster correction ($p < 0.01$); however the extent of the cluster was reduced. The second cluster extended across rostral aspects of the insula and into the pars opercularis with its peak coordinate sitting within the anterior insula ($X = -37.6, Y = 15.5, Z = 9.8$). **Table 2.2** summarises cluster statistics for both cortical thickness and IGI analyses. **Figure A.1** in the supplementary material depicts the clusters without smoothing with similar cluster extents and significant values.

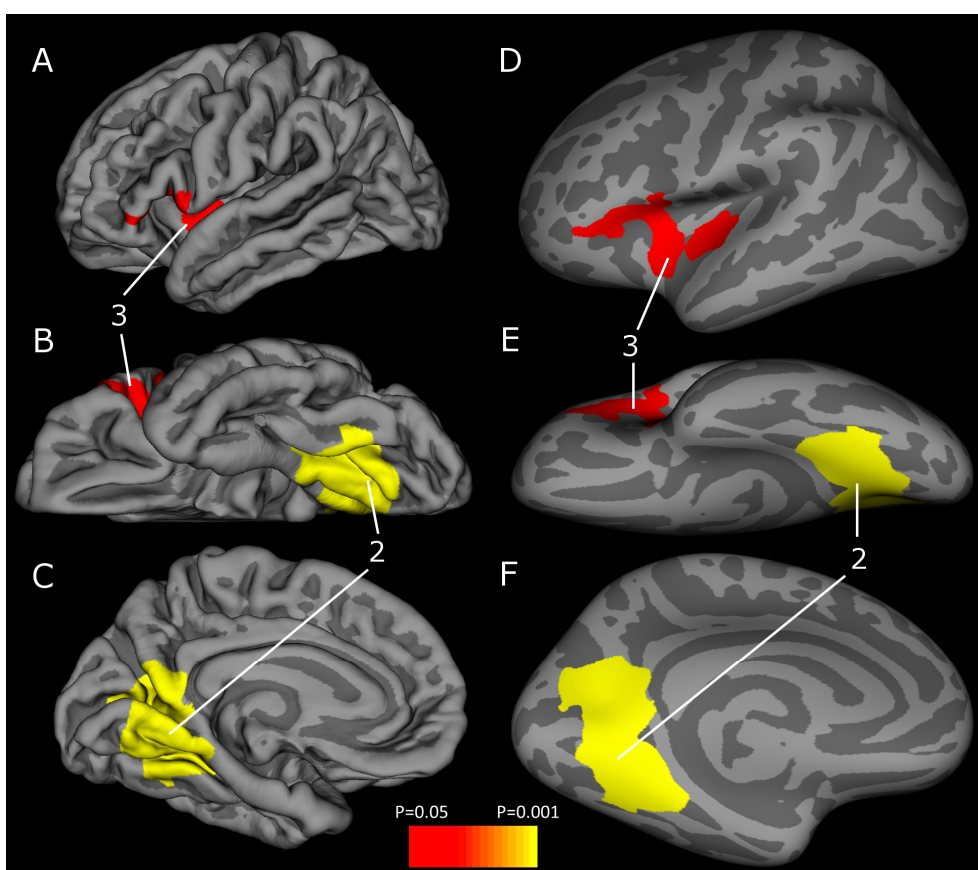


Figure 2.3. Significant clusters of reduced local gyrification index within the maltreated group.

*Notes: Significant local gyrification index clusters projected onto the pial and inflated left hemisphere in (A & D) lateral (B & E) inferior and (C & F) tilted inferior medial view. The significant clusters show decreased gyrification in maltreated children compared to controls. Cluster 2 survived cluster correction of $p < 0.01$, while cluster 3 survived cluster correction of $p < 0.05$. Cluster labels (numbers) correspond with those provided in **Table 2.2**.*

Table 2.2. Significant Clusters for cortical thickness and local gyrification index, corrected for multiple comparisons.

Cortical index	Cluster no.	Anatomical regions	L/R	Area (mm ²)	Talairach (x, y, z)			P _{cluster} ^b
					Maxima			
Cortical thickness								
	1	Ventral anterior cingulate / superior frontal	R	2160.51	8.3	37.0	-3.9	0.003
/GI ^a								
	2	Lingual gyrus	L	3954.83	-21.4	-61.3	8.9	0.0001
	3	Insula / pars opercularis	L	1825.13	-37.6	15.5	9.8	0.027

^a local gyrification index. ^b Cluster probability. All comparisons are maltreated < non-maltreated

Table 2.3. Parcellated regions presenting with significant surface area differences between maltreated and non-maltreated samples.

Cortical index	Region no.	Anatomical label	L/R	Maltreated		Non-maltreated		T values
				Mean	SD	Mean	SD	
Surface area								
	4	Entorhinal cortex	R	528.45	93.88	633.19	194.73	2.230*
	5	Middle temporal gyrus	L	4451.27	596.02	4929.48	471.78	2.908**
	6	Lingual gyrus	L	3409.77	482.75	3851.86	505.2	2.934**

*p<0.05 uncorrected, **p<0.05 corrected (FDR step-up controlling procedure). Values are in mm²

Secondary Analyses

When significant effects were detected, the associated cortical value was extracted and correlations were conducted with age of onset, duration and severity of each maltreatment subtype. No significant correlations were found between any of the cortical indices and measures of maltreatment experience.

In order to explore the potential impact of age and sex, several additional analyses were then conducted. Average cortical thickness in the right pre-frontal cluster was extracted for each participant (cluster 1, Table 2.2). The average *I*/GI values for each of the significant clusters within the left hemisphere (clusters 2 & 3, Table 2.2) and the mean surface area values for significant regions (clusters 4 - 6, Table 2.3) were also extracted for each participant. Initial standardised residuals of these values were then produced in SPSS co-varying for age, IQ and sex as these factors have been implicated in developmental changes to cortical thickness (Raznahan et al., 2011; Shaw et al., 2006; Shaw et al., 2008). Group comparisons were then conducted using these residuals; the previously observed pattern of group differences was unchanged for cortical thickness, surface area and local gyrification index.

Correlations were performed between mean cortical thickness, surface area and local gyrification values extracted from the significant clusters / regions for each participant and the conduct problems and hyperactivity scores obtained on the SDQ. No significant associations were detected ($p < 0.05$ threshold) and this pattern of results remained after co-varying for age and sex. Additional analyses exploring associations between structural values and neuropsychological functioning is reported in the supplemental material.

Group difference in SDQ scores

Although the two groups were matched on levels of anxiety, depression and PTSD symptoms, the maltreated group showed higher SDQ conduct problem and hyperactivity symptoms. A strong case has been made that when participants are not randomly assigned to groups, it is inappropriate to co-vary for variables intrinsically related to group assignment (Miller and Chapman, 2001). Consequently, hyperactivity and conduct symptoms, known to be strongly associated with

maltreatment experience, were not co-varied in the main analysis. Nonetheless, we repeated this analysis entering SDQ conduct problems and hyperactivity scores as covariates of no interest in order to explore whether variance in these domains could account for the pattern of neural differences observed across groups. Consistent with the main analysis, reduced cortical thickness in the maltreated group was observed in the ventral ACC, OFC and superior frontal gyrus cluster ($p < 0.01$); reduced gyrification was observed in the lingual gyrus ($p = 0.04$); and reduced surface area was observed the middle temporal gyrus ($p = 0.04$). Trend level group differences were found within the surface area clusters of the lingual gyrus ($p = 0.054$). No significant group differences were found within the local gyrification index cluster of the pars opercularis ($p = 0.12$).

2.4. Discussion

This study is the first to provide evidence of atypical cortical thickness, surface area and local gyrification in maltreated children. Compared to carefully matched peers, children referred to social services with documented experiences of maltreatment were found to have reduced cortical thickness in an extended right hemisphere pre-frontal cluster comprising the ventral ACC, superior frontal gyrus and anterior OFC. Maltreated children also presented with reduced cortical surface area within two gyral regions: the left middle temporal area and the left lingual gyrus. Finally, the maltreated group was found to have reduced gyrification in two left hemisphere clusters, the first located in the lingual gyrus and the second extending across the insula into the pars opercularis. These significant group differences were observed after controlling for age and sex across all three cortical parameters. The current findings suggest that the structural brain changes associated with maltreatment exposure go beyond previously documented volumetric differences in gray matter (De Brito et al., 2013) and help delineate the specific structural parameters that are altered by maltreatment exposure.

Areas of the extended frontal cluster showing reduced cortical thickness in our maltreated sample have been implicated in a variety of higher order emotional and cognitive processes. The ventral ACC has been implicated in emotional regulation (Etkin, Egner, & Kalisch, 2011; Ochsner & Gross, 2005), the superior frontal gyrus in working memory (Boisgueheneuc et al., 2006; Haxby, Petit, Ungerleider, & Courtney, 2000), and the OFC in social and emotional regulation and flexibility (Damasio, 1994; Schoenbaum, Saddoris, & Stalnaker, 2007). Reduced

GMV in the ACC has been reported in adults exposed to childhood maltreatment (Cohen et al., 2006; Kitayama et al., 2006). To our knowledge, structural differences in the ACC have not previously been reported in relation to maltreated children. As GMV is influenced by surface area and cortical thickness it is possible that prolonged exposure to maltreatment may have a cumulative impact on cortical thickness across development that is only observable as a reduction in GMV by adulthood. Alternatively, surface area differences may emerge at a later stage and independently contribute to the GMV differences observable in adulthood. Longitudinal studies are required to differentiate these possibilities.

The cluster showing reduced cortical thickness in our maltreated sample also extended into the superior frontal gyrus and OFC, consistent with volumetric studies in children. For example, reduced GMV in the superior frontal gyrus has been reported for children with histories of childhood abuse (Hanson et al., 2010; Tomoda et al., 2011). The cortical thickness cluster extends into the most anterior aspect of the OFC. Similarly, significantly reduced GMV in the OFC has been found in children exposed to maltreatment at home (Hanson et al., 2010), a pattern that may be associated with poorer social functioning in these children (Hanson et al., 2010). However there was no overlap with the OFC cluster which showed reduced GMV in the maltreated compared to non-maltreated children, identified in our previous VBM study, even though the majority of participants were common across studies (De Brito et al., 2013). These findings are consistent with other studies, which suggest that cortical thickness contributes only a portion of the variance to GMV measured by VBM (Palaniyappan et al., 2011).

We suggest that morphological disturbances across this extended PFC cluster in a community sample of maltreated children with no clinical diagnoses of psychiatric disorders may reflect latent neurobiological risk for future psychopathology such as PTSD (Geuze et al., 2008).

Our analysis also found three regions showing reduced surface area in the maltreated as compared with non-maltreated children. First, the maltreated group also exhibited reduced surface area within the middle temporal area, consistent with reports of reduced GMV in this same region in maltreated children (Hanson et al., 2010) and adults (Tomoda et al., 2011). In our previous VBM investigation, which had used an overlapping sample, we also found GMV abnormalities within this region (De Brito et al., 2013). It is possible that these previously seen GMV

differences are indicative of an underlying reduced surface area. Second, reduced surface area was also observed in the left lingual gyrus in the maltreated group, a finding we consider in more detail below.

Finally, the maltreated group, relative to their peers, also showed reduced local gyrification in two left-hemisphere clusters. The first cluster - in the lingual gyrus - overlapped with the region with reduced surface area. The lingual gyrus has been implicated in higher order processing of visual information (Mobbs et al., 2004; Puce, Allison, Asgari, Gore, & McCarthy, 1996), specifically in early stages of face processing (Luks & Simpson, 2004). GMV decreases in the right lingual gyrus have been reported for women with a history of sexual and physical abuse (Tomoda, Suzuki, et al., 2009). Functional studies have also identified altered lingual gyrus activation in adults reporting childhood histories of maltreatment during olfactory stimulation (Croy et al., 2010) and emotional face processing (van Harmelen et al., 2012). One suggestion is that alterations in visual regions in maltreated individuals may reflect an adaptation to stress exposure, reflecting attenuation in sensory systems and pathways communicating recurrent aversive and traumatic experiences (Teicher et al., 2012). The fact that we observe both cortical folding and surface area differences within this same area suggests that these indices are both affected by this adaptive process. Volumetric differences within the lingual gyrus, have not, to our knowledge, been identified within maltreated children before. This suggests that these cortical parameters of surface area and gyrification may represent precursors of observable GMV differences later in life. It is possible that the GMV reduction in the lingual gyrus observed in adults specifically reflects reduced gyrification and surface area in this region, rather than reduced cortical thickness.

A second cluster fell within the left insula, extending into the pars opercularis. Within healthy individuals the insula is thought to be part of a salience network that detects threat (Pichon, de Gelder, & Grèzes, 2011) integrating information into perceptual decisions about pain (Wiech et al., 2010) as well as playing a key role in the empathic perception of emotion states of others (Carlson, Greenberg, Rubin, & Mujica-Parodi, 2011; Paulus & Stein, 2006). Structural studies have identified GMV decrease in the insula in children (Edmiston et al., 2011) and adults (Dannlowski et al., 2012) who have experienced physical abuse and childhood maltreatment, respectively. Functionally, increased insula reactivity has

been reported during processing of angry faces in maltreated children (McCrory et al., 2011).

Several limitations of our study should be noted. Firstly, although self-report and parent-report measures of clinical symptoms were administered, no formal clinical psychiatric interviews were conducted. Therefore we cannot rule out the possibility that certain forms of psychiatric disorder were present in either group and went undetected. Secondly, our use of a cross-sectional design limits our ability to make causal inferences between exposure to maltreatment and the observed differences in cortical thickness, surface area and local gyrification. Longitudinal studies of high risk samples are required to investigate how neural differences associated with childhood adversity relate to future psychological and behavioural functioning. Finally, given the challenges inherent in accessing information about biological families in the maltreated group, we employed a univariate measure of socio-economic status (maternal education). However, a composite measure of SES would be preferable and more accurate in characterising economic and social functioning.

2.5. Conclusion

In summary this is the first study to investigate differences in cortical thickness, surface area and local gyrification in individuals exposed to maltreatment. We provide novel evidence that maltreated children with normative levels of internalising psychopathology present with significantly reduced cortical thickness within an extended cluster comprising the ventral anterior cingulate, superior frontal gyrus and OFC. In addition we observed significantly reduced cortical surface area in the maltreated group in two gyral regions: the left middle temporal area and the left lingual gyrus. Finally, local gyrification was found to be significantly reduced in the left lingual gyrus and the left insula / pars opercularis.

We suggest that these findings are significant in three important respects. Firstly, they raise questions about how we understand the developmental emergence of GMV differences in maltreated individuals. For example, while GMV differences in the ACC has been observed in adult samples, they have not been seen in children (McCrory et al., 2010). We suggest that reduced cortical thickness in the ACC may represent developmental precursors to these GMV differences observed in adult with histories of abuse. Secondly, our findings can help shed light

on the nature of previously reported GMV differences. As has been noted, volumetric techniques only capture an emergent index of several structural properties (Hutton et al., 2009; Voets et al., 2008) making it difficult to infer what specific structural feature is contributing to differences in local volume. So, for example, our finding of reduced surface area in the left middle temporal region suggests that differences in surface area and not cortical thickness are likely to be driving the previously reported GMV differences in this region (De Brito et al., 2013; Hanson et al., 2010). Thus, by investigating these discrete structural parameters we can better characterise the impact of maltreatment and the structural precursors to psychopathology later in life. Thirdly, consistent with previous structural investigations of maltreated samples, our findings point to aberration in brain regions associated with a broad range of autobiographical, emotional and regulatory processes that may underpin increased risk for psychopathology. Structural studies of clinical groups, particularly those with PTSD and depression, have also reported morphological abnormalities in these regions (Bremner et al., 2002; De Bellis & Kuchibhatla, 2006; Sprengelmeyer et al., 2011; Treadway et al., 2009; Van Tol et al., 2010). We suggest that the observed differences in cortical thickness, surface area and local gyrification in our community sample of maltreated children may represent neural markers of increased risk for psychopathology.

CHAPTER 3: A systematic investigation into the influence of maltreatment characteristics on grey matter volume in maltreated children and adolescents

3.1. Introduction

Maltreatment is a recognised public-health and social-welfare concern worldwide, with maltreated children at significantly increased risk of developing a range of behavioural and psychological difficulties including anxiety disorder, depression and post-traumatic stress symptoms (Keyes et al., 2012). While the substantial effects of maltreatment and abuse have been well documented over the past couple of decades (Cicchetti & Toth, 2005; McCrory et al., 2010), understanding the heterogeneity of an individual's response to maltreatment remains an outstanding challenge. A proposal by The National Research Council in 1993, challenged researchers to “unpack” the concept of maltreatment to promote a greater understanding of the mechanisms that lead from maltreatment to behavioural and psychological outcomes (Barnett et al., 1993).

In the past, many scientific investigations have viewed maltreatment as a dichotomous variable, comparing a group of maltreated individuals against non-maltreated peers or inappropriately restricting analysis to one dimension of maltreatment (Manly et al., 1994). Researchers have increasingly recognised that the experience of maltreatment is not a fixed concept, rather a heterogeneous phenomenon with a constellation of dimensions that relate to the underlying structure of maltreatment (eg. (Manly et al., 1994; McGee, Wolfe, & Wilson, 1997; Taussig, 2002). The most salient characteristics represented in the literature have been frequency and severity of abuse (Litrownik et al., 2005; Manly et al., 2001; Thornberry et al., 2001), including subtypes of maltreatment (Higgins & McCabe, 2000; Kinard, 2001; McGee et al., 1997; McGee et al., 1995; Petrenko et al., 2012), and chronicity or duration of abuse (English, Graham, Litrownik, Everson, & Bangdiwala, 2005; Thornberry et al., 2001; Wolfe & Jaffe, 1991). However, it still unclear as to what the shared and unique contributions these conceptually distinct dimensions might play in the impact of maltreatment on a cortical scale and how these associations may moderate the developmental outcomes on behavioural and trauma symptomatology. A better understanding of these facets of maltreatment has important implications for neurobiological models of developmental pathways following maltreatment and potentially for the assessment of individuals exposed to maltreatment and the formulation of intervention therapies.

A considerable number of behavioural studies have endeavoured to examine the differential impact different dimensions of maltreatment have on behavioural and psychological outcomes. Subtype and severity of maltreatment have been provided the most widespread research interest (Margolin & Gordis, 2000). Findings within the behavioural literature have pointed towards a relatively consistent association between physical abuse and externalising behaviour (Litrownik et al., 2005; Petrenko et al., 2012; Taussig, 2002). However, other relationships have been less clear; for example, internalising symptomatology has been associated with both neglect (Petrenko et al., 2012) and sexual abuse (Litrownik et al., 2005). Additionally, sexual abuse has also been associated with externalising behaviours (Litrownik et al., 2005). Furthermore, additional studies have provided more non-specific associations between subtypes of maltreatment and psychiatric problems (Mullen, Martin, Anderson, Romans, & Herbison, 1996; Silverman et al., 1996). The varied findings relating to subtype have been attributed to a number of methodological factors, such as the type of subtype included in the analysis, the analysis protocol and the included covariates (Petrenko et al., 2012).

Early studies into the unique effects of maltreatment subtypes were limited by examining one form of abuse when comparing behaviour against controls (e.g. Trickett & McBride-Chang, 1995), however maltreatment subtypes frequently co-occur with one another and are often highly correlated (Dong et al., 2004; Finkelhor et al., 2007; Higgins & McCabe, 2000), with approximately 33-95% of maltreated individuals experiencing more than one form of maltreatment (Herrenkohl & Herrenkohl, 2009). To view a maltreatment subtype as a variable autonomous of other subtypes could give rise to potentially exaggerated effects, therefore appropriate analysis techniques should be carefully considered to control for such confounds (English, Upadhyaya, et al., 2005; Petrenko et al., 2012). In addition, emotional abuse has occasionally been omitted from investigations as a number of researchers exert the view that emotional abuse is common across other forms of abuse and should therefore not be considered as a singular concept (Petrenko et al., 2012). However, emotional abuse has been found to have a strong relationship with mental health outcomes, therefore warranting inclusion in analyses on subtype by others (Arata, Langhinrichsen-Rohling, Bowers, & O'Brien, 2007). More recently, the potentially additive effects of other forms of adversity, such as exposure to community violence, have been emphasized in understanding the associations between childhood maltreatment and behavioural outcomes and should be considered when assessing the impact of subtype (Cecil et al., 2014).

Severity of childhood maltreatment has been found to consistently account for a considerable amount of variance in the sequelae of maltreatment, with a positive relationship between maltreatment severity and maladaptive outcomes frequently reported (Bolger & Patterson, 2001; English, Upadhyaya, et al., 2005; Litrownik et al., 2005; Manly et al., 2001; McGee et al., 1997). In particular, heightened severity ratings of maltreatment have been associated with poorer adjustment (Bolger et al., 1998), and internalising and externalising symptomatology (English, Upadhyaya, et al., 2005). Recent studies have suggested that exploring severity by maltreatment subtype is a more potent and consistent indicator of behavioural outcome (English, Upadhyaya, et al., 2005; Litrownik et al., 2005). Furthermore, independent associations have been underlined in previous studies, including physical neglect severity having an instrumental role in predicting internalising symptomatology, whereas severity of emotional maltreatment influences the incidence of externalising behaviour (Manly et al., 2001). As with maltreatment subtype, the methods used to define severity vary significantly and can be derived from substantiated official reports and self-reported perceptions of abuse. Theoretically, the use of these forms of assessment index potentially very different representations of abuse and raise interesting questions on how the perception of abuse may differentially moderate outcomes. Importantly, a number of these studies use chronicity and frequency as additional proxies to determine maltreatment severity (e.g. Kaufman et al., 1994; McGee et al., 1997). These dimensions are intrinsically nested and in ways that make interpretation and analysis challenging, such that severity and frequency interact to provide associations with maladaptive outcomes (Manly et al., 1994). Specifically, it has been found that low severity maltreatment that has occurred frequently is related to maladaptive behavioural outcomes (Manly et al., 1994). Consideration of these dimensional interactions are necessary when formulating severity scores and interpreting resultant associations with individual outcomes.

Accordingly, chronicity of abuse is being increasingly viewed as an important contributory factor in the impact of maltreatment of the individual. The concept of chronicity can represent different facets, including age of onset, duration, developmental period and frequency; researchers, however, have varied in how they define a chronicity proxy. Nevertheless, duration of abuse is a robust factor in predicting aggressive behaviours (Bolger & Patterson, 2001), successful peer relationship (Bolger et al., 1998), maladaptive social skills, and internalising and

externalising symptoms (English, Upadhyaya, et al., 2005). Several longitudinal studies have suggested that a child's developmental accomplishments gradually declines with persistent abuse and maltreatment (Egeland & Sroufe, 1981; Egeland, Sroufe, & Erickson, 1983), thus underlining the deleterious effect of prolonged abuse on functioning and the importance of capturing this particular dimension of chronicity in maltreatment research. Consequently, a number of researchers have suggested that chronicity is a more salient predictor of outcome than subtype (Bolger & Patterson, 2001; English, Graham, et al., 2005). The importance of chronicity of abuse as a salient dimension is nested in developmental theory (Cicchetti, 1989; Cicchetti & Toth, 1995), which proposes that disruption at one developmental stage may endanger successful accomplishment of subsequent stage-salient tasks at later developmental stages, therefore disruption across multiple stages of development might be particularly harmful (Cicchetti & Toth, 1995; Cicchetti & Toth, 2005). The overarching inference from these behavioural studies is that characteristics that underlie the concept of maltreatment play a vital and formative role in defining developmental behavioural and psychological outcomes. It is therefore crucial to integrate measures that serve to quantify these dimensions in maltreatment research to fully understand the heterogeneity in associations between maltreatment and individual outcomes.

As detailed in the introductory chapter, the dimensions that characterise maltreatment also exert an influence on atypical structure within maltreated individuals. However, investigations into the structural impact of maltreatment types remain complicated to interpret. Existing studies have failed to adequately control for a range of factors that may confound the interpretation of results, including IQ, pubertal status, SES and psychiatric symptoms.

The current study

The current study sought to tease apart the effects of maltreatment characteristics and psychiatric symptomatology on structural brain indices while controlling for the effects of IQ, pubertal status, SES and psychiatric symptoms. I investigated the following questions:

- 1) Is there a dose response relationship between maltreatment severity and grey matter volume in regions associated with maltreatment experience?

- 2) Do individual subtypes of maltreatment show diverse associations within these cortical regions?
- 3) Is increased duration of abuse associated with a greater decrease in grey matter volume within these cortical regions?
- 4) Is there a dose response relationship between exposure to community violence and grey matter volume in these cortical regions?
- 5) Is there an association between grey matter volume and internalising/externalising symptoms within the maltreated sample?
- 6) Is any association between maltreatment experience and psychiatric symptoms mediated by grey matter volume differences in children with maltreatment?

In relation to the above, I hypothesised that i) there would be a dose-response relationship between maltreatment severity and grey matter volume in regions associated with childhood maltreatment, ii) individual forms of maltreatment show diverse associations within these regions, iii) Increased duration of abuse would be negative associated with grey matter volume in regions associated with maltreatment, iv) there would be a dose-response relationship between exposure to community violence and grey matter volume in regions associated with maltreatment, v) grey matter volume in regions associated with maltreated will be associated with current externalising and internalising symptoms, vi) grey matter volume in certain regions associated with the experience of maltreatment mediate the relationship between maltreatment experience and psychiatric symptomatology.

3.2. Methods

Analytic procedure

We endeavoured to answer these research questions in two steps and using two samples.

Sample 1 comprised a group of maltreated (n=18) and non-maltreated (n=20) individuals recruited as part of an ESRC funded project between 2009 and 2012; this sample was used by de Brito et al., 2013 in their GMV study. This sample did

not have self-report measures of maltreatment experience, but had data from social services records on reported and verified maltreatment experiences, which could be scored according to the Kaufmann criteria (Kaufman et al., 1994). Furthermore, this sample did not have parent-rated measures of psychiatric symptomatology, but had a self-report measure of trauma symptomatology (Trauma Symptom Checklist for Children, (Briere, 1996).

Sample 2 comprised a group of maltreated (n=44) and non-maltreated (n=40) individuals recruited as part of an ESRC funded project between 2013 and 2014. This sample had a self-report measure of maltreatment experience (Childhood Trauma Questionnaire, (Bernstein & Fink, 1998) as well as data from social services records on reported and verified maltreatment experience, which could be scored according to the Kaufmann criteria (Kaufman et al., 1994). This sample also had a self-report measure of exposure to community violence (Children's Report of Exposure to Violence, (Cooley, Turner, & Beidel, 1995), a parent-reported measure of psychiatric symptomatology (Adolescent Symptom Inventory, (Gadow & Sprafkin, 2002), and a self-report measure of trauma symptomatology (Trauma Symptom Checklist for Children, (Briere, 1996).

Importantly, the maltreated groups of Sample 1 and Sample 2 differed significantly in their maltreatment history detailed in Table 3.4. Specifically, Sample 1 was characterised by a pattern of elevated severity and occurrence of physical abuse while Sample 2 was characterised by a pattern of elevated severity of neglect.

The analytic procedure comprised two Steps as follows (see Figure 3.1):

Step 1 used Sample 2 only and involved three phases:

- i. identification of regions of atypical structure within the maltreated group compared to the non-maltreated peers. Initially an analytic procedure adopted by de Brito and colleagues (2013) was applied. This was followed by a sensitive whole brain analysis using an effective normalisation technique.
- ii. investigation as to whether atypical structure within the maltreated group was associated with maltreatment severity (as measured by self-report which was available for Sample 2 only).

- iii. investigation as to whether atypical structure within the maltreated group was associated with exposure to community violence (as measured by self-report which was available for Sample 2 only).
- iv. investigation as to whether atypical structure within the maltreated group was associated with measures of psychiatric symptomatology (as measured by parent report)
- v. investigation as to whether atypical structure within the maltreated group mediated the relationship between maltreatment severity and psychiatric symptomatology (This analysis was contingent on observable associations between maltreatment exposure, psychiatric symptomatology and GMV).

Step 2 used Sample 1 and Sample 2 combined and involved three phases:

- i. identification of regions of atypical grey matter volume in the maltreated group using a whole brain analysis
- ii. investigation as to whether atypical structure within the maltreated group was associated with maltreatment severity, occurrence and duration (as measured by data from social services records scored by the Kaufman scale)
- iii. investigation as to whether atypical structure within the maltreated group was associated with psychiatric symptomatology, (as measured by child report on the TSCC).
- iv. investigation as to whether atypical structure within the maltreated group mediated the relationship between maltreatment severity and psychiatric symptomatology (This analysis was contingent on observable associations between maltreatment exposure, psychiatric symptomatology and GMV).

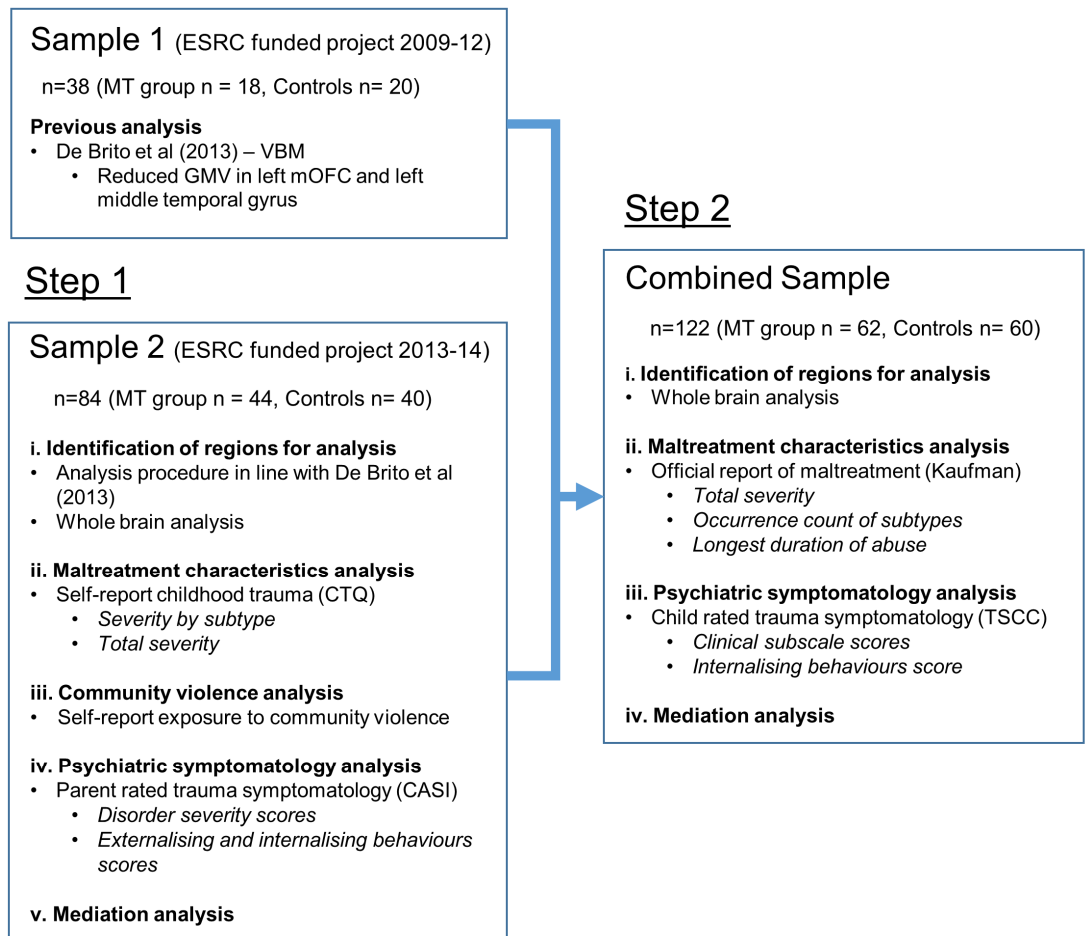


Figure 3.1. Schematic diagram of the analysis procedure for Chapter 3.

Notes: CTQ = Childhood trauma questionnaire. CASI = Child and Adolescent Symptom Inventory. Kaufman = Kaufman's four point scale. TSCC = Trauma Symptom Severity Scale. Differences between the maltreated groups of Sample 1 and Sample 2 are detailed in Table 3.4.

Participants

Children exposed to maltreatment aged 10-14 years (Table 3.2) were recruited from the London and South-East area in the course of two separate ESRC funded studies as detailed above. Children with documented exposure to maltreatment (total n=62) were recruited from Social Services (SS) departments in London and through adoption agencies. The SS team identified potential families in their caseload. Before contacting a family or foster family, agreement with regard to the suitability of a case was reached with the team. The social services team only put forward case that did not have a diagnosis of learning disability and who were judged as competent to assent. The allocated social worker contacted the family or foster family to introduce them to the research. Interested families were then

contacted by a member of the research team and a home visit was arranged to describe the study, answer questions and seek consent. For children living with their biological parents, assent was obtained from the child, and consent was obtained from one parent. Where there was shared parental responsibility, consent was obtained from the biological parent of the child if contactable, and SS. A number of children who had been adopted were recruited at a one day workshop at the Anna Freud Centre (London, UK) and via advertisements through adoption support groups and voluntary adoption agencies. Interested families were contacted by a member of the research team and a description of the study was provided over the phone and an information pack was delivered via email or post. Consent was then obtained from one of the adoptive parents and assent from the adopted child. All adopted children (n = 10) had been exposed to maltreatment and had been in the care of SS but had now been placed in an adoptive (rather than foster) placement.

Non-maltreated comparison children (n = 60) matched on age, self and parent reported tanner stage (presented as a composite), sex ratio, handedness, cognitive ability, socio-economic status and ethnicity (Table 3.1 & Table 3.2), were recruited from primary and secondary schools and youth clubs in the London area and via advertisement in local and London wide newspapers and on the internet. Exclusion criteria included previous contact with SS with regard to the quality of care or maltreatment of the child. Consent was obtained from the child and their parents.

A home visit was arranged for families wishing to partake in the study in which consent was obtained from one care giver and assent from the child. The home visit also served as an opportunity for the caregiver and child to complete a portion of the comprehensive battery of psychological measures (See Measures section and Table 3.1 & Table 3.2) and behavioural tasks. The home visit comprised of tasks, which form part of a larger longitudinal study investigating the impact of maltreatment on neuropsychological and behavioural development. No participant reported a history of head trauma, neurological disease, or contraindications for magnetic resonance imaging (MRI).

The total sample (n=122) comprised of a subset of participants (n=38) who had been included in a previous study examining the impact of maltreatment on cortical volume and discrete structural indices. For ease of reporting, the subset of participants previously included in a structural analysis are referred to as Sample 1

and the newly recruited participants (n=84) are referred to as Sample 2. The T1-weighted images from the earlier sample had been collected on the same MRI machine with the same magnetization prepared rapid gradient echo sequence. Within this previously collected sample, the comparison children were well matched on age, parent rated tanner stage, sex ratio, handedness, cognitive ability, socio-economic status and ethnicity. Matching between groups on all of these demographic variables was retained when combining the two samples. All procedures in the study were approved by University College London Research Ethics Committee (0895/002).

Measures

Maltreatment history

The SS case files for the maltreated group were independently rated on Kaufman's four point scale (Kaufman et al., 1994), which is rated from 0 = 'no abuse present' to 4 = 'evidence of severe abuse' by the social worker of the child in relation to neglect (n=50, M=3.22, SD=1.13) and physical (n=11, M=2.00, SD=1.18), sexual (n=15, M=1.07, SD=1.49) and emotional abuse (n=57, M=2.95, SD=0.91). While the data relating to the occurrence of witnessing domestic violence was available for all of the maltreated sample (n=30 witnessed domestic violence), severity scores were available for a subset of these participants (n=20, M=2.35, SD=1.46). Only 6 participants experienced one form of maltreatment (9.7%), while 25 participants experienced 2 forms of maltreatment (40.3%), with the remaining 31 participants experiencing 3 or more forms of maltreatment (50%). Information regarding the age of onset and duration of maltreatment was provided by the social worker where this was available.

Occurrence. The occurrence of each subtype of abuse was coded into dichotomous variables from Kaufman's four-point scale. A score of 1 or greater of the Kaufman scale was specified as occurrence of abuse. A total occurrence count was created from the summation across all subtypes of abuse in line with previous studies on maltreatment occurrence (Petrenko et al., 2012).

Severity. Severity within each subtype of abuse used Kaufman's four-point scale. A summation of Kaufman scores across all forms of abuse (i.e. emotional abuse, physical abuse, sexual abuse and neglect) was created to provide a total severity

score (minimum score = 1, maximum score = 16; see Table 3.9 for sample mean) in line with previous analyses of maltreatment severity on behavioural measures (Litrownik et al., 2005).

Duration. The maximum duration of abuse across subtypes was extracted to examine the association between maltreatment chronicity and grey matter volume. Using the maximum duration of abuse across all subtypes, a larger sample with duration information was obtained (n=57). Table 3.9 illustrates the characteristics defining the experience of maltreatment and abuse within the experimental group. 22 cases (n=14 from Sample 2) were double-rated by a senior social work professional; there was 57.10% agreement in relation to the presence of neglect, and 92.90% agreement for all other forms of abuse (emotional abuse, sexual abuse and physical abuse).

Self-reported experience of maltreatment

The Childhood Trauma Questionnaire (CTQ; (Bernstein & Fink, 1998) was administered to Sample 2 participants only. The CTQ is a 28 item self-report inventory that assesses perceptions of five types of childhood abuse and maltreatment (i.e. emotional abuse, physical abuse, sexual abuse, physical neglect and emotional neglect). Items are rated on a 5 point scale from '*never true*' to '*very often true*' and included statements such as '*My parents were too drunk or high to take care of my family*' and '*I had the perfect childhood*'. The CTQ has high internal consistency and high overall convergent and discriminant validity (Bernstein et al., 2003). A composite total score to indicate a cumulative perceived experience of maltreatment was created from the summation of the five subscales and represented high internal consistency ($\alpha = .88$).

Exposure to community violence

Exposure to community violence was assessed using items from the Children's Report of Exposure to Violence (CREV; (Cooley et al., 1995) in Sample 2 only. The CREV is a validated self-report measure that records the frequency of exposure to different severities and settings of violence, including scenarios such as '*seeing a stranger being stabbed*' and '*seeing a familiar individual being chased or threatened*'. Three subscales were included in this study: hearing about, witnessing and directly experiencing community violence. Participants rated how often they had experienced each type of violence in the past year from 0 '*never*' to 4= '*everyday*'.

Participants were provided the capacity to include additional information to clarify responses at the end of the questionnaire. A composite measure of community violence exposure was derived by averaging scores across the three subscales which represented high internal consistency ($\alpha = .77$).

Cognitive ability

All participants were administered the Vocabulary and Matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence to estimate full scale IQ (WASI; (Wechsler, 1999). None of the participants in the combined sample scored below 70 or above 130 on the WASI.

Socio-economic status

Socio-economic status was assessed using information collected from the parent or care giver, including highest level of education, household income, and current occupation. Highest level education was rated on a 6 point scale from 0 = 'no formal qualifications' to 5 = 'postgraduate qualification'. Household income was rated on an 8 point scale from 1 = '£0-10,000' to 8 = '£60,000 – 70,000+'. Current occupation of the primary care giver was classified by a single researcher using the National Statistics Socio-economic Classification's Standard Occupation Classification 2000 manual on a 4 class scale from 1 = 'managerial and professional occupation' to 3 = 'Routine and manual occupations' with 4 coding for never worked and long-term unemployed participants. A composite score was derived from the mean of these three scales.

Pubertal status

Pubertal development was assessed with the eight-item self-report and parent rated Puberty Development Scale (PDS; (Petersen et al., 1988). An average pubertal development scale and a two stage indicator of pubertal development based upon Tanner stage were derived from these scores. There was a 72.3% agreement between parent and child reported two level indicators of pubertal development.

Psychiatric symptomatology

The Trauma Symptom Checklist for Children (TSCC; (Briere, 1996) was used to assess acute and chronic posttraumatic symptomatology and other symptom

clusters. The 44 item self-report measure has five clinical scales (Anger, Depression, Anxiety, Posttraumatic stress and Dissociation) and 2 validity scales (under and hyper response). Each item is rated on a 4 point scale from 'never' to 'almost all the time'. Examples of the statements include: 'Getting mad and can't calm down' and 'Feeling afraid something bad might happen'. A composite measure of internalising problems was derived by averaging scores from the anxiety and depression subscales ($\alpha = .95$).

The Strength and Difficulties Questionnaire (SDQ; (Goodman, 1997), a 25 item self-report measure was included to assess general psychological and behavioural functioning. The SDQ included five behavioural scales (Emotional symptoms, Conduct problems, hyperactivity, Peer problems, and Prosocial behaviour) and a total difficulties score. Items were rated from 'not true' to 'certainly true' and included statements such as "I worry a lot" and "I am often unhappy, down-hearted or tearful".

Parents or care givers of participants in Sample 2 (n=84, MT=44) completed the Adolescent Symptom Inventory (ASI; (Gadow & Sprafkin, 2002) to assess symptoms on a collection of disorders, including generalised anxiety, major depressive disorder, PTSD and conduct disorder. Each scale contained between 7 and 9 items. Items were rated on a 4 point scale from 'never true' to 'very often true'. Two composite measures were created from the ASI subscales. An internalising problems scale was created by averaging values across the generalised anxiety, major depressive, dysthymic and posttraumatic subscales ($\alpha = .85$). Furthermore, an Externalising problems scale was created by averaging responses from the oppositional defiant disorder, conduct disorder and combined attention deficit hyperactivity disorders subscales ($\alpha = .81$).

Image acquisition

Participants were scanned with a 1.5 Tesla Siemens (Siemens Medical Systems, Munich, Germany) Avanto MRI scanner with a 32-channel head coil. A high-resolution, three-dimensional T1-weighted structural scan was acquired with a magnetization prepared rapid gradient echo sequence. Imaging parameters were: 176 slices; slice thickness = 1 mm; gap between slices = 0.5 mm; echo time = 2730 msec; repetition time = 3.57 msec; field of view = 256 mm x 256mm²; matrix size = 256 x 256; voxel size = 1 x 1 x 1 mm resolution. The scanning time was 5.5 min.

Foam padding was used against the sides and the back of the head of the participant, to minimize head motion. Ear buds attenuated scanner noise.

Image processing

All T1-weighted images were inspected for abnormalities and defects and the quality of each image was rated for quality in contrast and movement artefacts. If the image was thought to represent poor quality, the participant was excluded from the study. A total of 15 participants (MT=8, Con=7) from the initial sample were excluded due to concerns over image quality.

Data were processed using the Statistical Parametric Mapping Software version 8 (SPM; Wellcome Department of Imaging Neuroscience, London, UK) and the VBM8 toolbox (Christian Gaser, Department of Psychiatry, University of Jena) implemented in MATLAB R2012a (Mathworks, Sherborn, MA). Customised tissue probability maps were created in MNI (Montreal Neurological Institute) space for use with the VBM8 Toolbox. These customised tissue probability maps were produced using the matched template approach of the Template-O-Matic Toolbox based on the NIH study of normal brain development (NIH, Washington D.C., U.S.A) for SPM with each participant's age and sex used as defining variables.

The origin of all T1-weighted images were manually set to the anterior commissure. The images were then corrected for bias-field inhomogeneities, spatially normalised and segmented into grey matter, white matter and cerebrospinal fluid within the same generative model (Ashburner & Friston, 2005).

Participant's structural scans were normalised using two different techniques. To aid comparison with the findings of De Brito et al (2013), an identical normalisation technique was used which involved using a low-dimensional normalisation of the participant's grey matter segments to the study-specific tissue probability map. To provide a more effective and reliable intra-subject alignment, the participants segmented grey and white matter images were separately used to create a study specific template using the diffeomorphic registration algorithm implemented in the DARTEL toolbox (Ashburner, 2007). Following this, non-linear warping of the segmented grey matter images to the MNI space DARTEL template within the VBM8 Toolbox allowed for high dimensional normalisation.

Crucially, in both the comparison and whole brain analysis, the voxel values in the grey matter segments were only multiplied to the non-linear component of the registration to account for individual differences in brain size and to allow for the measurement of grey matter volume instead of grey matter density. The modulated grey matter images were exported with an isotropic voxel resolution of 1.5mm². Images were then smoothed with an 8mm full width at half maximum Gaussian kernel. Finally, all grey matter images were checked for homogeneity using the covariance structure of each image with all other images to check for cerebral abnormalities or movement artefacts. After spatial pre-processing, the smoothed, modulated and normalised images were used for voxel wise statistical analysis.

Statistical analyses

Group differences between the maltreated and comparison groups in grey matter volume were assessed using the general linear model, specifically a two-sample t-test, in SPM8. The model was run again with age, sex and IQ entered into the design matrix as covariates of no interest because of their known association with brain anatomy (Giedd & Rapoport, 2010), trend level group differences on age and IQ, and to aid comparison with De Brito et al (2013), who included these variables as covariates of no interest.

Multiple comparison correction was performed using Monte Carlo simulation with the AFNI program 3dClustSim (<http://afni.nimh.nih.gov/afni/>), which defines a cluster based extent threshold to limit the presence of type 1 errors. At an initial statistical threshold of $t(117)=2.62$, $p_{\text{uncorrected}} \leq 0.005$, the cluster threshold was defined as 338 contiguous voxels resulting in an alpha of ≤ 0.05 . Crucially, non-uniformity inherent in VBM data was addressed by implementing Gaussian random field theory within SPM8. Clusters that were found to be above this threshold were considered significant. A 10mm region of interest (ROI) sphere around the local maxima of each significant cluster was created and the mean grey matter volume for the region within the sphere was extracted using the MARSBAR region of interest toolbox (Matthew Brett, MRC Cognition and Brain Unit, Cambridge). These grey matter values were imported into SPSS v. 20 (IBM, Armonk, NY) to undertake further analysis to examine the relationship with maltreatment characteristics, psychiatric symptomatology and perceived social support as well as potentially confounding variables such as pubertal stage. Correlation matrices were used to

examine associations between maltreatment characteristics and the extracted grey matter values.

3.3. Results

Socio-demographic characteristics

Descriptive statistics between the maltreated and non-maltreated groups are presented in Table 3.1 & Table 3.2. Sample 1 descriptive statistics are presented in Table 2.1 of Chapter 2.

For Sample 1, the maltreated group did not differ from the non-maltreated group in sex, age, self and adult reported Tanner stage, handedness, IQ, SES and ethnicity (Table 2.1 in Chapter 2). Parent rated composite scores of internalising and externalising symptoms were higher within the maltreated group compared to the non-maltreated controls.

Within Sample 2, the maltreated group did not differ from the non-maltreated group in relation to sex, age, self and adult reported Tanner stage, handedness, IQ, SES and ethnicity (Table 3.1). As with Sample 1, parent rated composite scores of internalising and externalising symptoms differed significantly between the groups, with the maltreated group showing elevated symptom scores (Table 3.1).

For the combined sample, comprising Sample 1 and Sample 2, both groups remained matched on all demographic indices (Table 3.2). The maltreated and non-maltreated groups within this combined sample did not show differences in self-reported anxiety, depression and PTSD symptoms, but did differ in relation to conduct problems and hyperactivity symptoms which were elevated in the maltreated group.

Table 3.1. Demographic characteristics and questionnaire data for the maltreated and non-maltreated groups in Sample 2.

	<i>Control (n = 40)</i>		<i>MT (n = 44)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Demographics					
Age (in years)	12.70	1.07	12.28	1.56	0.15
WASI, 2 scale subset	108.73	10.53	105.61	13.86	0.25
Puberty development scale	2.27	0.64	2.02	0.65	0.08
Tanner stage					0.39
No. of pre/early pubertal (%)	8 (20)		14 (32)		
No. of mid pubertal (%)	15 (38)		19 (43)		
No. of late/post pubertal (%)	17 (42)		11 (25)		
Sex, N of males (%)	15 (38)		22 (50)		0.28
Ethnicity, N of Caucasian (%)	22 (55)		32 (73)		0.11
Handedness, N or right handed (%)	35 (87)		31 (70)		0.35
SES					
Composite score	2.96	0.87	2.79	1.12	3.48
CTQ					
Emotional abuse	5.89	1.03	8.26	4.09	0.00
Physical abuse	5.11	0.31	6.39	4.40	0.08
Sexual abuse	5.29	0.94	5.49	1.68	0.57
Emotional neglect	6.32	1.44	9.84	4.87	0.00
Physical neglect	5.43	0.84	8.13	3.65	0.00
Total	28.36	2.45	38.39	16.29	0.00
CASI					
Internalising	0.85	1.04	2.39	1.99	0.00
Externalising	2.15	1.60	4.76	3.62	0.00
CREV					
Total	8.27	6.59	10.89	10.86	0.19
Stranger	6.03	4.86	5.80	5.36	0.84
Familiar	1.92	2.25	3.18	3.80	0.07

All *p* values derived from t-tests with the exception of sex, ethnicity, handedness and Tanner stage comparisons which used Fisher's exact test.

Table 3.2. Demographic characteristics and questionnaire data for the maltreated and non-maltreated groups within the combined sample.

	Control (n = 60)		MT (n = 62)		p
	Mean	SD	Mean	SD	
Demographics					
Age (in years)	12.68	1.14	12.23	1.52	0.07
WASI, 2 scale subset	108.88	10.49	104.81	13.23	0.06
Puberty development scale	2.22	0.66	2.04	0.71	0.15
Tanner stage					0.60
No. of pre/early pubertal (%)	15 (25)		22 (35)		
No. of mid pubertal (%)	23 (38)		24 (39)		
No. of late/post pubertal (%)	22 (37)		16 (26)		
Sex, N of males (%)	25 (42)		33 (53)		0.21
Ethnicity, N of Caucasian (%)	31 (52)		39 (63)		0.27
Handedness, N or right handed (%)	53 (88)		46 (74)		0.21
SES					
Composite score	3.15	0.87	2.89	1.08	0.22
TSCC					
Anxiety	45.26	11.17	45.72	15.95	0.87
Depression	44.19	9.94	44.08	14.55	0.97
Anger	41.84	9.07	43.80	13.35	0.42
Post-traumatic Stress	43.02	8.30	45.60	14.48	0.31
Dissociation	43.28	11.46	45.88	13.92	0.33
Dissociation (Overt)	45.28	9.52	45.78	13.68	0.84
Dissociation (Fantasy)	44.33	11.28	46.90	14.63	0.35
SDQ					
Emotional symptoms	2.66	2.08	3.27	2.49	0.21
Conduct problems	1.60	1.48	2.75	2.01	0.00
Hyperactivity/inattention	2.67	1.80	4.33	2.70	0.00
Peer problems	1.48	1.37	2.04	1.87	0.11
Pro-social behaviour	7.83	1.72	7.84	1.80	0.99
Total difficulties	8.21	4.99	11.52	7.24	0.01

All p values derived from t-tests with the exception of sex, ethnicity, handedness and Tanner stage comparisons which used Fisher's exact test.

Total grey matter, white matter, cerebrospinal fluid and intracranial volume

Within Sample 2, there were no group differences on measures of grey matter, white matter, cerebrospinal fluid and total intracranial volume (Table 3.3). Within the combined sample there were no group differences on these global measures of volume. However, Sample 1 had a lower overall grey matter volume compared to the non-maltreated peers (Table 3.3).

Table 3.3. The global measurements of grey matter, white matter, cerebrospinal fluid and total intracranial volume between the maltreated and non-maltreated groups.

Sample 1					
	Control (n = 20)		MT (n = 18)		<i>p</i>
	Mean	SD	Mean	SD	
Grey matter	785.98	61.69	746.85	55.01	0.05
White matter	481.6	49.97	463.13	37.04	0.21
Cerebrospinal fluid	163.89	24.21	167.33	21.83	0.65
Total	1431.47	113.77	1377.31	96.01	0.12
Sample 2					
	Control (n = 40)		MT (n = 44)		<i>p</i>
	Mean	SD	Mean	SD	
Grey matter	763.78	65.88	765.17	67.79	0.92
White matter	478.19	55.26	469.54	48.86	0.45
Cerebrospinal fluid	175.41	25.71	175.26	28.52	0.98
Total	1417.38	121.82	1409.97	117.12	0.78
Combined					
	Control (n = 60)		MT (n = 62)		<i>p</i>
	Mean	SD	Mean	SD	
Grey matter	771.18	64.85	759.85	64.44	0.34
White matter	479.33	53.16	467.68	45.54	0.2
Cerebrospinal fluid	171.57	25.61	172.96	26.82	0.77
Total	1422.07	118.42	1400.49	111.63	0.3

All *p* values derived from t-tests

Analytic procedure

Due to the multifaceted approach to investigating the associations between grey matter volume, maltreatment characteristics and psychiatric symptomatology, the analytic procedure undertaken in this chapter is illustrated in Figure 3.1 and previously described in the methods section. The subsequent sections follow this procedure.

Step 1.

- i. Identification of regions of atypical structure associated with maltreatment in Sample 2.*

Analysis in line with De Brito et al (2013)

An identical pre-processing pipeline (low dimension registration to a customised study specific tissue probability map) and region of interest analysis (confined to the amygdala, cerebellum, prefrontal cortex, hippocampus and temporal lobes) was conducted on Sample 2 as previously applied to Sample 1, allowing a comparison with the findings reported in De Brito et al (2013). Age, sex and IQ were included in the SPM model as covariates of no interest. There was a failure to replicate the same pattern of findings and no regions of reduced grey matter were detected within the group difference analysis restricted to Sample 2. For completeness we explored trends for group differences at a whole brain level using an uncorrected statistical threshold of $p < 0.001$; no significant clusters of increased or decreased grey matter were observed in the maltreated group compared to the non-maltreated group.

The maltreatment histories between the two samples were compared as displayed in Table 3.4. As shown, Sample 1 were found to have had experienced significantly more exposure to physical abuse than the Sample 2 (44% vs. 7%) and the severity within those who experienced physical abuse was significantly greater ($p = 0.014$). Occurrences of neglect were similar between the two samples, however maltreated youth within Sample 2 experienced a greater severity of neglect ($p = 0.04$; Table 3.4). These markedly different group maltreatment histories may partially explain the failure to identify a similar pattern of reduced grey matter volume found previously in Sample 1 (De Brito et al., 2013).

Table 3.4. Comparison of the demographic variables and maltreatment history of the maltreated group in Sample 1 and Sample 2.

	Sample 1 (n = 18)		Sample 2 (n = 44)		p
	Mean	SD	Mean	SD	
Demographics					
Age (in years)	12.13	1.47	12.28	1.56	0.74
WASI, 2 scale subset	102.83	11.65	105.61	13.86	0.46
Puberty development scale	2.10	0.87	2.02	0.65	0.71
Sex, N of males (%)	11 (61)		22 (50)		0.58
Ethnicity, N of Caucasian (%)	7 (39)		32 (73)		0.02
Handedness, N or right handed (%)	15 (83)		31 (70)		0.09
Severity of abuse					
Physical abuse	2.38	1.19	1.00	0.00	0.01
Sexual abuse	2.25	1.50	2.33	1.53	0.95
Neglect	2.75	1.34	3.44	0.96	0.04
Emotional abuse	2.94	1.00	2.95	0.89	0.96
Total severity	6.61	3.71	5.64	2.42	0.23
Occurrence of abuse					
Physical abuse (%)	8 (44)		3 (7)		0.00
Sexual abuse (%)	5 (28)		3 (7)		0.08
Neglect (%)	16 (89)		34 (77)		0.48
Emotional abuse (%)	16 (89)		41 (93)		0.62
Domestic Violence (%)	10 (56)		20 (45)		0.58
Total occurrence	3.06	1.16	2.45	1.02	0.07

All p values derived from t-tests with the exception of sex, ethnicity, handedness and occurrence of abuse comparisons which used Fisher's exact test.

Sample 2: Whole brain analysis

Sample 2 data were also pre-processed using a more precise normalisation technique (DARTEL) which allows for improved inter-subject alignment in MRI analyses (Ashburner, 2007). A whole-brain approach was taken so as to not inappropriately constrain the analysis to previously defined regions and allow for the detection of group differences that may have not been detected using the low dimensional approach applied to Sample 1. The maltreated group, in comparison with the non-maltreated group exhibited reduced grey matter in two regions; the right supramarginal gyrus (x = 51, y = -34, z = 43; Z-score = 3.77; p = 0.03; K = 887; Figure 3.2 (A)) and the right medial temporal lobe (x = 41, y = -58, z = 12; Z-score =

3.78; $p = 0.03$; $K = 854$; Figure 3.2 (B)). Figure 1 visualises the location of these two regions on a study specific mean structural image of 84 participants. These regions did not reach significance at the more stringent initial threshold of $p < 0.001$. Although the grey matter voxel values in the grey matter segments were only multiplied to the non-linear component of the registration to account for individual differences in brain size, we ran ANCOVA with group as the between subject factor and total brain volume as a covariate as a secondary check. The same pattern of results were observed, and all comparisons reached significance ($p < .01$).

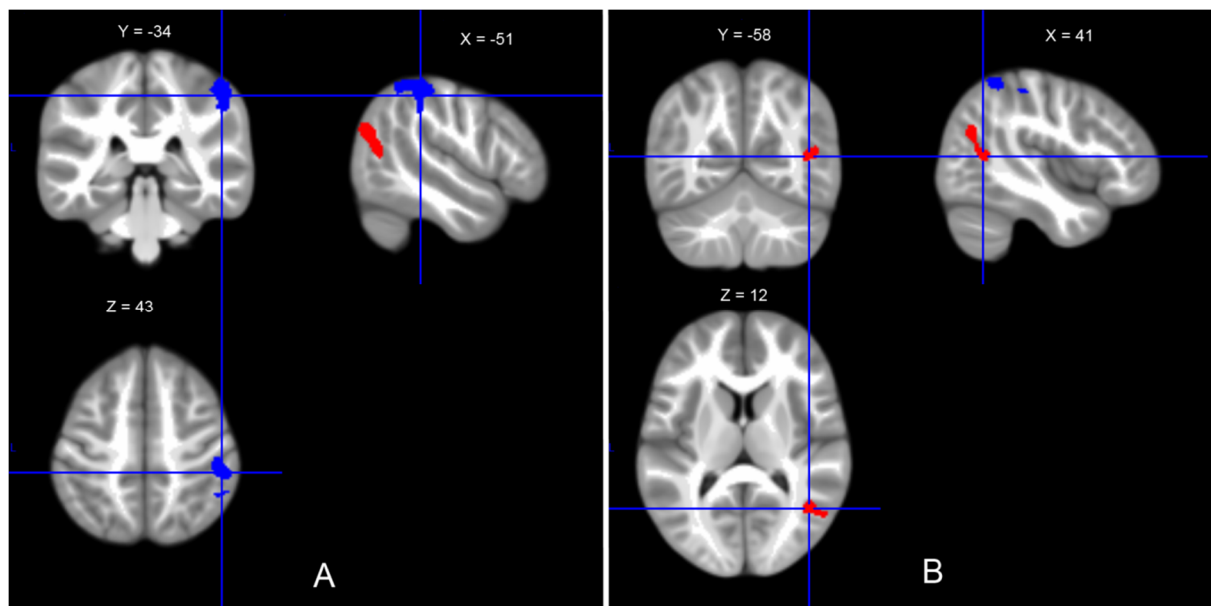


Figure 3.2. Clusters of significantly reduced GMV within the maltreated group of Sample 2.

Notes: Statistical parametric maps showing the foci of significant reduced grey matter among the maltreated children in Sample 1 ($n = 44$) relative to non-maltreated children in (A) right supramarginal gyrus (MNI coordinates: $x = 51$, $y = -34$, $z = 43$; Z-score = 3.77; $p = 0.03$; $K = 887$) and (B) right medial temporal gyrus (MNI coordinates: $x = 41$, $y = -58$, $z = 12$; Z-score = 3.78; $p = 0.03$; $K = 854$). SPM clusters are overlaid on a mean structural scan of Sample 2 participants. The clusters are corrected at an initial threshold of $p < 0.005$ ($\alpha < 0.05$).

The maltreated group in comparison with the non-maltreated group also exhibited increased grey matter in two regions; the right occipital lobe ($x = 24$, $y = -76$, $z = 39$; Z-score = 3.65; $p = 0.02$; $K = 840$; Figure 3.3 (C)) and the left pre-central gyrus extending into left inferior frontal cortex ($x = -57$, $y = 8$, $z = 27$; Z-score = 3.62; $p = 0.02$; $K = 1253$; Figure 3.3 (D)). Neither region was found to be significant at the more stringent initial threshold of $p < 0.001$.

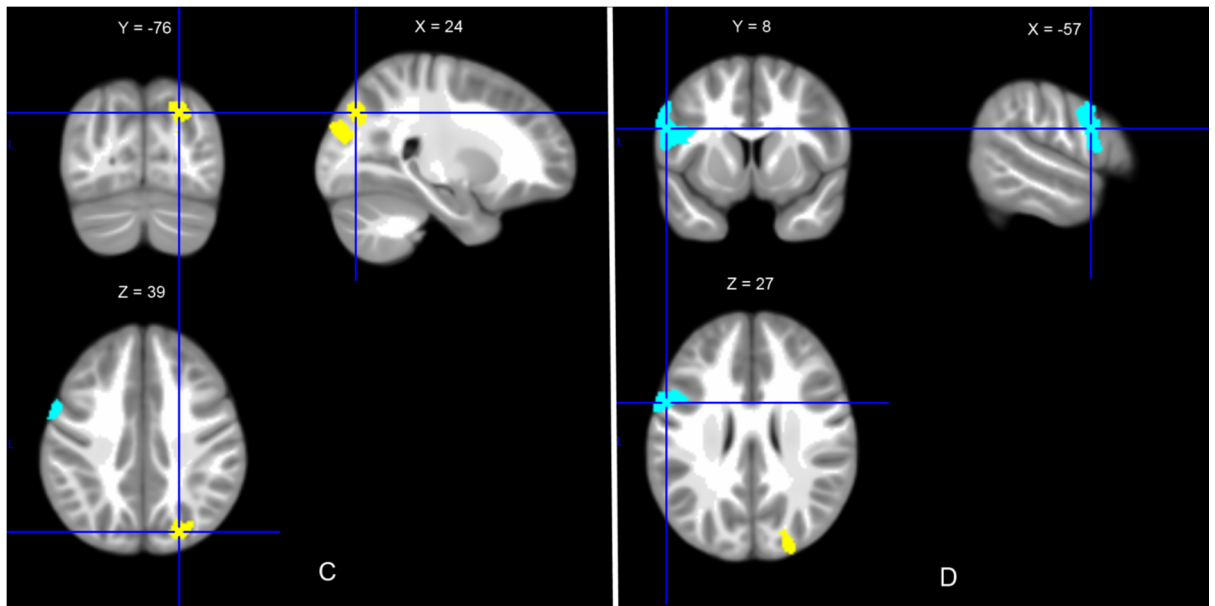


Figure 3.3. Clusters of significantly increased GMV within the maltreated group of Sample 2.

Statistical parametric maps showing the foci of significant increased grey matter among the maltreated children in Sample 1 ($n = 44$) relative to non-maltreated children in (C) the right occipital lobe ($x = 24, y = -76, z = 39$; Z-score = 3.65; $p = 0.02$; $K = 840$) and (D) and the left precentral gyrus ($x = -57, y = 8, z = 27$; Z-score = 3.62; $p = 0.02$; $K = 1253$). SPM clusters are overlaid on a mean structural scan from the 84 participants within Sample 1.

ii. GMV associations with maltreatment characteristics

Mean grey matter values were extracted from a 10mm sphere constructed around the local maxima of the three significant regions for further analyses into associations with maltreatment characteristics and trauma symptomatology within the maltreated group.

Correlations with self-reported measure of abuse

The descriptive statistics of the self-reported experience of maltreatment within the maltreated group of Sample 2 are displayed in Table 3.5. A negative correlation between mean GMV and total CTQ score was observed within the right supramarginal gyrus ($r = -.32, p = 0.032$; Figure 3.4). Furthermore, a negative association within right supramarginal gyrus and self-reported experiences of physical abuse was observed ($r = -.34, p < 0.02$). Although sexual abuse was negatively correlated with both the right medial temporal gyrus and the right supramarginal gyrus, this association was driven by four participants and Cooks distance scores for these participants exceeded the commonly accepted cut-off

value of 1. Neither of the two regions of grey matter increase within the maltreated group correlated with CTQ scores as a total composite or by subtype of abuse. To ascertain whether the bivariate correlations were artificially inflated by outliers, Cook's distance metric was used on these associations. Cook's distance scores did not reach a significant cut-off (>1) for the associations between right supramarginal gyrus and CTQ total score and physical abuse (None of the data points showed a value greater than 0.4). The associations between sexual abuse and the two regions of decreased grey matter did reach this cut-off and could confidently be attributed to outliers.

Table 3.5. Descriptive statistics for Self-reported measures of abuse and community violence within the maltreated group of the combined sample.

CTQ	Severity			
	Mean	SD	Min	Max
Emotional abuse	8.19	4.07	5.00	21.00
Physical abuse	6.26	4.20	0.00	23.00
Sexual abuse	5.44	1.60	5.00	14.00
Emotional neglect	9.71	4.71	5.00	24.00
Physical neglect	8.24	3.61	5.00	17.00
Combined total	38.05	15.75	23.00	90.00

CREV	Severity			
	Mean	SD	Min	Max
Total	10.89	10.86	0.00	46.00
Stranger	5.80	5.36	0.00	20.00
Familiar	3.18	3.80	0.00	14.00

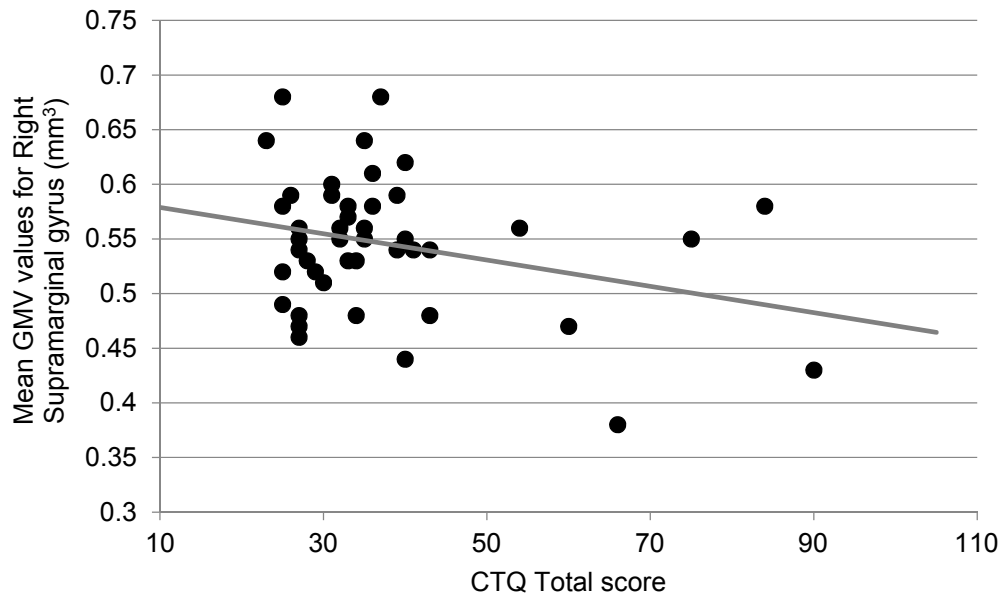


Figure 3.4. Correlation between mean grey matter values within the right supramarginal gyrus of the maltreated group in Sample 2 and total Childhood Trauma Questionnaire scores ($r = -.323, p < 0.05$).

iii. GMV associations with exposure to community violence

The descriptive statistics of the self-reported experience of community violence within the Sample 2 are displayed in Table 3.6. A negative trend was observed between experiences of community violence of familiar figures and both the right medial temporal gyrus ($r = -.29, p = 0.057$) and the right supramarginal gyrus ($r = -.29, p = 0.058$). Neither of the two regions of grey matter increase within the maltreated group correlated with experience of community violence scores.

Table 3.6. Correlation table between grey matter values within regions of decreased volume in the maltreated group and measures of experience of community violence.

CREV correlations	Total	Stranger	Familiar
Right medial temporal lobe	-0.26	-0.23	-0.29
Right supramarginal gyrus	-0.21	-0.11	-0.29

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

iv. GMV associations with psychiatric symptomatology

The right supramarginal gyrus had negative associations with both internalising and externalising composite scores created from the CASI (Table 3.7; Figure 3.5 for the association with externalising behaviours). The right supramarginal gyrus was negatively associated with specific disorders that were incorporated in the composite internalising and externalising disorder scores (Table 3.7). Cook's distance values for these data points did not exceed 0.4; excluding the one participant who showed a value of 0.4, both correlations remained significant.

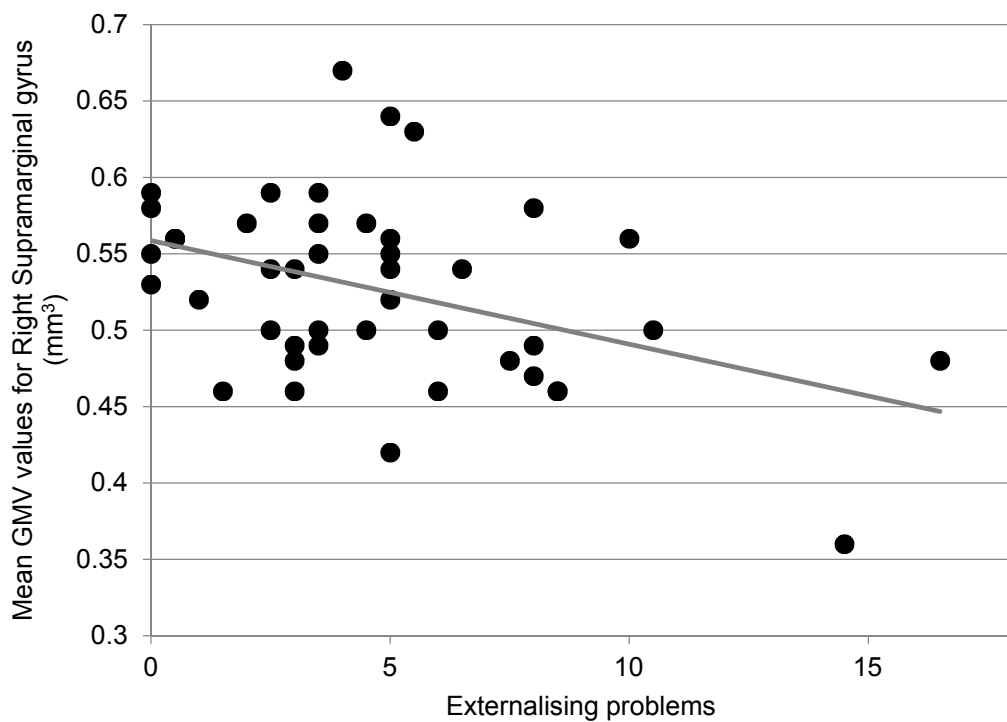


Figure 3.5. Scatter plot displaying the association between mean grey matter values for the right supramarginal gyrus within the maltreated group of Sample 2 and the externalising problems score ($r = -0.39$, $p < 0.003$).

Table 3.7. Correlations between mean grey matter values within regions of decreased volume in the maltreated group and measures of psychiatric symptomatology.

	Internalising composite score	Externalising composite score	MDD	Dysthymic	Anxiety	CD	ODD
Right MTL	-0.15	-0.18	-0.26	-0.27	0.01	-0.16	-0.16
Right SMG	-0.39**	-0.42**	-.38*	-.38*	-.31*	-.42**	-.34*

Note: SMG = Supramarginal gyrus; MTL = Middle temporal lobe *p<0.05, **p<0.01, ***p<0.001, MDD= Major depressive disorder.

v. Mediation analyses

CTQ total scores were positively correlated with composite scores of internalising ($\beta = .66$, $p<0.005$) and externalising symptoms ($\beta = .644$, $p<0.001$) as assessed by the CASI. Right supramarginal gyrus grey matter values were negatively associated with internalising ($\beta = -.39$, $p=0.009$) and externalising symptoms ($\beta = -.42$, $p=.005$). Mediation analyses indicated that GMV in the right supramarginal gyrus partially mediated the relationship between CTQ total score and externalising disorders ($\beta = 0.082$, LLCI = 0.0034, ULCI = .2257; Figure 3.6). The model exploring the mediation of the relationship between CTQ total score and internalising behaviour did not confirm statistically significant mediation.

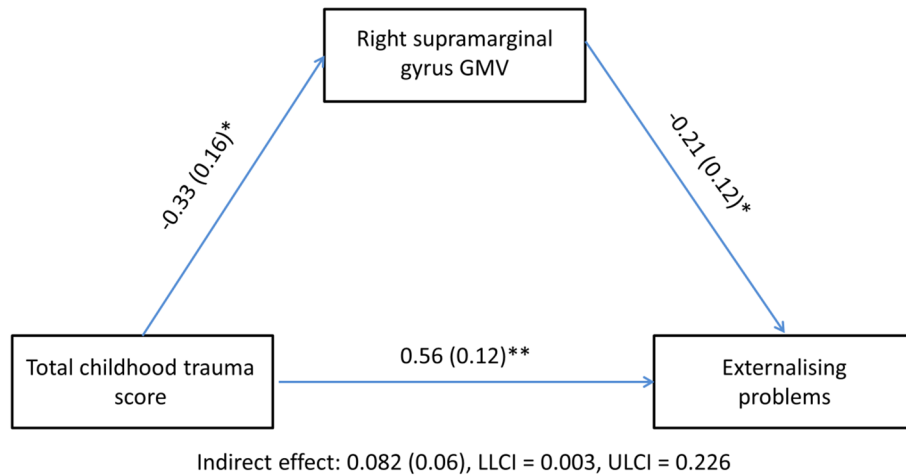


Figure 3.6. Right supramarginal gyrus partially mediates the relationship between childhood trauma and externalising problems within the maltreated group of Sample 2.

Notes: The values represent the standardised beta coefficients and standard errors within parentheses. * $p < 0.05$, ** $p < 0.005$

Step 2.

- i. *Identification of regions of atypical structure associated with maltreatment in the combined sample.*

Sample 1 and 2 were combined to explore group differences within a community sample presenting with a varied experience of childhood maltreatment. A precise inter-subject alignment (DARTEL) and whole-brain approach with monte-carlo simulation for the correction of multiple comparisons was taken for the sensitive detection of group differences. Customised tissue probability maps were created to reflect the combined sample's age and Sex.

The maltreated group was observed to have significantly reduced grey matter volume within five regions; bilateral medial temporal lobe, bilateral supramarginal gyrus and left medial orbitofrontal cortex. Table 3.8 details the cluster extents of these five regions. The two regions of bilateral medial temporal lobe remained significant at the more stringent initial threshold of $p < 0.001$. Figure 3.7 illustrates the extent of the significantly reduced regions of grey matter on a study specific mean structural. The maltreated sample displayed significantly increased

grey matter volume compared to the non-maltreated group within the left precentral gyrus ($x = -56, y = 5, z = 27$; Z-score = 4.28; $p = 0.02$; $K = 1225$; Figure 3.8).

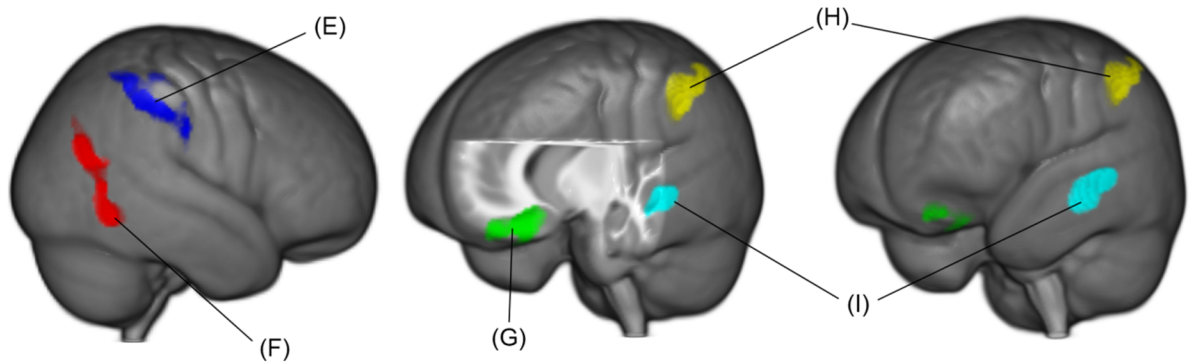


Figure 3.7. Clusters of significantly reduced GMV within the maltreated group of the combined sample.

*Notes: Statistical parametric maps showing the clusters of significantly reduced grey matter volume among the maltreated children ($n = 64$) relative to the non-maltreated children ($n = 60$) in I right supramarginal gyrus, (F) right medial temporal gyrus, (G) left medial orbitofrontal gyrus, (H) the left supramarginal gyrus and (I) the left medial temporal gyrus. SPMs are overlaid on a mean structural from the 122 participants. Cluster statistics are shown in **Table 3.8**.*

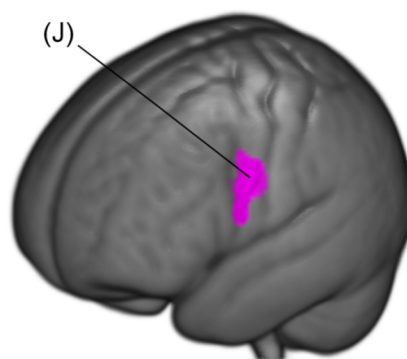


Figure 3.8. Cluster of significantly increased GMV within the maltreated group of the combined sample.

*Notes: Statistical parametric maps showing the cluster of significantly increased grey matter volume among the maltreated children ($n = 64$) relative to the non-maltreated children ($n = 60$) in (J) left precentral gyrus. SPM is overlaid on a mean structural from the 122 participants. Cluster statistics are shown in **Table 3.8**.*

Table 3.8. Whole brain group comparison within the combined sample. Cluster maxima are shown in bold. Letters in parentheses refer to the SPM clusters visualised in Figure 3.7 & Figure 3.8.

Brain region	Cluster	K	<i>p</i> value	Peak within cluster		MNI coordinates		
				T-score	Z-score	X	Y	Z
Controls > Maltreated								
Right supramarginal gyrus	E	1599	0.013	3.64	3.53	50	-34	43
NA				3.53	2.23	47	-52	62
NA				3.3	3.22	53	-31	62
Right middle temporal gyrus	F	2326	0.001	4.95	4.71	41	-60	12
Right Middle temporal gyrus				4.53	4.34	50	-53	15
Right Inferior temporal gyrus				4.23	4.07	50	-55	-6
Left medial orbitofrontal gyrus	G	1021	0.031	4.13	3.98	-12	26	-21
Left orbitofrontal gyrus				3.05	2.98	-11	45	-24
Left inferior frontal gyrus				2.59	2.54	-21	12	-21
Left supramarginal gyrus	H	1319	0.021	4.7	4.49	-60	-30	39
Left inferior parietal				3.59	3.49	-53	-42	48
NA				3.1	3.03	-56	-49	55
Left middle temporal gyrus	I	1397	0.021	4.67	4.46	-63	-19	-9
Controls < Maltreated								
Left precentral gyrus	J	1225	0.021	4.47	4.28	-56	5	27
Left precentral gyrus				3.59	3.49	-65	2	30
Left precentral gyrus				3.35	3.25	-59	8	39

K = Cluster size in voxels

The group differences also remained when co-varying age, sex and IQ. In order to investigate whether group differences in conduct problems or hyperactivity symptoms might account for our observed grey matter volume differences in these five regions of GMV reduction and 1 region of GMV increase, correlations were performed between GMV values within these regions and the conduct problems and hyperactivity symptom scores. No significant associations were detected ($p < 0.05$ threshold). Consequently, conduct problems and hyperactivity symptoms were not included as covariates in the main analysis. A strong case has also been made that when participants are not randomly assigned to groups, it is inappropriate to co-vary for variables intrinsically related to group assignment (Miller & Chapman, 2001).

ii. GMV associations with maltreatment characteristics

Dimensions of maltreatment

Characteristics of the combined sample's maltreatment histories are displayed in Table 3.9. Emotional maltreatment represented the most common form of maltreatment (94%), whereas physical and sexual abuse were the least common (19% and 13% respectively). Neglect was found to be the most severe form of maltreatment within the combined sample. The majority of the maltreated sample experienced two forms of abuse (40%), while only 10% experienced one form of abuse, 26% experienced three forms of abuse, 19% experienced four forms of abuse and 5% were classified as experiencing five forms of abuse. As shown, multi-type maltreatment occurred more frequently than the experience of a single form of maltreatment.

The associations between GMV values within each of the five regions showing group differences and maltreatment characteristics defined from official substantiated reports per the Kaufman criteria are displayed in Table 10. Grey matter volumes within the five cortical regions did not significantly correlate with any of the composite maltreatment characteristics scored according to Kaufman criteria (Table 3.10). Exploring these dimensions of maltreatment by subtype also did not present significant associations with any of the extracted grey matter volume values.

Table 3.9. Table detailing the maltreatment characteristics of the combined sample.

		Occurrence (%)			
Physical abuse		12 (19)			
Neglect		51 (82)			
Sexual abuse		8 (13)			
Emotional abuse		58 (94)			
Domestic Violence		31 (50)			
		Mean		SD	
Total occurrence		2.63		1.09	
		Severity			
		Mean		SD	
Physical abuse		1.92		1.16	
Neglect		3.24		1.12	
Sexual abuse		2.29		1.38	
Emotional abuse		2.93		0.92	
Domestic Violence ¹		2.33		1.43	
Total severity ²		6.03		2.76	
		Duration (months)			
		Mean	SD	Min	Max
Physical abuse		48.18	54.35	1.00	154
Neglect		70.98	50.87	5.00	158
Sexual abuse		26.50	26.20	6.00	84
Emotional abuse		65.47	52.76	1.00	158
Domestic Violence ¹		69.18	44.13	6.00	157
Longest duration		77.50	49.22	1.00	158

¹Domestic Violence severity scores were only computed for Sample 2 due to available information. ²Total severity scores were calculated from all subtypes excluding domestic violence due to lack of available information. Scores could range from 1 to 16. *Severity of abuse was derived from Kaufman's four point scale, rated from 0 = 'no abuse present' to 4 = 'evidence of severe abuse'.*

Table 3.10. Correlations between the mean GMV values and maltreatment characteristics.

	Total occurrence		Total severity		Longest duration of abuse	
Controls > Maltreated						
Left medial temporal lobe	-0.15	n.s.	0.175	n.s.	0.02	n.s.
Left Supramarginal gyrus	-0.21	n.s.	0.022	n.s.	0.05	n.s.
Left medial orbitofrontal gyrus	-0.18	n.s.	0.149	n.s.	-0.03	n.s.
Right medial temporal lobe	-0.16	n.s.	0.034	n.s.	-0.17	n.s.
Right supramarginal gyrus	-0.18	n.s.	0.182	n.s.	0.03	n.s.
Controls < Maltreated						
Left precentral gyrus	-0.25	n.s.	0.031	n.s.	-0.06	n.s.

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

iii. GMV associations with psychiatric symptomatology

Trauma symptom scores derived from the Trauma Symptom Checklist for Children (TSCC) were available for all of the combined sample. Associations between scores of the subscales of the TSCC and regions of grey matter reduction in the maltreated group were not significant. Furthermore, there were no significant associations between the region of grey matter increase in the maltreated group and TSCC subscales and the TSCC internalising composite score.

Exploring the associations between substantiated official reports of maltreatment and trauma symptoms for the combined sample (TSCC), it was found that there were no significant associations between any subtype of abuse on occurrence, severity or duration scores and trauma symptoms, including anxiety, depression and PTSD. Composite scores of total occurrence, total severity and longest duration of abuse were not associated with trauma symptoms measured by the TSCC. This lack of associations between maltreatment exposure and psychiatric symptomatology measures likely reflects heterogeneity in the response to the maltreatment experience among the children, as well as the low to sub-clinical rates of psychopathology in this sample as a whole.

iv. Mediation analyses

Maltreatment characteristics derived from social services records and psychiatric symptomatology did not significantly correlate therefore an exploratory mediation analysis involving atypical structure within the maltreated group was not undertaken.

3.4. Discussion

Using an analysis procedure detailed in Figure 3.1, the present study set out to systematically investigate the following questions:

- 1) Is there a dose response relationship between maltreatment severity and grey matter volume in regions associated with maltreatment experience?
- 2) Do individual forms of maltreatment show diverse associations within these cortical regions?
- 3) Is increased duration of abuse associated with a greater decrease in grey matter volume within these cortical regions?
- 4) Is there a dose response relationship between exposure to community violence and grey matter volume in these cortical regions?
- 5) Is there an association between grey matter volume and internalising/externalising symptoms within the maltreated sample?
- 6) Is any association between maltreatment experience and psychiatric symptoms mediated by grey matter volume differences in children with maltreatment?

The first step in the analytic procedure sought to identify regions of atypical structure within the maltreated group compared to the non-maltreated peers in sample 2. Our findings indicated that the maltreated group had reduced GMV compared to the controls within two regions: the right supramarginal gyrus and the right middle temporal region. The maltreated group also displayed increased GMV within the left precentral gyrus and the right occipital lobe. GMV within the right supramarginal gyrus was found to be significantly negatively associated with total maltreatment severity as well as individually with physical abuse severity. Exposure to community violence was not associated with GMV in any of the regions of

atypical structure within the maltreated group. Interestingly, GMV within this region was found to be negatively associated with both externalising and internalising symptoms. Exploratory mediation analysis indicated that GMV within the right supramarginal gyrus partially mediated the relationship between childhood maltreatment and externalising symptoms. GMV within the right middle temporal region, left precentral gyrus and right occipital lobe was not significantly associated with maltreatment severity or psychiatric symptomatology.

The second step of the analytic procedure, combining Sample 1 and 2, identified five regions of grey matter volume reduction in the maltreated group compared to the non-maltreated peers: bilateral supramarginal gyrus, bilateral temporal lobe and left medial orbitofrontal cortex. Furthermore increased GMV was reported in the left precentral gyrus of the maltreated group compared to the controls. GMV in none of the regions of atypical structure within the maltreated group were found to be significantly associated with the social services report of maltreatment severity, both as a total score or by subtype, or chronicity of abuse. Additionally, we did not find any significant associations with psychiatric symptomatology and GMV within these regions of atypical structure within the maltreated group.

Inspecting the sample demographics, the maltreated group were well matched with the non-maltreated peers on age, sex, ethnicity, IQ, socio-economic status and pubertal development which suggests that grey matter differences are unlikely to be associated with these variables. Surprisingly, community violence did not differ between the maltreated and non-maltreated groups. This may partly be due to the young age of the sample who may not have been exposed to sustained levels of community violence yet as studies have found that exposure and severity of community violence increases with age (Finkelhor, Turner, Ormrod, & Hamby, 2009). It may also reflect the fact that the maltreated and non-maltreated groups were well matched on socio-demographic variables, thus living in areas of similar levels of exposure to community violence.

Step 1: Investigation of the associations between maltreatment characteristics, psychiatric symptomatology and GMV within Sample 2.

Our initial aim within both of the steps (Figure 3.1) of this systematic analysis was to locate regions of atypical structure in the maltreated group, compared to the

non-maltreated peers. The first phase of Step 1 replicated the processing technique of a previous voxel-based morphometric study undertaken on Sample 1 (De Brito et al., 2013). The newly recruited sample, Sample 2, were pre-processed and analysed in line with the methods of De Brito et al (2013). To replicate the procedures of De Brito and colleagues study, analysis was restricted to an a-priori region of interest mask which included the amygdala, hippocampus, cerebellum, temporal lobes and frontal lobes. Surprisingly, no significant areas of grey matter reduction were observed within the maltreated sample compared to the non-maltreated peers. A conceivable explanation to this inability to replicate the previous findings may be due to the markedly difference maltreatment histories of the two samples. Sample 1 were characterised more by increased occurrence and severity of physical abuse and occurrence of sexual abuse, whereas Sample 2 were characterised more by a greater severity of neglect.

Sample 2 were pre-processed again using a high dimensional diffeomorphic registration technique (DARTEL; (Ashburner, 2007)). Using this technique, two areas of grey matter reduction, in the right supramarginal gyrus and right middle temporal lobe, and two areas of grey matter increase, in the left precentral gyrus and left occipital lobe were observed within the maltreated group compared to the non-maltreated peers. Examining the sample homogeneity, the resulting grey matter images from the DARTEL pipeline represented a much smaller squared distance from the mean and high covariance values compared to the low-dimensional pipeline, suggesting better inter-subject registration. The lack of findings using the low-dimensional pipeline could potentially be attributed to poorer inter-subject registration.

Our finding that a community sample of maltreated adolescences exhibit decreased GMV in the right supramarginal gyrus (SMG) is of interest, as this region has been implicated in emotional processing and empathy (Adolphs, Tranel, & Damasio, 2003; Adolphs, Tranel, & Damasio, 2001; Lamm, Batson, & Decety, 2007). Previous structural studies exploring the impact of childhood maltreatment have reported atypical structure within the right supramarginal gyrus in adults and children (Dannlowski et al., 2012; Hanson et al., 2010); n.b. Using the aal atlas as we have used within this study, the coordinates define the region as right supramarginal gyrus).

The GMV of the right supramarginal gyrus was significantly and negatively associated with self-reported trauma scores across maltreatment subtypes. Furthermore, exploratory analyses found a zero-order correlation between physical abuse and right supramarginal gyrus GMV. These findings suggest a dose-response relationship between experience of maltreatment and atypical structure within this region and support previous findings of similar relationships between grey matter volume and CTQ severity (Edmiston et al., 2011). Additional correlational analyses found a negative relationship between GMV within the right supramarginal gyrus and both externalising and internalising symptom scores derived from the parent-rated Child and Adolescent Symptom Inventory (CASI). These results indicate that greater GMV reductions within the right supramarginal gyrus within the maltreated group were associated with heightened externalising and internalising symptomatology.

A wealth of research has linked early maltreatment with the development of both internalising and externalising behaviours in adolescence and later life (e.g. Cicchetti & Toth, 2005; Norman et al., 2012) and proposed that cortical structure may mediate the relationship between early maltreatment and psychopathology (Gorka, Hanson, Radtke, & Hariri, 2014; Rao et al., 2010). We undertook an exploratory analysis to determine whether the right SMG may represent a similar mediating relationship. Our exploratory analysis indicated that the right SMG significantly mediated the relationship between total CTQ scores and externalising symptomatology but not internalising symptomatology. These findings, should however, be framed within the limitations of the study design; as it is a cross-sectional study one cannot assign a causal relationship between the variables, an assumption usually taken when performing mediation analyses. For instance, we cannot verify that externalising behaviours are a product of GMV reduction, as equally it may be that GMV reduction in this area is a consequence of externalising behaviours.

Even so, the functional importance of the right SMG is of interest to maltreatment research as lesion studies have found that damage to this area compromises human emotion recognition (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs et al., 2001). Specifically, the supramarginal gyrus has been implicated in 'covert online somatosensory representations', which may be incorporated in social perception (Adolphs et al., 2000). In particular, this region has been associated with processing the overlap between representations of one's self

and others in social perception (Lawrence et al., 2006) and the ability to project one's own mental state onto others in overcoming biased empathic judgments (Silani, Lamm, Ruff, & Singer, 2013). This ability to distinguish oneself from others' related representations is a vital process in social cognition and is consistent with the idea that somatosensory information about oneself crucial in emotional perspective-taking (Adolphs et al., 2000; Ruby & Decety, 2004; Singer & Lamm, 2009). Empathy is a core component of successful emotional processing (Cole, Michel, & Teti, 1994) and disruptions to emotional regulation are substantial in initialising maladaptive behavioural patterns seen in both internalising and externalising disorders (Eisenberg et al., 2001; Hill, Degan, Calkins, & Keane, 2006; Kim & Cicchetti, 2010; Suveg & Zeman, 2004). Keeping the limitations of the structural analysis and study design in mind, we hypothesise that atypical structure within the supramarginal gyrus may contribute to impairments in empathic processing and successful emotional perspective-taking.

Of importance, atypical volume within the SMG has been associated with a disorders related to distorted self-awareness (Berlucchi & Aglioti, 1997; Berlucchi & Aglioti, 2010) and major depressive disorder (Singh et al., 2013). Externalising disorders, such as conduct disorder, have also been found to be characterised by structural alterations in bilateral supramarginal gyrus in addition to frontal areas (Hyatt et al., 2012). Collectively these findings suggest a role of the supramarginal gyrus in the characterisation of a number of internalising and externalising disorders. Atypical volume within the SMG of the maltreated group may therefore represent a risk factor for the development of maladaptive behaviours in later life.

We also identified reduced grey matter in the right middle temporal gyrus in Sample 2. This result is consistent with previous structural imaging findings that have associated reductions in GMV within the right middle temporal gyrus with childhood experiences of maltreatment in samples of children and adults (Dannlowski et al., 2012; Hanson et al., 2010; Lim, Radua, & Rubia, 2014). Animal research has established a link between early life stress and cortical grey matter volume within bilateral middle temporal gyri (Jackowski et al., 2011). Functionally, the bilateral middle temporal lobe has been associated with playing a crucial role in mediating emotional processes such as sensitivity to emotional cues (Adolphs et al., 2003; Davidson, 2004); a domain commonly found to be compromised in a variety of psychiatric disorders and in maltreated individuals (Adolphs et al., 2003; Davidson, 2004; Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak & Tolley-Schell,

2003). GMV aberrations within this region may contribute to impairments in emotional regulation in adolescence and later life.

Additionally, two regions of grey matter increase were observed within the maltreated group compared to non-maltreated peers; the left precentral gyrus and the right occipital lobe. While the previously published structural analysis on Sample 1 did not observe relative increases in grey matter volume within the maltreated group, this absence of GMV increase is relatively uncommon in the wider research. A recent meta-analysis confirmed that relative increases in grey matter volume have been observed within both adolescent and adult maltreated samples (Carrion et al., 2009; Lim et al., 2014). Importantly, an increase in grey matter associated with maltreatment experience in a region of right occipital lobe very close to the cluster maxima we report was observed in an investigation recruiting a very similar adolescent sample (Hanson et al., 2010). Conversely, GMV decreases in left precentral gyrus have been noted in a voxel wise meta-analysis of structural research in maltreatment (Lim et al., 2014). However the coordinates reported can be defined as postcentral gyrus using the commonly used aal atlas, which may suggest two separable cortical regions.

Relatively little research in childhood maltreatment has focused on the left precentral gyrus. However functional studies have found atypical neural activation in maltreated women with PTSD showed during non-traumatic olfactory processing (Croy et al., 2010), maltreated adolescents during cognitive control tasks (Mueller et al., 2010) and depressive patients during working memory tasks (Wang et al., 2015). Disruption to this region has been implicated in network that supports cognitive processes that may mediate the psychiatric consequences of maltreatment (Bremner et al., 2003; Croy et al., 2010).

Step 2: Investigation of the associations between maltreatment characteristics, psychiatric symptomatology and GMV within a combined sample of maltreated adolescents.

The second step in the analysis procedure involved combining Sample 1 and Sample 2, providing a maltreated group with a diverse history of experiences of abuse subtypes and allowing for a large sample size (n=122). As with the first part of Step 1, we intended to identify regions of atypical structure associated with exposure to childhood maltreatment within the combined sample so as to provide

focus for the subsequent investigation into the influence of maltreatment characteristics. Group analysis on the combined sample revealed five areas of GMV reduction, the mOFC, bilateral SMG and bilateral MTG, and one area of GMV increase, the left precentral gyrus in the maltreated group compared to the non-maltreated group. The mOFC has particular interest to maltreatment research due to its associations with reinforcement based decision making and emotion regulation (Ochsner & Gross, 2005; Schoenbaum et al., 2007). Importantly, lesions to this region have been found to cause deficiencies in emotion, mood and social regulation (Damasio et al., 1994; Grafman et al., 1996). The subdivision of the medial portion of the orbitofrontal cortex has been associated particularly with the processing of negative emotions, commonly found to be altered in maltreated children (Northoff et al., 2000; Pollak et al., 2000). Furthermore, maltreatment has been attributed with heightened risk of major depression and conduct disorder, conditions characterised by atypical OFC structure (Bremner et al., 2002; Huebner et al., 2008; Lacerda et al., 2004; Narayan et al., 2007). Collectively these findings lead us to suggest that GMV aberrations within this region may contribute to impairments in emotional and social regulation in adolescence and later life.

The maltreated group also exhibited reduced grey matter volume in the left middle temporal gyrus. Meta-analyses have shown that grey matter reductions within the right MTL are more commonly found within maltreatment literature (Lim et al., 2014). However, the structure of the left middle temporal lobe is affected to a similar extent as the right MTL by early life stress in animal models (Jackowski et al., 2011). The middle temporal lobe has been reported as supporting lateralised characteristics of emotion processing; the left MTL is closely implicated with the processing of local and fine-grained aspects of emotional cues (Fusar-Poli et al., 2009; Kim & Hamann, 2007). While on the other-hand, the right MTL is reportedly involved in automatic processing of global aspects of emotional stimuli (Fusar-Poli et al., 2009; Kim & Hamann, 2007). Defects within these domains characterise a variety of psychiatric disorders (Etkin & Wager, 2007; Schneider, Gur, Gur, & Shtasel, 1995; Stuhrmann, Suslow, & Dannlowski, 2011). Atypical structure within either the left or right middle temporal lobe may represent compromised abilities in these separable functions of emotional processing. The finding of a reduction in grey matter volume within the left supramarginal gyrus, hasn't commonly been reported in the existing maltreatment literature (Lim et al., 2014). However, grey matter reductions within this region have been noted in behavioural disorders commonly associated with maltreatment (Greenwald, 2002; Huebner et al., 2008)

which may indicate deficiencies in particular processes common between the two groups.

Our primary aim of this investigation was to explore the influence of maltreatment characteristics on atypical grey matter volume within a maltreated sample. Using official substantiated reports to determine the occurrence of subtype, chronicity of abuse and severity of maltreatment, we investigated associations between these scores and raw grey matter values. Surprisingly, we found that there were no significant associations between GMV in regions of significant reduction or increase and any of the maltreatment dimensions. This is even more surprising given that self-reported accounts of childhood trauma were found to significantly correlate with GMV in the whole brain analysis of Sample 2. In addition, trauma symptomatology derived from the trauma symptom checklist for children did not significantly correlate with GMV values from any of the 7 regions of significant differences.

There are several possible considerations, which may help account for the lack of association between dimensions of maltreatment and atypical GMV. First, the official, substantiated reports of maltreatment may not provide a sensitive index of individual differences in maltreatment severity or chronicity. The use of case files obtained by child protection services in research has been criticised in the past for underestimating or wrongly classifying abuse (Gilbert, Kemp, et al., 2009; Runyan et al., 2005). The observable relationship between self-reported experiences of past trauma and grey matter volume within the supramarginal gyrus in Sample 2 but not when using information from official reports, would suggest that self-report measures of trauma may be more sensitive. Although, measures of maltreatment based on self-report are particularly susceptible to retrospective biases, therefore it is difficult to determine which measure represents a more reliable representation of the individual's trauma history (Hardt & Rutter, 2004). Second, there were no significant relationships between the self-report and official substantiated scales of maltreatment, both in total score and by subtype, which may suggest that they are tapping into markedly different constructs of maltreatment. It may be that perceptions of childhood trauma have a stronger relation to cortical structure than the objective experience of childhood maltreatment.

Limitations and future directions

The present findings should be interpreted in light of a number of limitations. First, the cross-sectional design of this study does not allow for causal interpretations to be made about the data. We cannot concretely say that the structural deficits in the maltreated group were the product of childhood experiences of maltreatment, for instance. Second, our measures of psychopathology relied on child and parent completed questionnaires rather than derived from a formal clinical psychiatric interview. Therefore, we cannot rule out the possibility that certain forms of psychiatric disorder were present in either group and went undetected. Third, as we recruited a non-clinical sample, we may have been underpowered to detect associations between GMV and psychiatric symptomatology, due to a restricted range in symptom severity below the clinical cut-off. Of course, this very limitation can also be viewed as a strength in terms the ability to attribute group differences to maltreatment rather than psychopathology. Last, a great amount of co-occurrence of abuse subtypes within this sample meant that it was not statistically legitimate to look at the influence of independent subtypes controlling for the other forms of maltreatment as much of the variance within the GMV would have been regressed out.

However this study was also characterised by a number of strengths. First, because the potential effects of age, sex, and IQ were controlled for in our design model, the observed group differences are unlikely to be due to these factors. Second, studies comparing and contrasting findings within similarly recruited samples are increasingly scarce in psychology and cognitive neuroscience and in recent years the topic of a 'replication crisis' has engulfed these disciplines. Replicating and contrasting a structural analysis of maltreatment has provided an important insight into possible heterogeneity of findings due to differences in maltreatment history. Last, this study represents a systematic whole brain exploration of maltreatment characteristics within a community sample of maltreated adolescents, representing novel evidence for the associations between maltreatment severity, grey matter volume and psychiatric symptomatology.

3.5. Conclusions

In the present chapter we described the first study, to our knowledge, to systematically investigate the influence of dimensions of maltreatment and the associations of psychopathology on grey matter volume within a community sample of maltreated adolescents. Furthermore we presented a comparison analysis

exploring the impact of maltreatment on grey matter volume within maltreated children compared to well-matched non-maltreated peers. Distinct findings in the comparison analysis were attributed to significantly different maltreatment histories between the two samples and underline the importance of documenting well-characterised childhood experiences of abuse in maltreatment in future research. Grey matter volume reductions within the right supramarginal gyrus of the maltreated group were significantly associated with both self-reported experiences of childhood trauma and parent-rated trauma symptomatology. An exploratory analysis found that the right supramarginal gyrus significantly mediated the relationship between childhood trauma and externalising symptomatology. Regions of significant grey matter reduction were also observed within the right middle temporal gyrus within Sample 2 and within the left supramarginal gyrus, left middle temporal gyrus and medial orbitofrontal gyrus of the maltreated group within the combined sample. Furthermore, two regions of grey matter increase were observed within the maltreated group compared to the non-maltreated peers; within the left precentral gyrus, and within the left occipital lobe in Sample 2. Investigation into the influence of maltreatment characteristics as measured by substantiated official reports were found not to be associated with any of the regions of grey matter reduction or increase. These findings were particularly surprising and contrary to our predictions.

These findings suggest that dimensions of maltreatment derived from subjective reports of trauma, as opposed to official reports, represent a dose-response relationship with certain localised regions of atypical grey matter volume within maltreated adolescences. Our findings also suggest that self-report measures represent a more sensitive index in estimating the impact of maltreatment characteristics on brain structure compared to social service records. We found tentative evidence that some of the GMV differences between maltreated and non-maltreated children are related to psychopathology symptoms and partly account for the association between maltreatment history and increased symptomatology. This suggests that the observed differences in grey matter volume in our community sample of maltreated adolescences may represent neural markers of aberrant emotional regulation, cognitive control and autobiographical memory; processes that are commonly disrupted in maltreated individuals and present a risk factor for later psychopathology. It remains to be seen whether some of the GMV differences implicated in our study, but which are currently not related to psychopathology

symptoms, will emerge as vulnerability factors for developing psychopathology at a later stage.

CHAPTER 4: An investigation of maltreatment characteristics and cortical structure using surface-based measures.

4.1. Introduction

The findings of the first empirical chapter (Chapter 2) established that maltreatment differentially impacts distinct cortical indices in addition to grey matter volume. It has been demonstrated that maltreated samples characterised by differential patterns of maltreatment experience present with variations in atypical structure across a number of regions (Chapter 3). Furthermore, it was demonstrated that cortical structure in selected regions may be associated with severity of childhood trauma and externalising behaviours in a dose-response manner. Investigations into the impact of maltreatment on discrete indices of cortical structural is sparse and underdeveloped, with a significant gap in our knowledge in how dimensions of maltreatment may influence these measures. The aim of the current chapter is to combine the thematic findings of the first two chapters and systematically investigate the influence of maltreatment characteristics on distinct surface-based measures of cortical structure.

The findings of Chapter 2, demonstrated that the investigation of the structural determinants of grey matter volume can better characterise the impact of maltreatment and the structural precursors to psychopathology later in life. As described in detail in the introduction of Chapter 2, these structural determinants, cortical thickness, surface area and local gyrification capture distinct evolutionary (Rakic, 1995), genetic (Panizzon et al., 2009; Raznahan et al., 2010) and cellular (Chenn & Walsh, 2002) processes (Raznahan et al., 2011). Previously observed group differences in volumetric analyses, such as in Chapter 3, may be attributed to alterations in surface-based measures of cortical structure (Mechelli, Friston, Frackowiak, & Price, 2005). Recent investigations into the structural representation of various clinical disorders have begun to employ both techniques of voxel-based and surface-based techniques (Jung et al., 2011; Labate et al., 2012; Lehmann et al., 2011; Palaniyappan & Liddle, 2012b).

Maltreatment characteristics

As discussed in depth in chapter 3, dimensions of maltreatment exert significant influence on behavioural outcomes associated with the experience of maltreatment during childhood. Subtype and severity of maltreatment have been of most interest

(Margolin & Gordis, 2000), with separable associations between subtypes and dose-response association with internalising and externalising symptomatology (Litrownik et al., 2005; Petrenko et al., 2012; Taussig, 2002). It may be hypothesized that certain dimensions of cortical structure are more sensitive to subtle variations in severity of adverse life events than others, maltreatment chronicity or distinct subtypes of abuse.

Psychiatric disorders

As briefly stated previously, surface morphology has been associated with a wide range of psychiatric disorders in, including depression (Lim et al., 2012; Mackin et al., 2013; Sheline et al., 2012), conduct disorder (Hyatt et al., 2012; Wallace et al., 2014) and anxiety disorders (Brühl et al., 2014; Frick et al., 2013). Adolescence represents a critical period in healthy development and a time in which many of these psychiatric disorders manifest (Paus, Keshavan, & Giedd, 2008; Uhlhaas & Singer, 2011, 2012). Adverse early life events increase the possibility of the emergence of a number of psychiatric disorders (e.g. Green et al., 2010; Kessler et al., 2010; Scott, Smith, & Ellis, 2010; Scott et al., 2011). By investigating individuals entering this developmental period and who have experienced adverse events in childhood, we may uncover vital clues about the emergence of many of these disorders.

Focussing on specific and precise measures of brain structure abnormalities has helped to better characterise and clarify discrepant findings within a number of psychiatric disorders. In particular, studies of cortical thickness in major depressive disorder, have characterised a pattern of thinning and thickening in medial frontal and temporal regions in adult (Lim et al., 2012; Mackin et al., 2013; van Eijndhoven et al., 2014) and adolescent samples (Fallucca et al., 2011; Reynolds et al., 2014). In relation to conduct disorder, for example, recent studies have demonstrated a consistent pattern of cortical thinning and local gyrification across the cortex, specifically in ventromedial frontal cortex and superior temporal cortices (Hyatt et al., 2012; Wallace et al., 2014).

Effects of stress on surface based measures

Experience exerts a substantial influence and organising effect on the development of the human brain (Elbert & Rockstroh, 2004). While structural adaptations may

serve to be initially adaptive and protective, they may represent neuro-anatomical substrates for the emergence of behavioural problems later in life. Here, I briefly consider related areas of research which have investigated exposure to extreme stress in adulthood (i.e. combat trauma) and associated post-traumatic stress disorders before focussing on investigations of experiences of childhood maltreatment, predominately in adult samples.

Combat trauma and PTSD

Combat veterans with concurrent PTSD display negative associations between symptom severity and cortical thickness in a number of regions including frontal and temporal regions (Corbo et al., 2014; Lindemer, Salat, Leritz, McGlinchey, & Milberg, 2013), specifically reductions in anterior cingulate cortex (Geuze et al., 2008). Atypical structure and function within these regions have been noted in wider PTSD populations (Dickie, Brunet, Akerib, & Armony, 2013; Rauch, Shin, & Phelps, 2006; Rauch et al., 2003; Woodward et al., 2006); the severity of the post-traumatic stress symptoms noticeably inversely associated with anterior cingulate volume (Woodward et al., 2006; Yamasue et al., 2003). Anomalous structure and function within this region is believed to underlie disruption to normative emotional regulation, due to dense connections between the anterior cingulate and both the amygdala and hippocampus (Phan, Wager, Taylor, & Liberzon, 2002). Corbo and colleagues examined the impact of early life trauma on these veterans and found that those who had experienced early adverse events displayed a positive relationship with cortical thickness in regions previously found to be associated with PTSD (Corbo et al., 2014). Consideration of an individual's experience of trauma across the lifespan therefore provides important contributory influence on the development of cortical structure.

Childhood maltreatment

A relatively sparse and underdeveloped literature exists for the investigation of childhood maltreatment and its impact of these separable indices of cortical structure. However a number of studies have made recent and valuable contributions to this area of research and suggest the need for further, more systematic, investigations.

Whittle and colleagues undertook an exploratory cortical thickness as part of a wider longitudinal study exploring the associations between childhood trauma and psychopathology on grey matter volume (Whittle et al., 2013). Interestingly, psychopathology at time point 2 significantly mediated the relationship between childhood maltreatment and a pattern of cortical thickening observed within the superior parietal cortex (Whittle et al., 2013). The concurrent VBM analysis did not detect structural variations within this region, highlighting the importance in diversifying the structural measures implemented in such investigations. Similar associations have been made between childhood trauma and structural alterations in the development of depression as childhood trauma scores of adults with a diagnosis of depression have been noted to be negatively associated with cortical thickness in frontal and temporal regions (Jaworska et al., 2014). Collectively, these studies underline the relevance of such structural measures in uncovering the pathways from childhood maltreatment to psychopathology.

Other investigations examining singular forms and subtypes of abuse, have observed cortical thinning within genital representation fields of the primary somatosensory cortex of sexually abused women (Heim, Mayberg, Mletzko, Nemeroff, & Pruessner, 2013) and cortical thickness reductions determined volumetric reductions within the lingual gyrus of women experienced domestic violence during childhood (Tomoda, Polcari, Anderson, & Teicher, 2012). Similarly, women reporting emotional abuse were found to show cortical thinning in anterior cingulate and precuneus regions which the authors suggested underlined disturbances in awareness and self-evaluation (Heim et al., 2013). The examination of duration of abuse on these cortical indices also provides critical clues to structural alterations associated with maltreatment. For instance, exposure to domestic violence during the ages of 11 to 12 and 12 to 13 was the most important predictor of thickness within the right lingual gyrus, over and above exposure at other ages (Tomoda et al., 2012). However, other investigations have found that duration of abuse was not significantly associated with cortical thickness changes, highlighting the potential heterogeneity in the conceptualisation of chronicity of abuse (Heim et al., 2013). Further investigations into the influence of duration of abuse are warranted to provide clarity in these divergent findings.

Following on from findings which show widespread reductions in cortical thickness across the cortex of institutionally reared children (McLaughlin et al,

2013); it has been proposed that surface area is a more prominent determinant of previously reported structural differences in institutionalised samples (Hodel et al., 2015). Furthermore, exploring chronicity, structural reductions were more prominent in individuals who had a discrete period of deprivation in early life compared to those who experienced more prolonged periods of deprivation (Hodel et al., 2015). While highlighting the relevance of chronicity in the associated atypical structure associated with abuse and neglect, this study also represents a growing trend of structural studies to report a number of indices in order to provide a better characterised picture of atypical structure associated with early life experiences.

The current study

The current study sought to tease apart the effects of maltreatment characteristics and psychiatric symptomatology on surface-based structural brain indices while controlling for the effects of IQ, pubertal status, SES and psychiatric symptoms. I investigated the following questions:

- 1) Is there a dose response relationship between maltreatment severity and the structural indices of cortical thickness, local gyrification index and surface area in regions associated with maltreatment experience?
- 2) Do individual forms of maltreatment show diverse associations within these cortical regions?
- 3) Does duration of abuse show distinct associations with cortical thickness, local gyrification index and surface area within these cortical regions?
- 4) Is there a dose response relationship between exposure to community violence and structural indices of cortical thickness, local gyrification and surface area within these cortical regions?
- 5) Is there an association between the structural indices and internalising/externalising symptoms within the maltreated sample?
- 6) Is any association between maltreatment experience and psychiatric symptoms mediated by the cortical differences in children with maltreatment?

In relation to the questions posed above, I hypothesised that i) there would be a dose response between maltreatment severity and structural indices of cortical

structure, cortical thickness, local gyrification index and surface area in regions associated with maltreatment exposure. However, in light of the findings of Chapter 3, I predicted that the self-report measure of maltreatment would represent a more sensitive measure tapping the experience of abuse and neglect and thus would show greater associations with structural indices. ii) Individual forms of maltreatment would show distinctive associations with structural indices in the regions targeted by the group differences analysis. iii) Increased duration of abuse would show distinctive associations with the separate measures of cortical structure within the targeted regions, due to differing developmental trajectories of these cortical indices. iv) Similar to the findings of Chapter 3, internalising and externalising symptoms would show significant associations with structural indices in regions associated with maltreatment. v) Certain structural indices will mediate the relationship between maltreatment exposure and externalising or internalising symptoms.

4.2. Methods

Analytic procedure

We sought to investigate the research questions in two steps and using two samples as before in Chapter 3.

Sample 1 comprised a group of maltreated (n=18) and non-maltreated (n=20) individuals recruited as part of an ESRC funded project between 2009 and 2012. This sample, including four maltreated and one non-maltreated participant, were used in Chapter 2. The participants included from Sample 1 in the combined sample were identical to those in Chapter 3 to aid in comparison between the volumetric and surface-based findings of this thesis. This sample did not have self-report measures of maltreatment experience and only data from social services records were available to estimate maltreatment characteristics.

Sample 2 comprised a group of maltreated (n=44) and non-maltreated (n=40) individuals recruited as part of an ESRC funded project between 2013 and 2014. This sample had self-report measures of maltreatment experience as well as data on maltreatment experience drawn from social services records.

Importantly, the maltreated groups of Sample 1 and Sample 2 differed significantly in their maltreatment history detailed in **Table 3.4**. Specifically, Sample 1 was characterised by a pattern of elevated severity and occurrence of physical abuse while Sample 2 was characterised by a pattern of elevated severity of neglect. The analytic procedure comprised two Steps as follows (see Figure 4.1):

Step 1 used Sample 2 only and involved three phases:

- i. identification of regions of atypical structure within the maltreated group compared to the non-maltreated peers. Initially the group analysis was constrained to regions of interest determined by the findings of Chapter. This was followed by a whole brain analysis of atypical cortical thickness and local gyrification index in the maltreated group. Group analysis of surface area was performed by parcellated gyral region.
- ii. investigation as to whether atypical structure within the maltreated group was associated with maltreatment severity (as measured by self report which was available for Sample 2 only).
- iii. investigation as to whether atypical structure within the maltreated group was associated with exposure to community violence (as measured by self-report which was available for Sample 2 only).
- iv. investigation as to whether atypical structure within the maltreated group was associated with measures of psychiatric symptomatology (as measured by parent report).
- v. investigation as to whether atypical structure within the maltreated group mediated the relationship between maltreatment severity and psychiatric symptomatology (This analysis was contingent on observable associations between maltreatment exposure, psychiatric symptomatology and structural indices).

Step 2 used Sample 1 and Sample 2 combined and involved three phases:

- i. identification of regions of atypical cortical thickness and local gyrification index in the maltreated group using a whole brain analysis. Group analysis of surface area was performed by parcellated gyral region.
- ii. investigation as to whether atypical structure within the maltreated group was associated with maltreatment severity, occurrence and duration (as

measured by data from social services records scored by the Kaufman scale)

- iii. investigation as to whether atypical structure within the maltreated group was associated with psychiatric symptomatology, (as measured by child report on the TSCC).
- iv. investigation as to whether atypical structure within the maltreated group mediated the relationship between maltreatment severity and psychiatric symptomatology (This analysis was contingent on observable associations between maltreatment exposure, psychiatric symptomatology and structural indices).

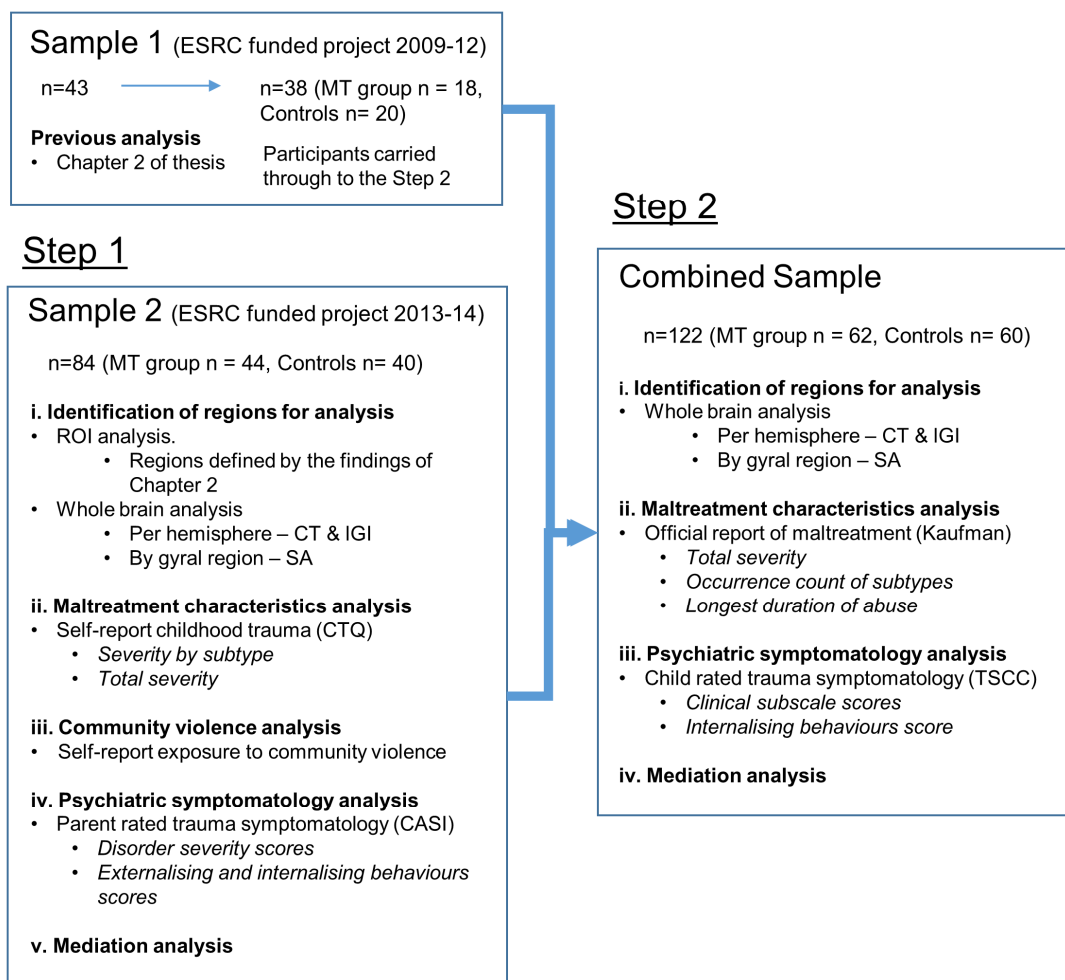


Figure 4.1. Schematic diagram of the analysis procedure for Chapter 4.

Notes: CT = cortical thickness. IGI = local gyrification index. SA = surface area.

Participants, measures, image acquisition and image pre-processing

Please see the methods section of Chapter 3 for information regarding the participants recruited, measures administered and the structural scanning parameters. The image pre-processing procedure was identical to what was described in the methods section of Chapter 2, however a newer version of FreeSurfer (v5.3.0; <http://surfer.nmr.harvard.edu>) was implemented. As the T1 images of participants included in Chapter 2 were pre-processed using an earlier version of FreeSurfer (v5.1.0), therefore these images were processed and analysed again using this newer version so the version of FreeSurfer and machine it was processed on was not a possible confounding factor in the interpretation of results across samples (Gronenschild, Habets, Jacobs, Mengelers, Rozendaal, Van Os, & Marcelis, 2012). We replicated the same pattern findings reported in Chapter 2 on the Sample 1 using the newer release of FreeSurfer.

Statistical analysis

Group differences between the maltreated group and the non-maltreated controls were assessed within the QDEC (query, design, estimate, contrast) application of FreeSurfer with two-sample t-test models. Cortical thickness measurements were smoothed with a full-width-at-half-maximum kernel of 15mm. Local gyrification index measurements were smoothed at 5mm and 0mm, due to IGI maps being inherently smooth (given that GI is calculated in a radius of 25mm). Excessive smoothing of the IGI data can contribute to the failure in computing Monte-Carlo null-z simulation to correct for multiple comparisons. Between group differences were corrected for multiple comparisons with a Monte Carlo z-field simulation at $p < 0.05$ (two-tailed). When regions of difference were found to be significant between the maltreated and non-maltreated groups, the mean structural value was extracted from the significant cluster in participant's native space.

These cortical thickness and local gyrification values were imported into SPSS v. 20 (IBM, Armonk, NY) to undertake further analysis to examine the relationship with maltreatment characteristics and psychiatric symptomatology as well as potentially confounding variables such as pubertal stage. Correlation matrices were used to examine associations between maltreatment characteristics and the extracted grey matter values.

Surface area was analysed at gyral level, based on the Desikan-Killiany parcellation atlas (Desikan et al., 2006), due to the surface area measure provided by FreeSurfer at a vertex level representing the extent the brain has to be stretched in order to fit into common space, and therefore not a genuine measure of surface area. The area values provided in the parcellation statistics files represent true estimates of area at the gyral level rather than a measure of areal expansion. Surface area values were extracted at a gyral level and inputted into SPSS. A mixed-model Analysis of Variance (ANOVA) was used to assess group differences in gyral level surface area across the whole cortex. Group (maltreated versus non-maltreated) was assigned as the between subject factor and both hemisphere (left versus right) and region (34 gyral regions) as the within-subject factors. Independent t-tests were used to examine group differences in gyral level cortical thickness. Due to the relatively large number of Independent t-tests, a false discovery-rate correction (Benjamini & Hochberg, 1995) was performed per hemisphere and per lobe to control for multiple comparisons. Those gyral regions that were identified as having significantly reduced or increased surface area values in the maltreated group compared to the non-maltreated peers were further investigated for associations with maltreatment experience and psychopathological symptoms within the maltreated group.

Cortical thickness, surface area, and local gyrification undergo dynamic changes during childhood and adolescence and are known to be influenced by gender, IQ and age (Giedd & Rapoport, 2010; Raznahan et al., 2011; Shaw et al., 2006). Although there were no significant group differences in age and sex, the models were re-ran with these variables and covariates of no interest and additional group comparisons were conducted within SPSS v.20 (IBM, Armonk, NY).

4.3. Results

Socio-demographic characteristics

The participants included within this chapter are comparable to the participants included in Chapter 3. As shown previously, within Sample 2, the maltreated group did not differ from the non-maltreated group in relation to sex, age, self-reported Tanner stage, handedness, IQ, SES and ethnicity (Table 3.1, Chapter 3). Similarly, the combined sample (Table 3.2, Chapter 3) did not differ on any of these previously

mention demographics and the maltreated and non-maltreated groups did not show differences in self-reported anxiety, depression and PTSD symptoms.

Group differences: Global measures of cortical structure

Within Sample 1, Sample 2 and the combined sample there were no group differences on measures of total intracranial volume as computed using the FreeSurfer pipeline (Table 4.1). Mean surface area across both hemispheres between the maltreated group and controls in Sample 1 was significantly greater in the control group compared to the maltreated group ($p = .04$; Table 4.1).

Table 4.1. Total intracranial volume (ICV) measurements between the maltreated and non-maltreated groups.

Sample 1					
	<i>Control (n = 20)</i>		<i>MT (n = 18)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Estimated ICV	1487211.0	120724.2	1418509.0	100928.5	0.07
Mean CT	2.66	0.11	2.62	0.07	0.18
Mean IGI	3.20	0.14	3.14	0.12	0.15
Mean surface area	2670.14	212.20	2537.08	174.16	0.04

Sample 2					
	<i>Control (n = 40)</i>		<i>MT (n = 44)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Estimated ICV	1475216.0	124246.9	1457313.4	122295.1	0.51
Mean CT	2.64	0.09	2.67	0.11	0.30
Mean IGI	3.16	0.11	3.19	0.12	0.33
Mean surface area	2635.16	245.56	2612.50	223.10	0.66

Combined Sample					
	<i>Control (n = 60)</i>		<i>MT (n = 62)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Estimated ICV	1479214.0	122189.4	1446047.6	117034.3	0.13
Mean CT	2.65	0.09	2.65	0.10	0.86
Mean IGI	3.18	0.12	3.17	0.12	0.94
Mean surface area	2646.82	233.75	2590.61	211.50	0.17

ICV: Intracranial volume; CT: cortical thickness; IGI: local gyrification index; All values were computed across both hemispheres. All p values derived from t-tests

Analytic procedure

The analytic procedure is illustrated in Figure 4.1 and the subsequent sections of the results follow the steps described in the aforementioned figure and the methods section.

Step 1

i. Identification of regions of atypical structure associated with maltreatment in Sample 2.

Regions of interests (ROI) were created from the significant group differences observed in Chapter 2, to examine whether these observable differences were replicated in Sample 2. Mean cortical thickness and local gyrification values were extracted from these ROIs and group differences were examined in SPSS. Furthermore, mean cortical thickness and local gyrification values were extracted from the parcellated regions in which the significant clusters detailed in Chapter 2 extended to account for spatial changes in maximal local differences.

Maltreatment histories of Sample 1 and Sample 2

As discussed in Chapter 3, the sample demographics and maltreatment histories were markedly different between the two samples (Table 3.4, Chapter 3). Briefly, Sample 1 had significantly more exposure to physical abuse than the sample 2 (44% vs. 7%) and the severity within those who experienced physical abuse was significantly greater ($p = 0.014$). Occurrences of neglect were similar between the two samples, however maltreated youth within sample 2 experienced a greater severity of neglect ($p = 0.04$; Table 3.4, Chapter 3).

Cortical thickness

ROI analysis

The mean cortical thickness values extracted from the rostral anterior cingulate cluster, observed in Chapter 2, between the maltreated ($M = 2.94$, $SD = .19$) and non-maltreated groups ($M = 2.98$, $SD = .18$) was not significantly different ($t(82) = .96$, $p = .34$). When mean cortical thickness was included in the model as a covariate, the groups were not significantly different ($F(2,81) = 2.98$, $p = .09$). Figure A.2 in the supplementary results plot the group differences within this region for Sample 1 and Sample 2. Exploration of group differences by parcellated region that the significant frontal cluster extended into (medial orbitofrontal cortex, superior frontal cortex, rostral ACC, caudal ACC and frontal pole), did not yield any significant results or trend level differences.

Whole brain analysis

The cortical thickness analysis identified one cluster, in the left hemisphere, that was increased within the maltreated group compares with the control subjects (Figure 4.2; Monte Carlo null-z simulation corrected $p < 0.05$). Annotation based on the Desikan-Killiany parcellation atlas (Desikan et al., 2006) of the group structural data indicated that the peak coordinate fell within the lateral occipital lobe (Table 4.2; $X = -30$, $Y = -91$, $Z = 10$) with the cluster extending into superior parietal cortex. No other significant clusters survived whole brain cluster correction in either hemisphere. Including age, sex and IQ as covariates of no interest in the model did not change the pattern of results and a significant cluster of increased cortical thickness in the left lateral occipital cortex was observed ($X = -30$, $Y = -92$, $Z = 10$; $\text{Max log}_{10} = -2.39$; $p_{\text{cluster}} < 0.005$; Area = 1172mm²).

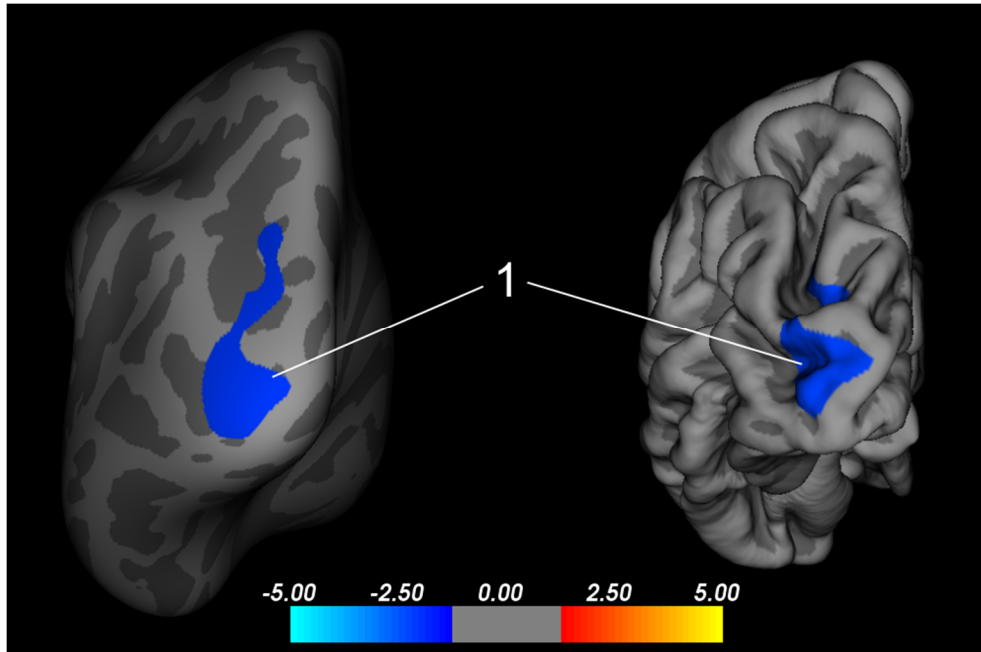


Figure 4.2. Cluster of significantly increased cortical thickness within the maltreated group of Sample 2.

Notes: Relative increase of cortical thickness in the maltreated sample compared to non-maltreated peers within a cluster covering the left superior parietal and lateral occipital regions ($X = -30$, $Y = -91$, $Z = 10$; $p_{cluster} < 0.005$; Area = 1128mm^2). Cluster has been corrected for multiple comparisons with Monte Carlo null-z simulation ($p < 0.05$). The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster labels (numbers) correspond with those provided in Table 4.2.

Local gyrification

ROI analysis

The mean local gyrification values extracted from the significant insula cluster, seen in Chapter 2, between the maltreated ($M = 4.98$, $SD = .37$) and non-maltreated groups ($M = 4.87$, $SD = .33$) was not significantly different ($t(82) = -1.47$, $p = .15$). Similarly, the mean local gyrification values extracted from the significant lingual cluster, were not significantly different ($t(82) = -.73$, $p = .47$) between the maltreated ($M = 3.12$, $SD = .21$) and non-maltreated groups ($M = 3.09$, $SD = .21$). Including mean local gyrification index across the cortex as a covariate did not affect the significance in the insula cluster ($F(2,81) = 1.16$, $p = .28$) or the lingual gyrus cluster ($F(2,81) = .014$, $p = .91$). Figure A.3 and Figure A.4 of the supplementary results display the group differences within these ROIs for Sample 1 and Sample 2. Exploring the mean local gyrification values by the constituent parcellated regions of the two significant local gyrification clusters, none of the 12 regions investigated displayed significant differences between the maltreated and non-maltreated groups.

Whole brain analysis

The local gyrification analysis identified three significant clusters, two clusters within the left hemisphere and one cluster within the right hemisphere with increased surface area within the maltreated group compared to the control subjects (Figure 4.3 and Figure 4.4). These clusters survived Monte Carlo null-z simulation ($p < 0.05$). The first cluster within the left hemisphere (Figure 4.3, cluster 2), was observed to contain its peak within the insula cortex (Table 4.2; $X = -34$, $Y = 13$, $Z = -3$) extending slightly into the pars triangularis based on annotation from the Desikan-Killiany atlas (Desikan et al., 2006). The second cluster (Figure 4.3, cluster 3) within the left hemisphere, extended across the fusiform gyrus and into parahippocampal gyrus with the peak located within the parahippocampal gyrus on the border with fusiform gyrus (Table 4.2; $X = -35$, $Y = -23$, $Z = -23$). The cluster of significant increase in local gyrification within the right hemisphere (Figure 4.4, cluster 4) was located within the superior parietal cortex (Table 4.2; $X = 24$, $Y = -78$, $Z = 28$). Table 4.2 summarises the cluster statistics for both the cortical thickness and local gyrification statistics for Sample 2. The same patterns of significant results, with slightly reduced cluster extents, were observed when including age, sex and IQ as covariates of no interest in the statistical model.

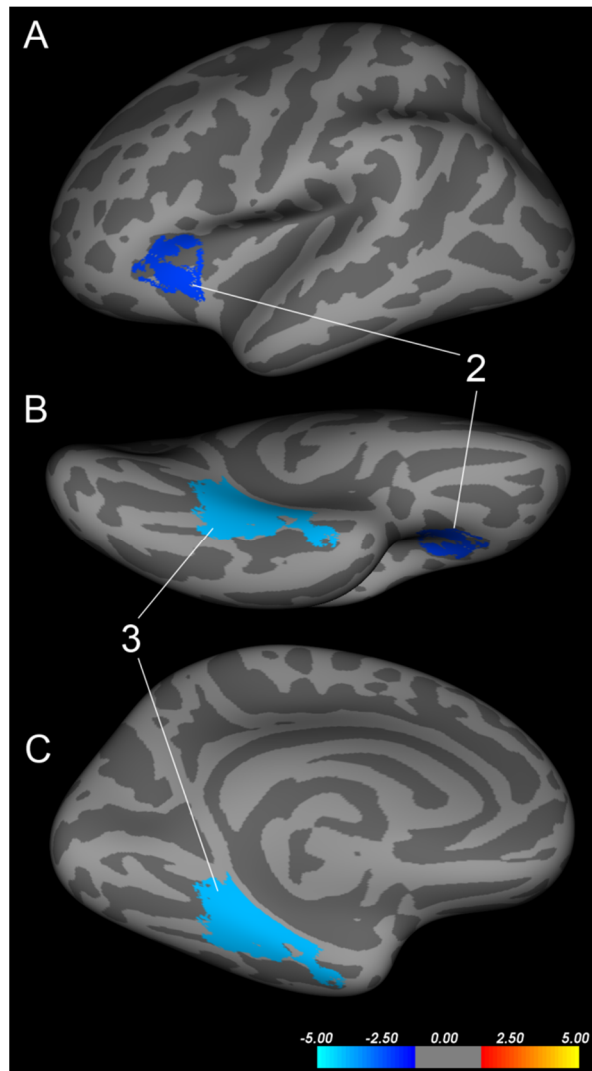


Figure 4.3. Clusters of significantly increased local gyrification index within the maltreated group of Sample 2.

Notes: Significantly increased local gyrification clusters within the left hemisphere projected onto an inflated surface. The maltreated group shows relative increases in local gyrification index in the compared to non-maltreated peers within cluster 2 covering the fusiform gyrus and parahippocampal gyrus ($X = X = -35, Y = -23, Z = -23; p_{cluster} < 0.001; \text{Area} = 1489\text{mm}^2$) and cluster 3 located within the insula ($X = -34, Y = 13, Z = -3; p_{cluster} = 0.005; \text{Area} = 624\text{mm}^2$). Cluster has been corrected for multiple comparisons with Monte Carlo null-z simulation ($p < 0.05$). The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster labels (numbers) correspond with those provided in Table 4.2.

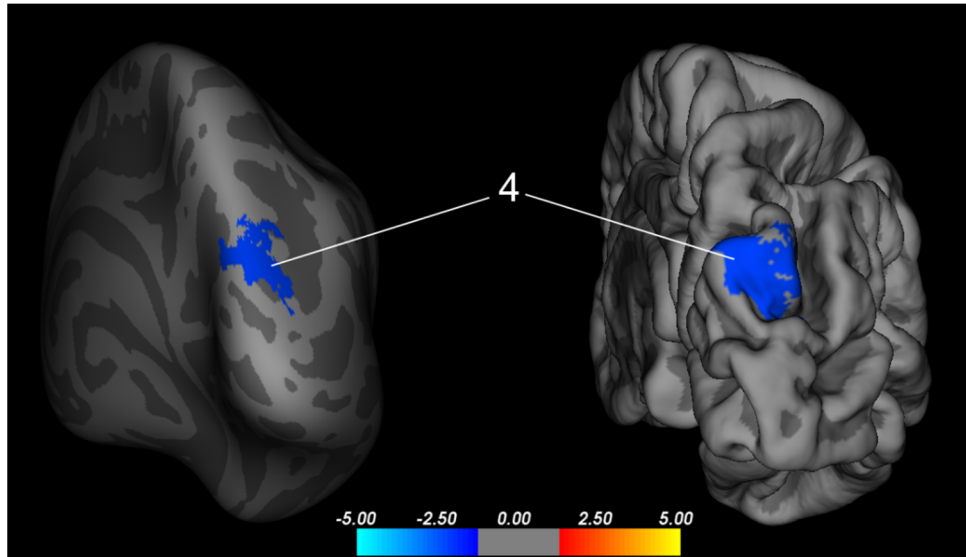


Figure 4.4. Cluster of significantly increased local gyrification index within the maltreated group of Sample 2.

Notes: Significantly increased local gyrification cluster within the right hemisphere projected onto an inflated surface. Cluster 4 shows relative increases of local gyrification in the maltreated sample compared to non-maltreated peers within a cluster located within the superior parietal cortex ($X = 24, Y = -78, Z = 28$; $p_{cluster} = 0.005$; Area = 637mm^2). Cluster has been corrected for multiple comparisons with Monte Carlo null-z simulation ($p < 0.05$). The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster labels (numbers) correspond with those provided in Table 4.2.

Table 4.2. Significant clusters for cortical thickness and local gyrification within Sample 2. Corrected for multiple comparisons.

	Cluster no.	L/R	max- log ₁₀	$P_{cluster}^a$	Area (mm ²)	Local Maxima (X, Y, Z)		
Cortical thickness								
<i>Control > Maltreated</i>								
Lateral occipital / Superior parietal	1	L	-2.26	0.005	1128.6	-30	-91	10
Local gyrification								
<i>Control > Maltreated</i>								
Insula	2	L	-2.26	0.0055	624.71	-34	13	-3
Parahippocampal gyrus / Fusiform gyrus	3	L	-4	<0.001	1489.3	-35	-23	-23
Superior parietal	4	R	-2.26	0.005	637.98	14	-83	31

L=left; R=right; ^a Cluster probability

Surface Area

Surface area values were extracted by gyral region and analysed in SPSS. Group wise comparisons were performed limited to the a-priori regions used within the gyral-region based analysis in Chapter 2 (Lingual gyrus, middle temporal, superior temporal, inferior temporal, lateral orbitofrontal, insula, entorhinal cortex, parahippocampal, superior frontal, pars opercularis, temporal pole, medial orbitofrontal and rostral anterior cingulate). No significant group differences were observed between the maltreated group and the non-maltreated peers both at a false discovery-rate correction and uncorrected level.

Analysis across the whole cortex

There was no main effect of group on surface area ($F(1,82) = .196, p = .66$), neither was there an interaction between group and gyral region ($F(33,50) = 1.08, p = .369$) or a three way interaction among group, gyral region and hemisphere ($F(33,50) = .704, p = 7.63$). Independent t-tests found that one gyral region, within the left isthmus cingulate region had significantly more surface area within the maltreated group compared to the non-maltreated peers at an uncorrected level and when corrected for multiple comparisons by lobar region ($t = -2.93, p = <.005$). When correcting for multiple comparisons across the 34 gyral regions, surface area differences between the groups in the isthmus cingulate did not reach the adjusted critical value. The mixed-model ANOVA was re-run with age and gender as covariates, given the influence of age and IQ on cortical development (Shaw et al., 2006; Shaw et al., 2008). The addition of these covariates did not alter the gyral level results (the p values remained below the critical value).

ii. Associations between structural indices and maltreatment characteristics

Mean cortical thickness and local gyrification values were extracted from clusters of significant difference between the maltreated and non-maltreated groups and imported into SPSS for secondary analysis to explore the associations with maltreatment characteristics and symptomatology. The mean surface area values of the one area that represented a significant increase within the maltreated group compared to the non-maltreated group corrected at a lobar level, the isthmus cingulate, were carried through for exploratory secondary analysis. Interpretations of

potential associations between mean surface area values in this region and maltreatment characteristics and symptomatology should be considered in the light that this region did not reach significance when FDR corrected for multiple comparisons across the 33 gyral regions by hemisphere.

Correlations with self-reported measure of abuse

The descriptive statistics of the self-reported experience of maltreatment within the maltreated group of sample 2 are displayed in Table 3.5, Chapter 3. No correlations between total CTQ scores and extracted local gyrification and cortical thickness values were observed. However a positive association between local gyrification values within the insula and self-reported emotional neglect ($r = .31$, $p = .038$, Figure 4.5) and sexual abuse ($r = .31$, $p = .046$) was found. None of the remaining regions of local gyrification increase, nor the cluster of cortical thickness increase, correlated significantly with self-reported reports of abuse.

To ascertain whether the bivariate correlations were artificially inflated by outliers, Cook's distance analysis for outliers was used on these associations. Although sexual abuse was positively correlated with local gyrification values within the Insula, this association was driven by four participants and Cooks distance scores exceeded the commonly accepted cut-off value of 1. Individual Cook's distance scores for all the included participants in the association between local gyrification values within the left Insula and Emotional neglect scores derived from the CTQ did not reach a significant cut-off (none were greater than 0.24). Excluding the three participants with the largest cooks distance scores (range = 0.24 – 0.13) did not change the pattern or significance of results.

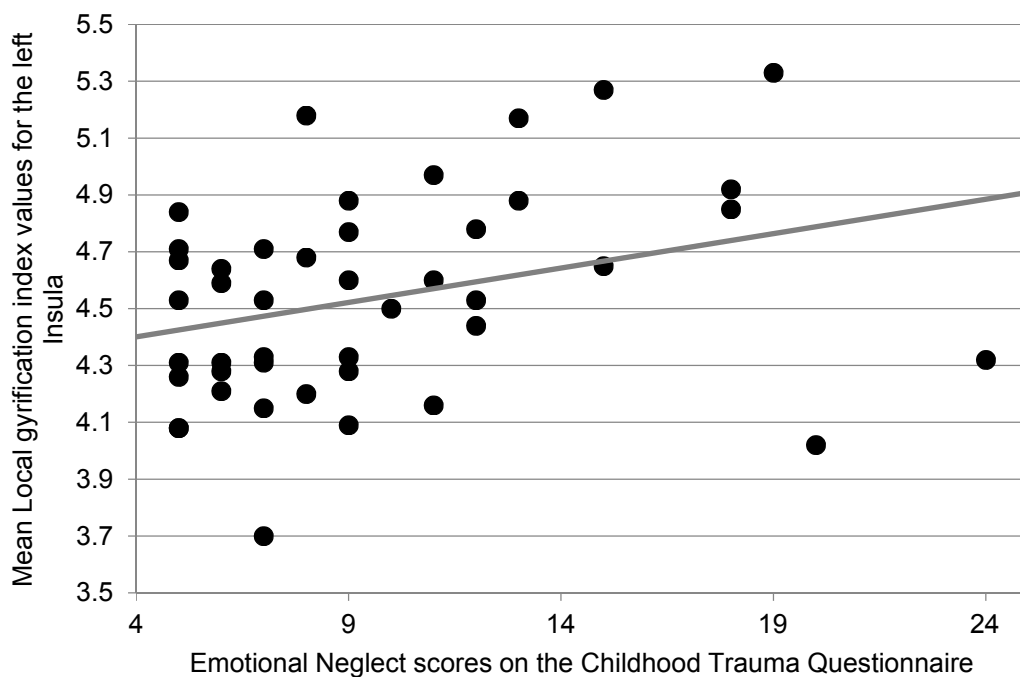


Figure 4.5. Correlation between mean local gyrfication values within the left Insula cortex of the maltreated group in sample 2 and Emotional neglect scores on the self-report Childhood Trauma questionnaire ($r = .313, p = .038$).

iii. Associations between structural indices and exposure to community violence

Mean cortical values extracted from the significant clusters of increased cortical thickness and local gyrfication index were not significantly associated with the total exposure to community violence score, nor with the composite scores of familiar or stranger community violence scores (Table 4.3)

Table 4.3. Correlation table between mean cortical values and self-report scores of exposure to community violence.

	CREV		
	Total	Stranger	Familiar
Cortical Thickness			
Lateral occipital / Superior parietal	-0.18	-0.12	-0.20
Local Gyrfication			
Insula cortex	-0.06	-0.17	0.01
Parahippocampal /Fusiform gyrus	0.05	0.16	-0.08
Superior Parietal	0.08	0.04	0.17

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

iv. Associations between structural indices and psychiatric symptomatology.

There were no significant associations between mean cortical thickness, local gyrification or surface area values and internalising and externalising composite scores from the CASI (Table 4.4). Exploring the associations between the mean values of these cortical indices within significant regions of group differences and individual psychiatric disorder severity as measured by the CASI, it was found that there were no significant associations.

Table 4.4. Correlations between mean cortical values in the maltreated group and measures of psychopathological symptomatology.

	Internalising composite score	Externalising composite score
Cortical Thickness		
Lateral occipital / Superior parietal	-0.141	-0.116
Local Gyrification		
Insula cortex	0.117	0.26
Parahippocampal /Fusiform gyrus	-0.027	-0.118
Superior Parietal	-0.154	-0.158

*p<0.05, **p<0.01, ***p<0.001

v. Mediation analyses

Self-report measures of maltreatment severity and psychiatric symptomatology did not significantly correlate, nor did any of the structural indices and psychiatric symptomatology, therefore an exploratory mediation analysis involving atypical structure within the maltreated group was not undertaken.

Step 2

- i. *Identification of regions of atypical structure associated with maltreatment.*

Sample 1 and 2 combined: Group differences

Participants from Sample 1 and Sample 2 were combined to examine group differences within a community sample presenting with a diverse experience of subtypes of childhood maltreatment. Whole brain analyses as illustrated in Figure 4.1 were applied to the combined sample.

Cortical thickness

ROI analysis

Extracting the mean cortical thickness values from the ROI representing the significant right hemisphere rostral anterior cingulate cluster shown in chapter 2 (Figure 2.1), there was a significant group difference ($t(120) = 2.92, p = .004$) between the maltreated ($M = 2.93, SD = .18$) and non-maltreated group ($M = 3.02, SD = .16$). This significant difference remained when mean cortical thickness across the cortex was included as a covariate of no interest to the statistical model ($F(2,119) = 12.76, p = .001$).

Whole brain analysis

The maltreated group was observed to have significantly reduced cortical thickness in one cluster in the right hemisphere compared with the non-maltreated control group (Figure 4.6, Cluster 6; Monte Carlo null-z simulation corrected $p < .05$). Annotation, on the basis of the Desikan-Killiany atlas (Desikan et al., 2006), of the group structural data indicated that the peak fell within the rostral anterior cingulate cortex (Table 4.5, Cluster 6; $X = 8, Y = 35, Z = -4$) with the cluster extending into orbitofrontal cortex and anteriorly across the superior frontal cortex. No other significant clusters survived whole brain cluster correction. This significant cluster within the combined sample group analysis overlaps considerably with the cluster of significant cortical thickness reduction reported in Chapter 2 within Sample 2. As shown in Table 4.5, the extent of the cluster is reduced; however the peak coordinate has remained the same. Including age, sex and IQ in the statistical model as covariates of no interest did not change the vertex level results in

significance ($X = 8, Y = 37, Z = -4$; $\text{Max log}_{10} = 3.10$; $p_{\text{cluster}} < .001$; Area = 1458mm^2) and the cluster extent was only slightly reduced while still extending into the same cortical regions.

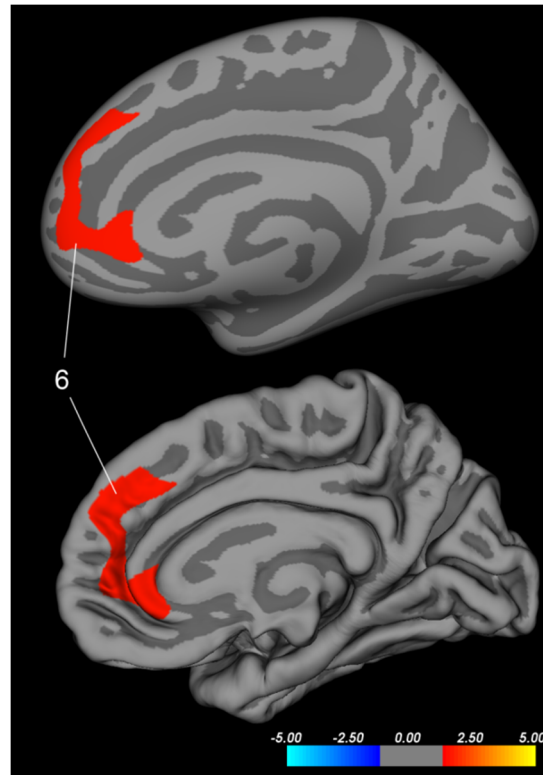


Figure 4.6. Cluster of significantly reduced cortical thickness within the maltreated group of the combined sample.

Notes: Significantly cortical thickness cluster in the combined sample analysis projected onto the inflated and pial surface in medial view. The maltreated group displayed significantly reduced cortical thickness within cluster 6. The peak fell within the rostral anterior cingulate cortex ($X = 8, Y = 35, Z = -4$) with the cluster extending into orbitofrontal cortex and anteriorly across the superior frontal cortex. The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster statistics are shown in Table 4.5.

Local Gyrification

ROI analysis

The mean local gyrification values from the significant clusters found in Sample 1, were not significantly different between the maltreated and non-maltreated groups in neither the insula ($t(120) = -.19, p = .99$) or lingual gyrus ($t(120) = .57, p = .57$) clusters. This pattern of non-significant results remained when including mean local gyrification across the whole cortex as a covariate in both the insula ($F(2,119) = .01, p = .91$) and lingual gyrus ($F(2,119) = .64, p = .43$) clusters.

Whole brain analysis

The local gyrification analysis within the combined sample identified one significant cluster of increased local gyrification within the left hemisphere within the maltreated group compared with the non-maltreated control subjects (Figure 4.7, Cluster 7; Monte Carlo null-z simulation corrected $p < .05$). The significant cluster's peak was identified within the superior parietal cortex (**Table 4.5**, Cluster 7, $X = -25$, $Y = -58$, $Z = -53$) with the cluster extending into inferior parietal cortex. Including age, sex and IQ as nuisance factors did not change the vertex wide results. Including age, sex and IQ as covariates of no interest in the statistical model did not significantly change the vertex wise results ($X = -21$, $Y = -79$, $Z = -37$; $\max\text{-log}_{10} = -2.01$; $p_{\text{cluster}} = .01$; Area = 416mm²), however the cluster extent was reduced and the local maxima was relocated within the superior parietal cortex. **Table 4.5** summarises cluster statistics for both cortical thickness and local gyrification analyses.

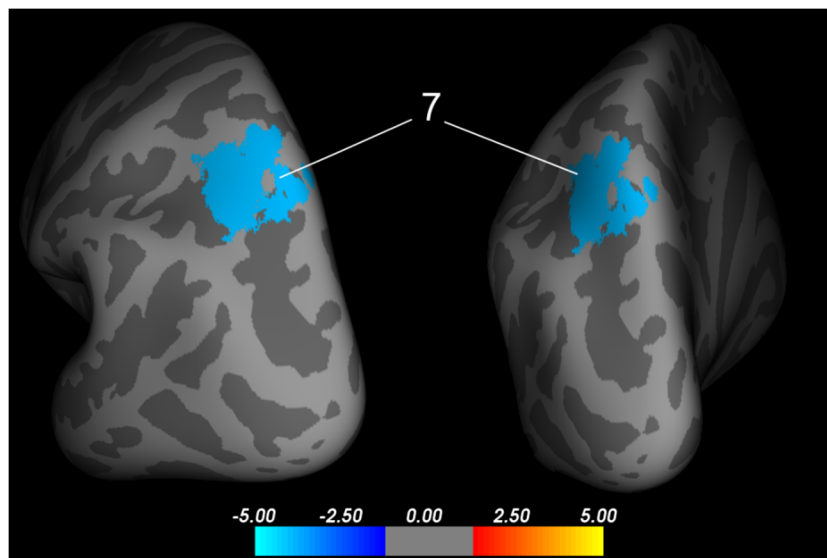


Figure 4.7. Cluster of significantly increased local gyrification within the maltreated group of the combined sample.

*Notes: Significant local gyrification index cluster in the combined sample analysis projected onto the inflated in posterior views. The maltreated group displayed significantly increased cortical folding within cluster 7. The peak fell within the superior parietal cortex ($X = -25$, $Y = -58$, $Z = -53$) with the cluster extending into inferior parietal cortex. The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster statistics are shown in **Table 4.5**.*

Table 4.5. Significant clusters for cortical thickness and local gyrification within the combined sample, corrected for multiple comparisons.

	Cluster no.	L/R	max-log ₁₀	P _{cluster} ^a	Area (mm ²)	Local Maxima (X, Y, Z)		
Cortical thickness								
<i>Control > Maltreated</i>								
Rostral ACC / Superior frontal	6	R	3.4	0.0004	1579.5	8	35	-4
Local gyrification								
<i>Control < Maltreated</i>								
Superior parietal	7	L	-4	0.0001	1128.8	-25	-58	-53

L=left; R=right; ^a Cluster probability

Surface area

There was no main effect of group on surface area ($F(1,118) = 0.19, p = .17$), neither was there an interaction between group and gyral region ($F(33,88) = 1.92, p = .08$) nor a three way interaction among group, gyral region and hemisphere ($F(33,88) = 1.00, p = .45$). Independent t-tests per gyral region found that bilateral Entorhinal cortex, supramarginal gyrus and right inferior parietal cortex displayed significantly reduced surface area in the maltreated group compared to control non-maltreated subjects. The surface area reduction within the right inferior parietal cortex was the only region to survive FDR correction for multiple comparisons by lobar region ($t = 2.26, p < .005$). No regions of decreased surface area survived FDR correction for multiple comparisons across the 33 gyral regions. Running Individual one –way ANOVAs with age, sex and IQ as covariates did not change gyral level results and those regions specified previously did not change in significance and no new regions were identified as significantly different between the groups.

Possible influence of Conduct Problems and Hyperactivity

In order to investigate whether group differences in conduct problems or hyperactivity symptoms might account for our observed differences in cortical thickness, local gyrification or surface area, correlations were performed between extracted mean values across these cortical indices, and conduct problem and hyperactivity scores. There were no observed significant correlations between conduct problem and hyperactivity scores and any of the mean extracted cortical values. Consequently, conduct problems and hyperactivity symptoms were not included as covariates in the main analysis. As specified in Chapter 2 and 3, a strong case has also been made that when participants are not randomly assigned

to groups, it is inappropriate to co-vary for variables intrinsically related to group assignment (Miller & Chapman, 2001).

ii. Associations between structural indices and maltreatment characteristics

Maltreatment characteristics

Characteristics of the combined sample's maltreatment histories have been previously described in Chapter 3 (Table 9). The associations between areas of significant group differences across the three cortical indices and dimensions of maltreatment, severity, duration and occurrence, were investigated. There were no significant associations between mean values of these cortical indices and the total scores within the dimensions of severity, occurrence and duration of abuse (Table 4.6). Associations between mean cortical values and the dimensions of severity and duration of abuse were investigated by subtype, however no significant associations were observed.

Table 4.6. Correlations between the mean cortical values across the three structural indices, and maltreatment characteristics.

	Hemisphere (L/R)	Total occurrence	Total severity	Longest duration of abuse
Cortical thickness				
<i>Control > Maltreated</i>				
Rostral ACC /Superior frontal	R	-0.13	0.02	0.22
Local gyrification				
<i>Control < Maltreated</i>				
Superior parietal	L	0.18	0.09	-0.07

*p<0.05, **p<0.01, ***p<0.001

iii. Associations between structural indices and psychiatric symptomatology.

Associations between trauma symptom scores derived from the Trauma Symptom Checklist for Children (TSCC;(Briere, 1996) and the regions of significant difference between the maltreated and non-maltreated groups across the three cortical indices were examined. Across the 6 subscales of the TSCC and the composite internalising score, there were no significant associations with mean cortical values in any significant regions of discrete structural indices.

iv. Mediation analyses.

No mediation analyses were conducted given the lack of associations between maltreatment characteristics, psychiatric symptomatology and atypical structure, exploratory mediation analyses were not undertaken.

4.4. Discussion

The current study sought to tease apart the effects of maltreatment characteristics and psychiatric symptomatology on surface-based structural brain indices while controlling for the effects of IQ, pubertal status, SES and psychiatric symptoms. Using the analytic procedure illustrated in Figure 4.1, I investigated the following questions:

- 1) Is there a dose response relationship between maltreatment severity and the structural indices of cortical thickness, local gyrification index and surface area in regions associated with maltreatment experience?
- 2) Do individual forms of maltreatment show diverse associations within these cortical regions?
- 3) Does duration of abuse show distinct associations with cortical thickness, local gyrification index and surface area within these cortical regions?
- 4) Is there a dose response relationship between exposure to community violence and structural indices of cortical thickness, local gyrification and surface area within these cortical regions?

- 5) Is there an association between the structural indices and internalising/externalising symptoms within the maltreated sample?
- 6) Is any association between maltreatment experience and psychiatric symptoms mediated by the cortical differences in children with maltreatment?

The initial identification of atypical regions of cortical structure within the maltreated group in Step 1 (Figure 4.1) found increased cortical thickness in an extended cluster that incorporated lateral occipital and superior parietal regions. In addition, increased local gyrification index was observed in a region of left insula, a cluster extending across left parahippocampal and fusiform gyrus and right superior parietal cortex. Surface area differences between the maltreated and non-maltreated group did not reach significance after correction for multiple comparisons. Our findings indicated that only local gyrification index within the left insula cortex was significantly positively correlated with maltreatment severity, in particular only severity of emotional neglect. No other regions of atypical structure within the maltreated group were found to be associated with maltreatment severity. Furthermore, psychiatric symptomatology was not significantly associated with structural indices within any of the regions of atypical structure.

In step 2, combining Samples 1 and 2 (Figure 4.1), the maltreated group was found to display reduced cortical thickness within an extended cluster that incorporated anterior cingulate cortex, superior frontal gyrus and orbitofrontal cortex. Local gyrification increase within the maltreated group compared to the non-maltreated peers was observed within left superior parietal cortex. Surface area differences between the groups again did not survive correction for multiple comparisons. Analysis of associations between structural indices in these regions of atypical structure and maltreatment characteristics indicated that the measures of maltreatment severity, occurrence or duration of abuse were not significantly associated with the structural measures. Psychiatric symptomatology also was found to not be significantly associated with structural indices within any of these regions of atypical structure.

Step 1: Investigation of the associations between maltreatment characteristics, psychiatric symptomatology and surface-based measures within Sample 2.

The first aim of the current analysis was to identify regions of atypical structure within the maltreated group compared to the well-matched non-maltreated peers in order to constrain the analysis of the associations between cortical structure, maltreatment characteristics and psychiatric symptomatology. ROIs created from the significant clusters reported in the group analysis of Chapter 2, initially constrained the group analysis, however we did not detect significant differences across the three structural indices within these ROIs. A trend level for cortical thickness decrease in the frontal ROI, when accounting for mean cortical thickness, was observed for the maltreated group. This finding may suggest that this region is commonly associated with the generic experience of abuse but the structural changes are particularly sensitive to more severe forms of abuse, a characteristic evident in the maltreated group of Sample 1. The investigation of the group differences in the local gyrification index cluster of the left insula presented opposing directions of change between the two samples: observed decreases in Sample 1 but increases in Sample 2. One possibility is that the differing maltreatment histories of the two samples, a greater preponderance of neglect or physical abuse, may be exerting different influences on gyrification. Interestingly, discrepancies have also been observed in the behavioural literature in which neglect and physical abuse are related to opposing patterns of atypical emotional face recognition (Pollak et al., 2000). A more mundane, but likely possibility, however, is that these differences may be due to sampling the natural variance in cortical folding in the control groups. Plotting the group differences by sample (as shown in supplementary Figure A.3), supports this view, suggesting that variation within the control sample may complicate the interpretation of findings.

The whole brain analysis of Sample 2 presented a different pattern of atypical structure to those reported for Sample 1 (Chapter 2).

Cortical Thickness: There is a scarce amount of literature exploring the impact of childhood maltreatment on cortical thickness, therefore comparison of our findings with the existing literature is limited. The finding of increased cortical thickness within a cluster of the lateral occipital cortex extending into aspects of superior parietal cortex is of interest as other researchers have made links between maltreatment and structural alterations to the superior parietal cortex (Edmiston et

al., 2011; Irle, Lange, & Sachsse, 2005). Psychopathology has also been found to significantly mediate the relationship between childhood maltreatment and cortical thickening in the superior parietal region across adolescence (Whittle et al., 2013). The superior parietal cortex has been closely linked with the processing of autobiographical memories as part of the tempo-parietal network (Wagner, Shannon, Kahn, & Buckner, 2005); a domain that maltreated individuals with psychiatric disorders are commonly found to possess deficits in (Anda et al., 2006). Concurrently, grey matter alterations have been found in the occipital cortices of adult women who have had childhood experiences of sexual abuse (Tomoda, Navalta, et al., 2009) and victims of intimate partner violence (Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002); albeit in an opposing direction of change. Tomoda and colleagues posited that structural differences within this region are an adaptation to attenuate the development of sensory pathways relaying recurrent aversive or traumatic experiences (Teicher, Tomoda, & Andersen, 2006; Tomoda, Navalta, et al., 2009). This hypothesis could similarly apply to our current maltreated sample, in which structural changes within this region may confer an adaptation specific to the abuse experienced; neglect characterised by sensory and affective deprivation, effectively amplifies sensory pathways to potential sensory stimuli, observed as structural increases.

Local gyrification: the pattern of local gyrification index increases within the maltreated group of Sample 2 contrast markedly with the pattern of relative IGI decreases in Sample 1. The first left hemisphere cluster fell within the insula cortex which forms part of a salience network, detecting environmental threat and integrating perceptual decisions about pain, as well as playing a key role in the empathic perception of emotional states (Carlson et al., 2011; Paulus & Stein, 2006; Pichon et al., 2011; Wiech et al., 2010). Interestingly, secondary investigations found that self-report emotional neglect scores was positively associated with mean local gyrification index values extracted from this region in the maltreated group. While structural alterations in this region may very well be sensitive to subjective reports of childhood neglect, the supplementary figure (Figure A.3) suggests that the opposing patterns of structural change between the samples are very likely due to variation within the control group and as such it is difficult to determine whether this region is sensitive to these maltreatment experiences over above other regions.

A second cluster of increased local gyrification index fell within the parahippocampal gyrus extending into the fusiform gyrus. Within healthy individuals,

the parahippocampal gyrus, a region of the limbic system, has a role in memory consolidation and social communication cues (Goldin, Manber, Hakimi, Canli, & Gross, 2009), whereas the fusiform gyrus is strongly linked with the effective processing of facial stimuli (Kanwisher, McDermott, & Chun, 1997; Sergent, Ohta, & Macdonald, 1992). Strong connections between these two structures have been proposed to underlie the structural basis for the integration of internal and external environments (Powell et al., 2004). Clinical studies exploring cortical structure have identified increases in parahippocampal/fusiform gyrus volume in social anxiety disorders (Talati, Pantazatos, Schneier, Weissman, & Hirsch, 2013) and increased parahippocampal gyrification in first episode schizophrenia (Schultz, Koch, Wagner, Roebel, Nenadic, et al., 2010; Schultz, Koch, Wagner, Roebel, Schachtzabel, et al., 2010). The emergence of both disorders have been closely associated with the experience of childhood maltreatment (Bruce, Heimberg, Blanco, Schneier, & Liebowitz, 2012; Varese et al., 2012). Social anxiety is highly prevalent in psychosis (Pallanti, Quercioli, & Hollander, 2004), and it has been suggested that it is not an epiphenomenon, but may pre-date or emerge concurrent with psychosis (Michail & Birchwood, 2009). Atypical structure within this regions may support a common underlying construct, such as the processing of internal versus external representations (Kapur, 2003; Mansell, Clark, & Ehlers, 2003), common to both of these disorders. Therefore we hypothesise that atypical gyrification within the maltreated sample may pose a risk factor for the emergence of these psychiatric disorders in later life.

Surface area: Our findings one parcellated cortical region to be significantly different in cortical surface area between the maltreated and non-maltreated groups, the left isthmus cingulate cortex. However this group difference did not survive correction for multiple comparisons. Limiting the analysis to regions that were previously found to be have significantly reduced surface area in Sample 1 (Chapter 2), we did not find a similar pattern of significantly reduced surface area, rather there were no regions that were found to be significantly different between groups.

Step 2: Investigation of the associations between maltreatment characteristics, psychiatric symptomatology and surface-based measures within a combined sample of maltreated adolescents.

The second step on the analysis within this empirical chapter (Figure 4.1) involved the combination of Samples 1 and 2 to identify regions to focus the subsequent

analyses into associations between brain structure, maltreatment characteristics and psychiatric symptomatology.

Cortical thickness: The cluster of cortical thickness decrease observed in the group comparison of the combined sample was consistent with the findings of reduced cortical thickness in a near identical cluster as detailed within Chapter 2. The replication of this finding within a combined sample of maltreated individuals with diverse experiences of childhood maltreatment may suggest that this is a cortical region commonly responsive to experiences of abuse and neglect. Trend level differences within the ROI analysis of the frontal cluster of Sample 2, however could indicate that this region is more sensitive to severe forms of abusive acts of commission such as physical abuse compared to neglect; heightened levels of these types of abuse characterised Samples 1 and 2 respectively. The finding of atypical structure within this frontal region is consistent with animal models of stress detailing a causal relationship between early environmental stress and structural alterations (Arnsten, 2009). As detailed in the conclusion of Chapter 2, the anterior cingulate, medial OFC and the superior frontal gyrus have been found to be associated with a number of cognitive processes in the typical population, collectively, emotional regulation and flexibility (Etkin et al., 2011), and working memory (Boisgueheneuc et al., 2006; Haxby et al., 2000). Certainly, functional neuroimaging studies have detailed altered function, during emotionally evocative tasks, of the medial frontal areas in psychiatric disorders, such as PTSD (Britton, Phan, Taylor, Fig, & Liberzon, 2005; Etkin & Wager, 2007; Lanius et al., 2010) which hold emotion modulation disruption as a core factor in its development and maintenance (Amstadter, 2008). As well as smaller grey matter volume (Shin, Rauch, & Pitam, 2006), thinner prefrontal cortices have characterised patient samples of combat veterans with PTSD (Geuze et al., 2008), suggesting the role of this region in the presence of maladaptive behaviours in response to severe forms of environmental stress and threat. Structural alterations in the maltreated sample could indicate the 'scaffolding' of similar divergent patterns of emotional regulation, a potential latent vulnerability to the development of psychiatric disorders such as PTSD.

Local gyrification index: The maltreated sample compared to the non-maltreated peers showed reduced local gyrification within the left superior parietal cortex. This finding was not evident in the individual analyses of Sample 1 and Sample 2. This finding only within the combined sample could potentially reflect an

increase in statistical power with an increase in sample size which enables the detection of atypical structure within this region. The cluster, however, did not overlap with the cluster identifying increased cortical thickness within the maltreated group in Sample 2, suggesting that there are separable results, rather than differences in cortical thickness within Sample 2 driving local gyrification differences within the combined sample, for instance. Functionally, this region forms part of the posterior attention system (Petersen & Posner, 2012; Posner & Rothbart, 2000) with strong connections to anterior attention systems, including the anterior cingulate, which develop at a much later stage. It is thought that this anterior attention system exerts regulatory control over the posterior regions in voluntary control of attention (Petersen & Posner, 2012). The parietal region, through its connections with temporal regions, has been implicated in autobiographical memory and working memory (Cabeza, 2008; Wager & Smith, 2003; Wagner et al., 2005), with a proposal that it is involved in these domains through its flexible allocation of attention in the manipulation of information (Koenigs, Barbey, Postle, & Grafman, 2009). Furthermore this region has shown altered functional activity, as measured by EEG, during delayed attentional disengagement to facial emotion in maltreated children (Pollak & Tolley-Schell, 2003). Attentional problems have been found to mediate the relationship between maltreatment and emotional dysregulation (Shields & Cicchetti, 1998). Both emotional processing and autobiographical memory processing are domains found to be disrupted in the wake of maltreatment (e.g. Pollak et al., 2000; Valentino et al., 2009), it could be hypothesised that atypical structure within this region may support a common underlying process across emotional and autobiographical memory systems, specifically the allocation of attention to salient stimuli. This may be particularly notable in light of atypical structure within the medial prefrontal regions, an area holding strong connections with the superior parietal cortex in the successful regulation of attention.

Surface area: The combined sample was found to show significantly reduced surface area in bilateral Entorhinal cortex, supramarginal gyrus and right inferior parietal cortex displayed within the maltreated group compared to control non-maltreated subjects. As we had found with the group analysis of Sample 2, these group differences did not survive correction for multiple comparisons. These results were contrary to what we had predicted suggested further investigation into the impact of maltreatment on cortical surface area to clarify the discrepancy in the patterns of findings between **Chapter 2 and 4**.

Associations with maltreatment characteristics and trauma symptomatology

In line with the volumetric findings from Chapter 3, there were no significant interactions with maltreatment characteristics and any of the indices derived from the surface based analyses. Previous volumetric studies have found that severity of PTSD is inversely correlated with anterior cingulate volume (Woodward et al., 2006; Yamasue et al., 2003), therefore, although it was hypothesised that we might witness a similar association within this region with psychiatric symptomatology, specifically internalising and post-traumatic stress symptoms, this did not emerge in our analysis. Local gyrification index values within the left superior parietal cortex were not significantly associated with maltreatment characteristics or trauma symptomatology. This firstly suggests that the lack of associations between the official substantiated reports of maltreatment scored according to Kaufman criteria and grey matter findings in Chapter 3 were not due a lack in sensitivity in grey matter volume to capture variations in the dimensions of maltreatment. Conversely, it is more likely that the scales derived from the Kaufman scale were not a sensitive measure to index the individual variations and subtleties of the experience of maltreatment. This is supported by the findings, both within this chapter and Chapter 3, that the self-report measures of childhood trauma severity were significantly associated with structural variations in regions found to be atypical in the maltreated group. It is reasonable to propose that these two measures of maltreatment experience, the CTQ and the Kaufman scale, are tapping into markedly different constructs, one a subjective experience of maltreatment and the other verifiable records of maltreatment having occurred and being detected. The subjective account of maltreatment may certainly provide a better representation of the lasting impact of the negative experiences, particularly as it may reflect lasting negative cognitions and behaviours associated with the experience, such as rumination or self-blame. The objective record of abuse and neglect would not necessarily be sensitive to these factors and thus may have less relation to the potential differences in structure that may support negative and maladaptive behaviours born from the experience of maltreatment.

Relation of the surface-based findings to the VBM findings

Interestingly, the areas of cortical thickness reduction and local gyrification index increase did not overlap with the areas of grey matter reduction or increase

reported in Chapter 3. While differences in the normalisation techniques between VBM and FreeSurfer may have induced region variations that cause certain local differences to be occluded, it may also be that maltreatment impacts these cortical indices in separable ways. Maltreatment exposure may exert a small influence on these separable indices of cortical structure, undetectable on a whole brain scale, however becoming observable using the cumulative metric of GMV which aggregates these independent structural indices. This hypothesis would therefore suggest that future structural studies endeavour to combine the multiple approaches in quantifying structure differences to provide a well-characterised picture of the impact of maltreatment on the brain.

Limitations and future directions

There are a number of limitations and strengths to the current study. The primary limitation is the finding that differences in the degree of structural variation between the non-maltreated groups in Samples 1 and 2 may have driven the opposing directions of local gyrification index group differences in Sample 1 and Sample 2. Furthermore the lack of a self-report measure of childhood trauma within Sample 1 hindered our ability to explore subjective accounts of abuse within one of the largest community samples of maltreated adolescents to date. Moreover, it limited our exploration into how subjective and objective accounts of abuse may be differentially associated with atypical structure. A significant strength of this study is the attempt to integrate diverse structural measures to provide a clearer understanding to the heterogeneous structural alteration that are associated with childhood maltreatment. As detailed in the introduction, there is a growing trend for multi-method structural studies which could represent an important step in future research in uncovering the pathways from maltreatment to maladaptive outcomes across the lifespan.

4.5. Conclusion

In this chapter we demonstrated that two maltreated groups with markedly different maltreatment histories present with both overlapping and differing patterns of atypical structure when compared to well-matched non-maltreated peers. It appears that in relation to cortical thickness, reductions in a frontal cluster were at trend level within Sample 2. The combined sample analysis found a robust pattern of cortical

thickness decrease in prefrontal regions suggesting that this region is commonly impacted by the generic experience of abuse.

A pattern of local gyrification *increases* (as opposed to decreases) were observed in Sample 2. This was different from the finding observed for Sample 1. Although one might conclude that the difference is driven by different maltreatment profiles of the two samples (predominantly neglect and deprivation in Sample 2; higher incidence of physical abuse, in Sample 1), the examination of the data suggests that it is more likely that it is the different spread of data in the non-maltreated comparison groups that could be driving these results.

No associations between maltreatment characteristics and structural indices were found, indicating perhaps that dimensions extracted from official substantiated reports of maltreatment are not sufficiently sensitive to account for individual differences in the structural impact of maltreatment experience. It could be hypothesised that the apparent sensitivity of the self-reported versus the official reports of abuse to structural alterations could reflect that these scales are tapping into different experiential constructs and that subjectivity has a greater influence in determining structural changes. Equally, the sensitivity of the social services report may be poor in relation to maltreatment characteristics. This proposal is consistent with the finding of significant associations with self-reported emotional neglect scores and local gyrification index values in the left insula cluster within the maltreated group.

Collectively, we believe that these findings of structural differences in a community sample of maltreated adolescent without diagnoses of psychiatric disorders may represent latent neural markers of behavioural disruption, particularly within emotional regulation, attentional allocation to salient stimuli and autobiographical memory in later life. These are processes that are commonly atypical in maltreated individuals and may underlie the mechanisms associated with related psychiatric vulnerability.

CHAPTER 5: An investigation into the sexually dimorphic impact of maltreatment on grey matter volume.

5.1. Introduction

As stated in the introduction of this thesis, there is heterogeneity in response to the experience of childhood maltreatment at multiple levels of functioning, including behavioural, cognitive and cortical integrity. Understanding the basis for the heterogeneity in response to maltreatment can help inform understanding of the pathways that lead from maltreatment to maladaptive and negative behaviours. Gaining better understanding of these pathways is necessary if we are to advance effective therapies and interventions for victims of childhood maltreatment. One key factor that may contribute to such heterogeneity is an individual's sex. Differences between males and females are evident at many levels of the nervous system (Cahill, 2006) and while there are many similarities between the two sexes stress response, there are also many noticeable differences (Kudielka & Kirschbaum, 2005; Witelson, 1991). Therefore an individual's long-term response to adverse and stressful environments, including childhood maltreatment, may be partly characterised by their sex. In a 2006 review of the importance of sex differences in neuroscience, it was stated that currently the primary challenge is to "*identify those regions that differ most fundamentally between males and females and from which many sex differences...presumably arise*" (Cahill, 2006). At present, there is an apparent lack of literature investigating the sexually dimorphic impact of maltreatment on adolescent's cortical structure. Moreover, existing analyses have been restricted to a-priori regions of interest potentially leading to biased representation of sexually divergent anatomy (Friston et al., 2006). A whole brain analysis exploring the interaction between sex and maltreatment is needed to help clarify the association between maltreatment and sex differences in the sequelae of maltreatment. This analysis may have implications for how investigators explore the functional and structural correlates of maltreatment and for clinicians in the way they conceptualise the antecedents of many behavioural outcomes in maltreated individuals.

Sex differences in normative populations

Hormonal and neurochemical differences

Much of what we currently understand about sex differences in normative populations covers multiple levels of processing and functioning. The ontogeny of sexual dimorphism within the brain is born from hormonal and genetic influences which can mould its' structural organisation (McEwen, 2010; Tobet et al., 2009; van

Amelsvoort, Compton, & Murphy, 2001). Primarily, males and females have partly different hormonal systems, evident in the distinct circulating gonadal hormones, which have a substantial impact on the brain and behaviour. The brain is responsive to gonadal hormones, such that the hypothalamus and hippocampus are affected by both circulating oestrogens and androgens and undergo sexual differentiation (McEwen, Gould, Orchinik, Weiland, & Woolley, 2007). A meta-analysis exploring sex specific difference in dopaminergic, serotonergic and GABAergic markers concluded that males and females brain are at best neurochemically distinct (Cosgrove et al., 2007). Importantly, genetic factors which do not act on circulating steroid hormones, but influence neurogenesis, cell migration and cell differentiation among other process have also been suggested to contribute to brain sexual differentiation (Arnold, 2004; Tobet et al., 2009). Therefore It is important to consider that the hormonal, genetic, and neurochemical environments of males and females are fundamentally different.

Structural differences

The most consistent finding within the neuroscience literature exploring the influence of sex on brain structure, is that males have generally larger brains than females, even when taking into account total body size and total intracranial volume (Allen et al., 2003; Cosgrove et al., 2007; Kitayama et al., 2007; Luders et al., 2009; Shin et al., 2005). Similarly, the ratio between grey matter and white matter varies between the sexes, with females possessing proportionally more grey matter to white matter volume than males (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999; Luders et al., 2005).

Local grey matter differences, in which males possess greater grey matter volume than females, in subcortical structures, such as the amygdala, thalamus and putamen, and on the cortical surface, including the middle temporal gyrus, left inferior gyrus and right occipital and lingual gyrus (Chen et al., 2007; Koolschijn & Crone, 2013; Peper et al., 2009). Conversely, females compared to males have shown comparatively increased GMV within dorsal, anterior, posterior and ventral cingulated cortices and right inferior parietal lobule (Chen et al., 2007). In relation to the functional properties of these cortical regions, authors have suggested that males have increased grey matter within primary visual and visuospatial regions, whereas females show comparatively larger GMV within language related regions,

suggesting divergent abilities in each of these domains (Brun et al., 2009; Harasty et al., 1997). Hemispheric differences between the sexes have similarly been noted, with the suggestion that females possess greater hemispheric symmetry in grey matter volume compared to males (Gur et al., 1999; Hiscock et al., 1995). Substantial sex differences in white matter structures are equally prevalent in the current literature, but are beyond the scope of the current thesis (Gong et al., 2011; Yan et al., 2011).

Functional differences

Functional findings from fMRI and EEG suggest that male and female brains may use different neural mechanisms for performing a number of cognitive processes (Cahill, 2006). Sexually dimorphic activation patterns of language and visuospatial processing have been identified, suggesting that language processing is more strongly lateralised in males than in females and visuospatial abilities are confined more to parietal regions in males compared to females (Gur et al., 2000; Kansaku & Kitazawa, 2001; Shaywitz et al., 1995; Weiss et al., 2003). Resting state fMRI, have implicated differing patterns of functional asymmetry between the two sexes (Biswal et al., 2010) with a greater lateralisation of resting state function in the right hemisphere for males and left hemisphere in females (Wang, Shen, Tang, Zang, & Hu, 2012).

Emotional processing has also garnered a great deal of interest within investigations of functional neuroimaging investigations of sex differences. Differential neural signatures have been observed between the two sexes when viewing emotional faces (Fusar-Poli et al., 2009). Specifically, females show comparatively greater activation within limbic and prefrontal regions compared to males, who show greater activation within the right subcallosal gyrus (Fusar-Poli et al., 2009). The sex of the emotional faces has additionally been found to evoke differential neural response, such that males respond with greater activation than females in the visual cortex and anterior cingulate to emotional male faces than emotional female faces (Fischer et al., 2004). Such phenomena have been suggested as a male tendency for enhanced vigilance to potentially dangerous situations, which in this case could be represented by another male who might be more likely to represent physical danger than a female.

The recall of emotional memories has also been characterised by differential neural patterns of activation within males and females; increased lateralisation to the right hemisphere is a common finding within males and a transposed pattern within females (Cahill, 2006; Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2004; Canli, Desmond, Zhao, & Gabrieli, 2002). Furthermore, during emotional memory recall females are found to exhibit a greater overlap with regions associated to current emotional state compared to males, suggested to contribute to a greater enhancement of emotional content in memory recall (Canli et al., 2002). A meta-analysis of functional neuroimaging emotional processing studies highlighted a consistent pattern of heightened activation within the bilateral amygdala and orbitofrontal cortex within males compared to females in emotional processing tasks (Sacher, Neumann, Okon-Singer, Gotowiec, & Villringer, 2013). Conversely females show a distinct neural pattern portrayed by heightened neural activity during emotional processing tasks in a number of clusters including the bilateral thalamus, anterior and posterior cingulate cortex (Sacher et al., 2013).

However, it is crucial to consider that there are instances where there is not an isomorphic relationship between neural response and behavioural functioning. For example, within one particular study, similar memory retrieval performance was observed within males and females; however the regions of activation associated with the task were significantly different between the two sexes (Piefke, Weiss, Markowitsch, & Fink, 2005). A common suggestion is that neural differences are compensated by other physiological processes, such as circulating sex hormones, which therefore produce sexually analogous behavioural responses (De Vries, 2004). It has been further argued that cortical sexual dimorphisms may exist to prevent, rather than produce, maladaptive behaviours and functioning which may be inappropriate or disadvantageous to the individual, potentially through differences in gonadal hormones or sex chromosomal gene expression (De Vries, 2004; De Vries & Södersten, 2009). This gives rise to an important consideration when interpreting neuroimaging output. One must be mindful of the inherent limitations of functional and structural neuroimaging, particularly what it can and can't tell us about behaviour and the potential vulnerabilities of reverse inference.

Collectively, the functional brain imaging findings suggest that males and females may possess distinct neural patterns for a number of cognitive processes and systems. How these neural differences correspond with differences in

behaviour is not fully known and in some instances, neural differences may be homogenised by other physiological processes.

Developmental trajectories

Developmental trajectories of cortical structure have been found to follow sexually divergent routes to maturity, with a 1-2 years earlier peak in subcortical and cortical grey matter trajectories in females than in males (Lenroot & Giedd, 2010).

Regionally, areas such as the hippocampus show sexual dimorphism in growth during adolescence (Suzuki et al., 2005). Myelination within the hippocampus, an area rich in sex steroid receptors, occurs more rapidly in girls from age 6 onwards (Benes et al., 1994). Such difference in developmental trajectories could possibly enhance the vulnerability to stress in females during the period when sexual abuse is more likely to occur (Benes et al., 1994). Differing developmental rates of alterations in the ratio of grey to white matter between the two sexes are also significant; males show a more prominent age related grey matter volume decrease and white matter volume increase compared to females (De Bellis, Keshavan, et al., 2001). However, cerebral white matter increases linearly at a faster pace within females than males (Koolschijn & Crone, 2013). Sex differences in grey matter trajectories are also observed at a regional level, showing an earlier grey matter volume peak in the frontal and parietal lobes in females than males (Lenroot et al., 2007), a pattern which has been suggested as being linked to pubertal development. Interestingly, sexually divergent developmental trajectories, such as within the amygdala and the hippocampus, have been suggested to related to observed sex differences in the age of onset, prevalence and symptomatology associated with many neuropsychiatric disorders of childhood (Giedd et al., 1997).

Differences in psychopathology

Epidemiological and clinical studies consistently show sex differences in the prevalence rates of many forms of psychopathology, with a greater male preponderance of externalising behaviour and a greater female preponderance of internalising behaviour (e.g. Crijnen, Achenbach, & Verhulst, 1997; Leadbeater, Kuperminc, Blatt, & Hertzog, 1999; Martel, 2013; Shirtcliff & Essex, 2008). In particular, females appear at greater risk of developing PTSD and major depressive disorder (MDD) compared to males (Holbrook, Hoyt, Stein, & Sieber, 2002; Kessler, Berglund, Demler, Jin, & Walters, 2005), with some estimates suggesting a 2 times

greater risk (Halbreich & Kahn, 2007). Additionally, investigators have stipulated that there is a general distinction between male and female prevalence in early onset and adolescent onset disorder (Rutter, Caspi, & Moffitt, 2003). Early onset neuropsychiatric disorders, including autism, developmental language disorder and attention deficit disorder have been found to have a larger male preponderance (Fombonne, 1999; Gaub & Carlson, 1997; Robinson, 2008), whereas females show a greater prevalence of adolescent onset disorders, including depression and eating disorders (Bebbington, 1998; Nielsen, 1990).

Sex differences in the prevalence of a number of psychiatric disorders is paralleled by markedly different neural characteristics between males and females within these disorders. Sex has been suggested as a key mediator of the effects of genes and/or environment on regional vulnerabilities to MDD (Major Depressive Disorder; (Sjöberg et al., 2006; Walf & Frye, 2006). For instance, females with MDD show relative reductions in GMV within limbic regions compared to controls, whereas males with MDD are observed to have GMV reductions in striatal regions compared to controls (Kong et al., 2013). It has been suggested that these separable structural differences between the sexes reflect discrete psychiatric characteristics (Kong et al., 2013). Such a suggestion implies that sex represents a key mediator in the effect of environment and genes on vulnerabilities and characteristics of psychiatric disorders (Heim & Binder, 2012). An understanding of the sexually dimorphic response to maltreatment, a strong environmental influence on the development of psychiatric disorders (e.g. Cicchetti & Toth, 2005), may help researchers paint a better understanding of the possible structural antecedents and predispositions of maladaptive behaviour later in life.

Sexually dimorphic responses to maltreatment

As mentioned in the Introduction, insight into the heterogeneity of individuals' response to maltreatment continues to represent a challenge for researchers and practitioners (Afifi & MacMillan, 2011; Herman-Smith, 2011). It is evident that there is sexual dimorphism in the development and functioning of the brain and in subsequent behaviour and emergence of neuropsychiatric disorders. One could therefore confidently hypothesise that sexual dimorphism would be plausible in the response to stressful and negative environments during development, such as with child maltreatment. De Bellis and Keshavan (2003) proposed that sex differences in the emergence of psychiatric disorders stem from three factors: (i) differences in the

nature of maltreatment (ii) sex differences in hormonal environment and (iii) differences in the effect of maltreatment on brain development. These are addressed in turn below.

Experience of maltreatment and psychopathology

It is important to consider that the experience and reporting of abuse is not equivalent between males and females. For instance, females are more likely to have their abuse substantiated and also experience more forms of sexual abuse (Maikovich-Fong & Jaffee, 2010). Additionally, males are more likely to be sexually abused by strangers, whereas females are at greater risk of being sexually abused by family members (Finkelhor, Hotaling, Lewis, & Smith, 1990; Gold, Elhai, Lucenko, Swingle, & Hughes, 1998; Gold, Lucenko, Elhai, Swingle, & Sellers, 1999). These apparent differences in the reporting and experience of abuse translate into differences in representation of males and females in research, particularly with regard to the developmental correlates of childhood sexual abuse which is mainly confined to female victims (Bailey & McCloskey, 2005; Briggs & Hawkins, 1996; Cermak & Molidor, 1996; Valente, 2005). Furthermore, such differences can complicate the interpretation of brain imaging findings, as it may be ambiguous to interpret whether any sexually dimorphic findings represent dimorphic reactions to a common experience or instead understandably distinct neurodevelopmental consequences of distinct experiences.

Researchers have also noted that females experience more negative consequences associated with maltreated compared to males and present with lower levels of resilience in the presence of maltreatment (Campbell-Sills, Forde, & Stein, 2009; Lansford et al., 2002; Thompson et al., 2004). One rather mainstream, but only partly substantiated view, is that adolescent males react differently to stress than females, typically externalising their behaviour, manifesting as anger, whereas their female counterparts tend to internalise behaviour (Hoffmann & Su, 1997; Ireland & Widom, 1994). Certainly, cultural factors may influence socially permissible behaviours of males and females following stressful situations. Behavioural responses following initial stress responses may develop very differently, not just due to genetic or hormonal reasons, but also due to how societal expectations shape these responses. For example, in many cultures males may be expected to withhold outward displays of emotion or distress compared to females during stressful environments, potentially shaping the development of behavioural

responses to subsequent stressful situations. These apparent differences in response to developmental stressors, potentially driven in part by what is culturally acceptable behaviour for each sex, may contribute to the emergence of differential patterns of psychopathology in later life. Females but not males with a history of physical abuse have been found to have significantly higher lifetime rates of major depression than non-maltreated peers (MacMillan et al., 2001). Furthermore, an investigation exploring the negative consequences associated with the experience of early institutional care found that males were more vulnerable to externalising symptoms while the majority of internalising symptoms were confined to females (Bos et al., 2011).

Stress and the hormonal response

Reactivity to developmental stressors, such as childhood maltreatment, may differ across sexes given that the development of stress-sensitive corticostriatal-limbic regions is sexually dimorphic (Giedd et al., 1997; Lenroot et al., 2007; Meaney et al., 1996). The Adaptive Calibration Model was created to account for the differential response to traumatic stress based on sex (Del Giudice, Ellis, & Shirtcliff, 2011). The model suggests that around the time of puberty, stress system recalibration occurs due to differential life history strategies between the two sexes (Del Giudice et al., 2011; Doom, Cicchetti, Rogosch, & Dackis, 2013). This theory suggests that differences in adrenal hormones underlie distinctions in stress reactivity and regulation between males and females, with past environmental stress being the moderator in the degree of differences between the two sexes. Within these models, males are believed to exhibit low stress responsivity, manifesting as more callous and unemotional behaviour (Del Giudice et al., 2011). However, girls are predicted to become more fearful and anxious, potentially developing internalising symptoms. Such traits are associated with heightened sympathetic and HPA reactivity (Del Giudice et al., 2011). Such sex and maltreatment experience interactions have been observed in predicted diurnal cortisol levels and salivary cortisol levels (Doom et al., 2013; Kudielka & Kirschbaum, 2005). Sex differences in the developmental trajectories of stress responsivity are linked with puberty. While no differences in baseline cortisol levels are observed in pre-pubertal children, during puberty, where females commonly mature faster, heightened cortisol levels may be seen compared to males (Del Giudice et al., 2011; Jessop & Turner-Cobb, 2008; Netherton, Goodyer, Tamplin, & Herbert, 2004).

Sex differences in the Impact of maltreatment on cortical structure

Investigations into the potentially sexually dimorphic impact of maltreatment on cortical structure are scarce and are mainly limited to adult populations relying on retrospective reports many years after the experience of maltreatment. Early animal studies suggested that sex differences in response to early maltreatment were focussed locally in the corpus callosum (Juraska & Kopcik, 1988). Recent human studies have replicated this finding showing that corpus callosum volume is disproportionately affected in maltreated males than females (De Bellis & Keshavan, 2003; De Bellis, Keshavan, et al., 1999; Teicher et al., 2004). Elsewhere, a more recent study suggested that childhood emotional abuse was associated with reduced hippocampal volume in males compared with maltreated females (Samplin, Ikuta, Malhotra, Szeszko, & DeRosse, 2013). Globally, it has also been observed that males show more evidence of reduced GMV than females (De Bellis, Hall, et al., 2001; De Bellis & Keshavan, 2003; De Bellis, Keshavan, et al., 1999). A whole brain analysis of sex differences associated with the impact of maltreatment on brain structure, either within a sample of maltreated adolescents or adults, represents a significant omission in the existing literature. In part, this may be due to a general apprehension about investigating sex differences within neuroscience as often results can be construed in an unfavourable light, interpreted to fit a certain political or social ideology, or seen to perpetuate restrictive cultural norms and conventions. There is therefore a need for sensitivity in framing and interpreting findings with regard to both the extant literature, and the limitations of the methodology.

The current study

At present, very little is known regarding the sexually dimorphic impact of childhood maltreatment on regional grey matter volume. A systematic study employing volumetric based morphometry to investigate the interaction between sex and the experience of abuse is needed to provide a basis to better understand the sexually divergent developmental sequelae of maltreatment to psychopathology. The aims of the present study are two-fold. First, to investigate whether previously reported regions of grey matter reduction or increase within maltreated individuals compared to non-maltreated peers are in fact driven by one sex. The regions I will be exploring are the regions of atypical structure within the maltreated group, reported in Chapter

3: bilateral middle temporal lobe, bilateral supramarginal gyrus and left medial orbitofrontal cortex. Second, to understand whether there are any areas of cross-over interaction between sex and experience of abuse within a whole brain analysis of grey matter volume. If such cross-over interactions exist, they would reveal new areas of group difference that would not be detected in traditional group difference analyses that collapse both sexes and look for group differences associated with maltreatment (as opposed interaction between sex and maltreatment). We predicted that:

- (i) local decreases and increases in grey matter volume observed within maltreated adolescents compared to non-maltreated peers will be driven more so by males than females in line with existing literature suggesting greater GMV decreases in males;
- (ii) sex and experience of maltreatment may interact to produce differential local volumes of grey matter across the cortex, specifically in regions sensitive to the stress response;

5.2. Methods

Please see the methods section of Chapter 3 for information regarding recruitment of the maltreated ($n = 60$) and non-maltreated groups ($n = 60$) within the combined sample ($n = 122$), the measures administered and structural scanning parameters. The image processing procedure using VBM is described in the methods section of Chapter 3 and the DARTEL procedure for intra-subject alignment and normalisation was implemented on the participant's grey matter segments used in this Chapter.

Statistical analyses

A flexible factorial model was implemented within SPM8 to examine the interaction between group and sex on grey matter volume. Three factors were created for all participants; the first being a 'replication' factor defined as 'subjects' and group and sex defined as the remaining factors. Age and IQ were included in the model as nuisance variables because of their known association with brain anatomy (Giedd & Rapoport, 2010) and trend level group differences on age and IQ. The model was re-run excluding the covariates to understand their potential influence on the results. The main effects of each factor as well as the interaction between group and sex

were modelled in the design matrix. T-tests were performed to test whether any main effect of group or sex, or group x sex interaction could be observed.

Multiple comparison correction was performed using Monte Carlo simulation with the AFNI program 3dClustSim (<http://afni.nimh.nih.gov/afni/>), which defines a cluster based extent threshold to limit the presence of type 1 errors. At an initial statistical threshold of $t(117)=2.62$, $p_{\text{uncorrected}} \leq 0.005$, the cluster threshold was defined as 338 contiguous voxels resulting in an alpha of ≤ 0.05 . Crucially, non-uniformity inherent in VBM data was addressed by implementing Gaussian random field theory within SPM8. Clusters that were found to be above this threshold were considered significant.

A 10mm sphere was created around the local maxima of significant clusters and the raw grey matter values within the sphere were extracted using the MARSBAR region of interest toolbox (Matthew Brett, MRC Cognition and Brain Unit, Cambridge). The grey matter values were imported into SPSS v.20 (IBM, Armonk, NY) for further analysis to examine the relationship between grey matter volume within each group split by sex and potentially confounding variables such as pubertal stage.

Main effects of group and sex were also investigated within the same flexible factorial model. Significant regions of grey matter differences were further investigated by extracting the raw grey matter values within a 10mm sphere centred on the local maxima. Extracted mean grey matter volumes were imported into SPSS for further analysis.

5.3. Results

Socio-demographic characteristics

Descriptive statistics between the maltreated and non-maltreated groups are presented in Table 5.1. The maltreated group did not differ from the non-maltreated group in relation to sex, age, self-reported Tanner stage, handedness, IQ, SES and ethnicity. Socio-demographic characteristics between males and females are shown in Table 5.2. There was a sex difference in relation to pubertal development; however this pattern of relative pubertal maturity in females was similar across the two groups and there was no Group x Sex interaction ($F(1,118) = .098$, $P = .755$). A

2x2 ANOVA was used to explore whether there were Group x Sex interactions on the remaining socio-demographic variables. None of these dimensions were found to represent an interaction with Group and Sex and thus were not considered to potentially confound the interpretation of the results. Although the two groups were similar in terms of their levels of anxiety, depression and PTSD symptoms, the maltreated group showed higher SDQ conduct problems and hyperactivity symptoms (Table 5.1). As stated in Chapter 2 a strong case has been made that when participants are not randomly assigned to groups, it is inappropriate to co-vary for variables intrinsically related to group assignment (Miller & Chapman, 2001). Consequently, conduct problems and hyperactivity symptoms were not included as covariates in the main analysis

Table 5.1. Demographic characteristics of the maltreated and non-maltreated groups within the combined sample.

	<i>Control (n = 60)</i>		<i>MT (n = 62)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Demographics					
Age (in years)	12.68	1.14	12.23	1.52	0.07
WASI, 2 scale subset	108.88	10.49	104.81	13.23	0.06
Puberty development scale	2.22	0.66	2.04	0.71	0.15
Tanner stage					0.60
No. of pre/early pubertal (%)	15 (25)		22 (35)		
No. of mid pubertal (%)	23 (38)		24 (39)		
No. of late/post pubertal (%)	22 (37)		16 (26)		
Sex, N of males (%)	25 (42)		33 (53)		0.21
Ethnicity, N of caucasian (%)	31 (52)		39 (63)		0.27
Handedness, N or right handed (%)	53 (88)		46 (74)		0.21
SES					
Composite score	3.15	0.87	2.89	1.08	0.22

All p values derived from t-tests with the exception of sex, ethnicity, handedness and Tanner stage comparisons which used Fisher's exact test.

Table 5.2. Demographic characteristics of the male and female participants.

	<i>Males (n = 58)</i>		<i>Females (n = 64)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Demographics					
Age (in years)	12.61	1.47	12.31	1.25	0.23
WASI, 2 scale subset	106.09	12.47	107.47	11.78	0.53
Puberty development scale	1.84	0.56	2.39	0.70	0.00
Tanner stage					0.00
No. of pre/early pubertal (%)	34 (59)		3 (5)		
No. of mid pubertal (%)	19 (33)		28 (44)		
No. of late/post pubertal (%)	5 (8)		33 (52)		
Ethnicity, N of Caucasian (%)	32 (55)		38 (59)		0.72
Handedness, N or right handed (%)	45 (78)		54 (84)		0.55
SES					
Composite score	2.78	1.05	2.96	0.96	0.32

All *p* values derived from t-tests with the exception of sex, ethnicity, handedness and Tanner stage comparisons which used Fisher's exact test.

Community violence

Community violence did not differ significantly between males and females and there was no interaction between Sex and Group on total community violence ($F(1, 118) = .561, p = .456$). Within the maltreated group occurrence of abuse across subtypes did not differ by sex and within those participants who experienced abuse, the severity did not differ by Sex (Table 5.3). Therefore any perceivable Group x Sex interactions are unlikely to be due to differences in the objective experience of maltreatment between males and females.

Table 5.3. Maltreatment characteristics of the male and female participants within the maltreated group.

	<i>Males (n = 33)</i>		<i>Females (n = 29)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Severity of abuse					
Physical abuse	2.20	1.10	1.71	1.25	0.50
Sexual abuse	1.00	0.00	2.80	1.30	0.12
Neglect	3.11	1.17	3.39	1.08	0.37
Emotional abuse	3.00	0.91	2.86	0.93	0.56
Total severity	5.76	2.73	6.34	2.81	0.41
Occurrence of abuse					
Physical abuse (%)	5 (15)		7 (24)		0.52
Sexual abuse (%)	3 (9)		5 (17)		0.46
Neglect (%)	28 (85)		23 (79)		0.74
Emotional abuse (%)	30 (91)		28 (97)		0.62
Domestic Violence (%)	17 (52)		14 (48)		1.00
Total occurrence	2.61	0.93	2.79	1.18	0.49

Note: Severity scores for domestic abuse are not captured by the Kaufman scale. All p values derived from t-tests

Global measures of cortical volume.

The combined sample did not differ on any of the global indices of volume. Overall grey matter, white matter, cerebrospinal fluid and total volume was greater in males than in females (Table 5.4). Sex by Group interactions were not significant for overall grey matter ($F(1,118) = .359, p = .559$), white matter ($F(1,118) = 2.395, p = .124$), cerebrospinal fluid ($F(1,118) = .496, p = .483$), and total volume ($F(1,118) = 1.480, p = .226$). Importantly, the grey matter segments were only multiplied by the non-linear component of the registration during the normalisation procedure therefore accounting for individual differences in brain size.

Table 5.4. Global measures of cortical volume between the maltreated and non-maltreated groups, and between males and females.

By group					
	<i>Control (n = 60)</i>		<i>MT (n = 62)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Grey matter	771.18	64.85	759.85	64.44	0.34
White matter	479.33	53.16	467.68	45.54	0.20
CSF	171.57	25.61	172.96	26.82	0.77
Total	1422.07	118.42	1400.49	111.63	0.30

By sex					
	<i>Males (n = 37)</i>		<i>Females (n = 47)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Grey matter	796.93	63.98	738.99	57.11	0.00
White matter	492.31	50.50	458.97	48.56	0.00
CSF	183.04	25.82	169.26	26.71	0.02
Total	1472.28	112.05	1367.22	103.14	0.00

CSF = Cerebrospinal fluid; All values are measures of volume given in mm³. All p values derived from t-tests

Influence of sex on grey matter differences associated with maltreatment

The regions of atypical structure that were explored for sex differences were the five regions of atypical structure within the maltreated group in Chapter 3: bilateral middle temporal lobe, bilateral supramarginal gyrus and left medial orbitofrontal cortex. The mean GMV values were extracted from a 10mm sphere located at the local maxima of the cluster. These values were inputted into SPSS to examine whether the group differences were driven by one sex more so than the other. Sex and group did not significantly interact within the regions of the left middle temporal gyrus ($F(1, 118) = 1.63, p=.20$), the right middle temporal gyrus ($F(1, 118) = 2.97, p=.09$) nor the left medial orbitofrontal cortex ($F(1, 118) = .61, p=.44$).

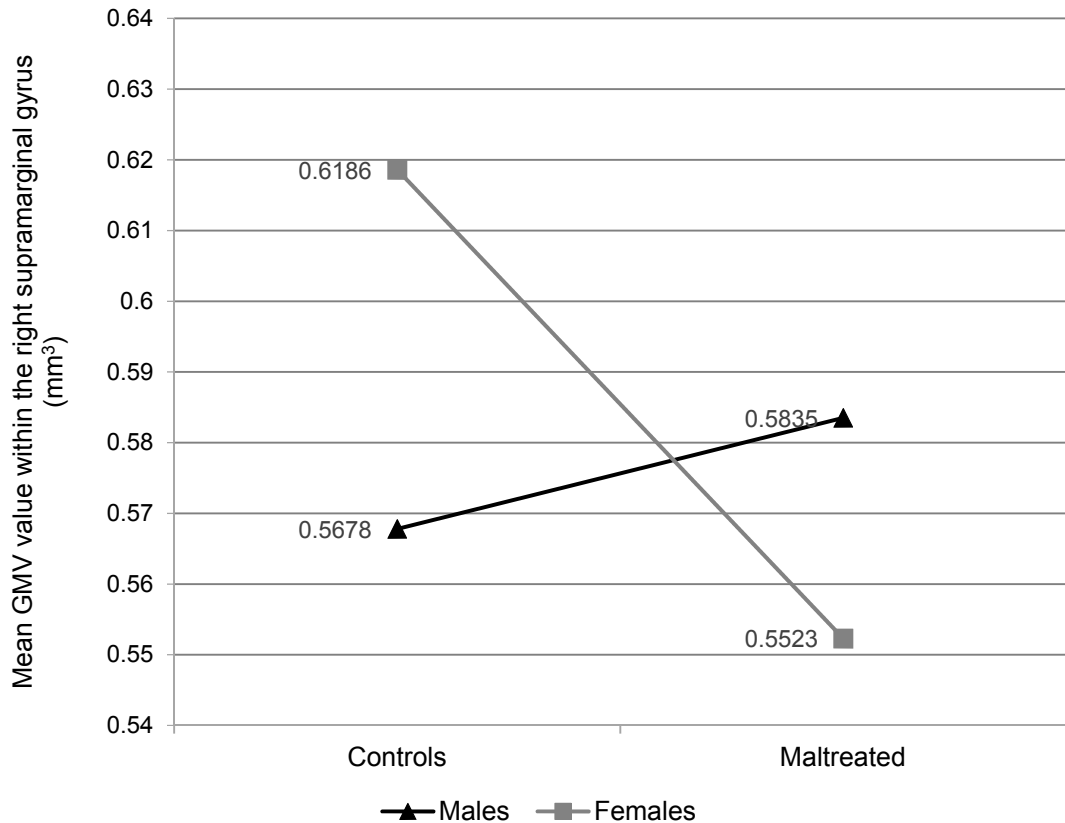


Figure 5.1. Plot of mean grey matter values within the right supramarginal gyrus split by group and sex.

Notes: A significant reduction in grey matter volume is observed within the females ($p = 0.008$), whereas there relative difference in the male participants is not significant ($p = .985$).

Significant sex x group interactions were found within left supramarginal gyrus ($F(1, 118) = 12.57, p < 0.001$) and the right supramarginal gyrus ($F(1, 118) = 6.17, p = .01$). Plotting these results (Figure 5.1 & Figure 5.2) and inspection of the means, it was found that a group difference was only present within the females for the left supramarginal gyrus ($p < 0.001$; males, $p = .788$) and the right supramarginal gyrus ($p = 0.008$; males, $p = .99$). On the basis of these findings it appears that the females within the maltreated group are driving the main effects of group seen within bilateral supramarginal gyrus. Including pubertal scale as a covariate in the model did not change the pattern of results and there was a significant interaction between sex and group within the left supramarginal gyrus ($F(1, 117) = 13.23, p < 0.001$) and the right supramarginal gyrus ($F(1, 117) = 6.31, p = .01$).

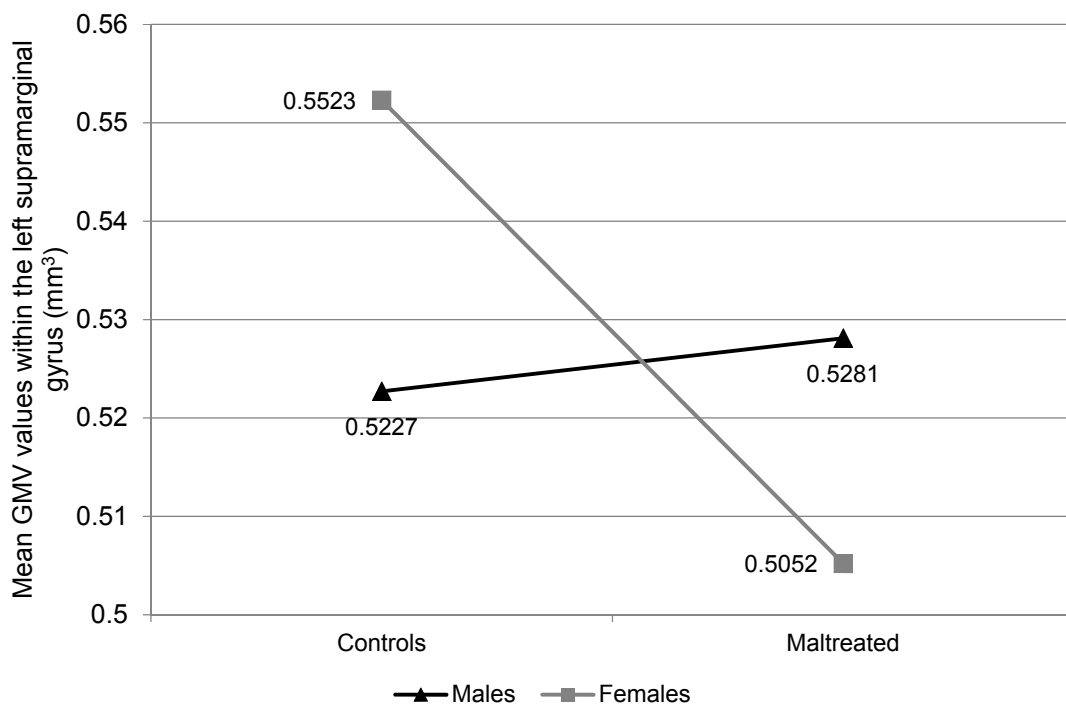


Figure 5.2. Plot of mean grey matter values within the left supramarginal gyrus split by group and sex.

Notes: A significant reduction in grey matter volume is observed within the females ($p < 0.001$), whereas there relative difference in the male participants is not significant ($p = .79$).

Whole brain analysis of sex differences following maltreatment on grey matter volume.

The flexible factorial within SPM modelled the interaction between the factors, maltreatment experience and sex. The whole brain analysis revealed a significant cluster within the left postcentral region ($x=-63, y=-13, z=34$; Z-score = 3.76; $k = 1671$; $p = 0.004$; $\alpha = 0.05$) representing a reduction in grey matter in the maltreated sample of females compared with non-maltreated sample of females and an increase in grey matter in the maltreated males compared with non-maltreated males. This cluster was also significant at the more stringent initial threshold of $p < 0.001$ ($x=-63, y=-13, z=34$; Z-score = 3.76; $k = 634$; $p = 0.019$; $\alpha = 0.05$). Figure 5.3 highlights the extent of this cluster on a study specific mean structural scan ($n = 122$). The grey matter values within this significant cluster were extracted for secondary analyses and to further establish the relation of the GMV between group and sex. The GMV values for males and females within each group were plotted (Figure 5.4) and post hoc multiple comparisons were implemented to determine

relative differences between groups and sex. The model was re-run excluding age and IQ as covariates and the same significant cluster was observed within the left post central region ($x=-63$, $y=-13$, $z=33$; Z-score = 4.45; $k=1911$; $p < 0.001$; $\alpha = 0.05$) for the interaction between sex and group, however the local maxima had shifted one degree in the z-axis and the cluster extent was slightly larger.

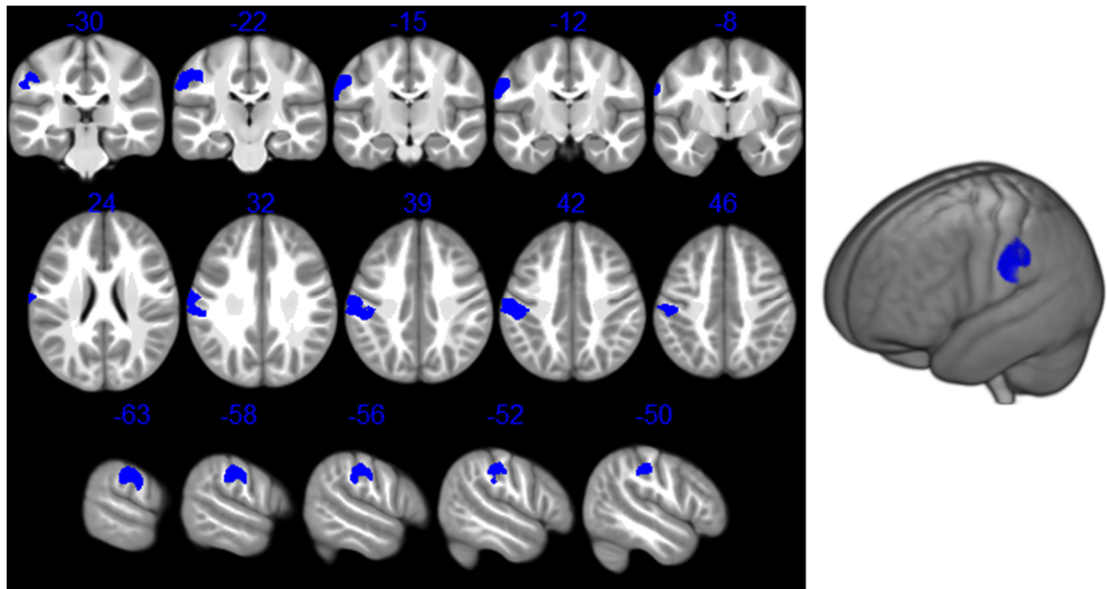


Figure 5.3. Cluster of a significant interaction between group x sex in GMV within the left postcentral gyrus.

Notes: The statistical parametric map showing the focus of the significant interaction between Group x Sex in the left postcentral gyrus ($x=-63$, $y=-13$, $z=34$; Z-score = 3.76; $\alpha = 0.05$). Slice labels are shown above each image indicating the MNI coordinate in the Y, Z and X axis from the top to the bottom. SPM is overlaid on a mean structural from the 122 participants.

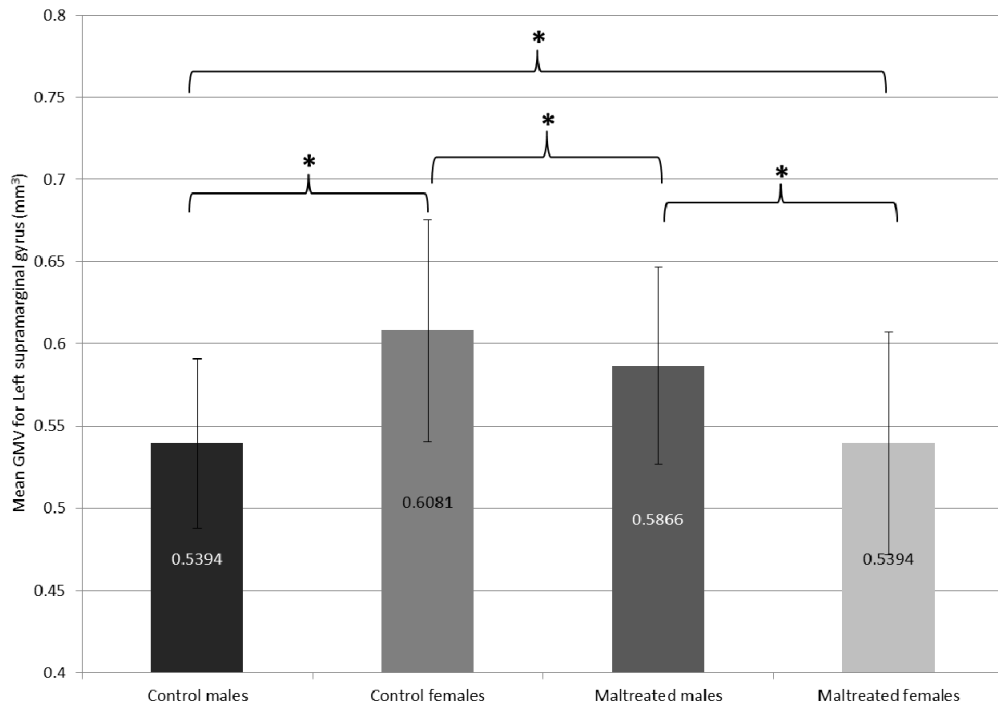


Figure 5.4. Extracted grey matter values from the left postcentral gyrus plotted by sex and group.

*Notes: Sex differences were apparent within both control and maltreated groups, however the direction of difference between males and females was divergent within the maltreated and control groups. * <0.05 .*

Including pubertal status as a covariate within a 2X2 ANOVA of mean GMV extracted from the postcentral cluster did not change the pattern of results ($F(1,117) = 27.68, p < 0.001$) as shown in Figure 5.4. A 2x2 ANOVA with Age, IQ and pubertal status as covariates revealed that pubertal status did not alter the interaction ($F(1,115) = 19.618, p < 0.001$). No significant group or sex main effect was observed. The model was also run without covariates, and with just age and IQ as covariates and the same pattern of results was maintained. Furthermore, including total brain volume as a covariate did not alter the pattern of results.

Associations with psychiatric symptomatology

The extracted grey matter values within the significant region of the postcentral gyrus were extracted and imported into SPSS to explore associations with psychiatric symptomatology and dimensions of maltreatment. A 2x2 ANOVA exploring sex x group interactions in psychiatric symptomatology found no main effect of Sex and no Sex x Group interaction for trauma symptomatology as measured by the TSCC. No main effect for group was observed for any of the

subscales of the TSCC, including anxiety, depression, PTSD and the internalising composite score. No correlations were observed between extracted grey matter values and psychiatric symptomatology within either the maltreated male or females.

5.4. Discussion

The present chapter sought to investigate sex differences in the impact of childhood maltreatment on cortical grey matter within a community sample of adolescents. We examined the interaction between sex and the childhood experience of abuse within a whole brain analysis of grey matter volume. We further investigated whether previously observed group differences in grey matter volume were driven by one of the two sexes and whether sex differences within grey matter volume were apparent irrespective of history of childhood maltreatment. Two principal findings emerged from this study. First, the findings of bilateral supramarginal gyrus grey matter reduction in the main effect of group were found to be primarily driven by the female participants, while the other regions associated with maltreatment exposure, bilateral middle temporal lobe and medial orbitofrontal cortex, appear to be driven by both males and females. Second, a disordinal interaction between sex and experience of maltreatment was observed within a region of the postcentral gyrus. To our knowledge this is the first time sex differences within a community sample of maltreated adolescents has been explored at a whole brain level and the findings represent an important contribution to the existing literature on the heterogeneity of cortical abnormalities associated with maltreatment.

Influence of sex on main effects of group

In the previous chapter we demonstrated that the experience of childhood maltreatment was associated with grey matter reductions in a number of cortical regions, among them, the bilateral supramarginal gyrus. We replicated this finding using a different statistical model within SPM, as such this partly serves as a check to ensure that both models were correctly defined. Furthermore, we wanted to investigate whether any of these areas of grey matter volumetric increase and decrease were driven by one sex. Our post-hoc analysis within SPSS using a 2x2 ANOVA revealed that the relative decreases in grey matter volume in the bilateral supramarginal gyrus within the maltreated adolescents compared to non-maltreated peers were only apparent within the females. These findings suggest that the

relative grey matter decreases within the maltreated females are driving the main effect of group within these two regions. This finding was contrary to our prediction that atypical grey matter volume observed within maltreated adolescents compared to non-maltreated peers will be driven more so by males than females and particularly surprising given the existing literature points towards greater GMV decreases associated with maltreatment in males than females (e.g. De Bellis & Keshavan, 2003). As discussed in chapter 2, the supramarginal gyrus has been associated with emotion recognition (Adolphs et al., 2001) and lesions within this region have been found to impair recognition of human emotional expressions (Adolphs et al., 2000). Furthermore, certain aspects of empathy, such as egocentricity and the ability to distinguish oneself from other related representations, are believed to be strongly associated with the supramarginal gyrus (Silani et al., 2013; Singer & Lamm, 2009). Disruption solely within females' supramarginal gyrus grey matter volume could support sexually divergent patterns in emotional or empathic processing. Such potential differences may produce variance in the prospective trajectories of maltreatment to maladaptive behaviour and risk for psychiatric disorders. The comparatively "spared" supramarginal gyrus of the maltreated males, may (possibly) suggest a normative underlying function of the region, similar to that of the control males. As with the postcentral finding, one would need to complement this hypothesis with an investigation into sex differences in emotional and empathic processing in maltreated adolescents.

Sex by maltreatment experience interaction

In addition, a disordinal interaction between sex and experience of childhood maltreatment was found within a region of the postcentral gyrus. This disordinal interaction represented a pattern of greater grey matter volume within the control females compared to the control males, however those who had experienced childhood maltreatment displayed an inverted pattern of grey matter decrease between males and females, in other words, maltreated females displayed reduced local gyrification index within the postcentral gyrus compared to maltreated males. The postcentral gyrus is a region previously represented in the existing maltreatment literature and reductions in the postcentral gyrus grey matter volume have been reported to be related to experience of maltreatment in a number in adults and children with histories of abuse (Dannlowski et al., 2012; Hanson et al., 2010; Lim et al., 2014). A recent meta-analysis, in particular, stated that reductions within the postcentral gyrus were highly replicable and found in 11 combinations of

studies (Lim et al., 2014). A main effect of group, however, was not observed in this postcentral region within our current sample.

Previous investigations into sex differences of the cortical structure within normative samples have shown that the most significant and largest grey matter differences are within the bilateral pre and postcentral, indicating larger grey matter volume within females compared to males (Luders et al., 2005). Authors have suggested that one of the reasons for the noticeable volumetric differences within this area is due to a high density of sex steroid receptors during critical periods of development, therefore making it more susceptible to circulating gonadal hormones (Goldstein et al., 2001).

The functional significance of the postcentral gyrus in the context of maltreatment has not been extensively investigated, however a number of studies have associated this area with functional processes that are typically detrimentally affected after the occurrence of maltreatment. While the postcentral gyrus has been traditionally associated with sensorimotor processing such as the encoding of bodily sensations (Sato, Terada, Onouchi, Takeda, & Kuzuhara, 2002), other investigators have established the role of postcentral gyrus in emotional processing. In particular, activity in the postcentral region has been linked to trait emotional awareness (Lichev et al., 2014) and is considered to play a key role in using social cues to understand the emotional states of others and in basic emotion processing (Keysers, Kaas, & Gazzola, 2010; Ruby & Decety, 2004), a key component in successful and adaptive emotional regulation (Cole et al., 1994).

Importantly, the postcentral gyrus has been found to have a sexually distinct neural role in the processing of emotional content. Notably, females but not males have been found to exhibit correlations between current emotional experience when re-counting emotional memories and neural activity within the postcentral gyrus (Canli et al., 2002). In addition, a more recent fMRI study in which participants were asked to actively increase or decrease their emotional response to the viewing of negative stimuli, a sexually divergent pattern of neural activation was observed within the postcentral gyrus (Domes et al., 2010). This is of interest, given that maladaptive affective regulation is found in individuals with histories of maltreatment and also is considered instrumental in the relationship between maltreatment and forms of psychopathology (e.g. Cicchetti & Lynch, 1995; Leist & Dadds, 2009; Masten et al., 2008; Pollak, 2008; Pollak et al., 2000; Shields, Cicchetti, & Ryan,

1994). Moreover, disturbances in emotional regulation have been implicated in the aetiology of many internalising and externalising symptoms (Kim & Cicchetti, 2010). Such psychiatric disorders may accordingly have associations with alterations or abnormalities in cortical structure. For instance, postcentral gyrus grey matter structure has been found to be associated with depressive symptoms, anxious depression and conduct disorder (Leung et al., 2009; Tiihonen et al., 2008; Vasic, Walter, Hose, & Wolf, 2008; Wehry et al., 2015; Yuan et al., 2008). These disorders have been found to have differing prevalence in males and females (Kessler et al., 2005).

The postcentral gyrus, which has been found to play a neurally distinct role in successful emotional regulation between the two sexes, may represent an area in which sexually dimorphic abnormalities in structure support divergent adaptive emotional processing patterns in the presence of maltreatment. These subtle differences in affective processing may characterise differing trajectories associated with risk of distinct psychiatric disorders. However, it is necessary to systematically investigate sex differences during emotional processing between maltreated and non-maltreated adolescents to identify differences both in behaviour and in neural activity.

No sex by group interactions, or main effects of sex within the maltreated group, were observed for internalising symptoms measured by the TSCC or on internalising and externalising symptomatology within a subgroup of participants who had CASI questionnaire data. This lack of sex by group interaction suggests that there isn't an isomorphic relationship between brain structure and psychiatric symptomatology. The potential explanations for this are three-fold. First, structural differences may support subtle cognitive and behavioural differences that are not captured by these diagnostic scales which assess a number of different disorders within a brief questionnaire. Second, these structural differences may represent latent neural markers for the development of psychopathology later in life and thus associations between structure and symptomatology are not ostensible in adolescence. Last, other physiological processes may compensate for structural differences, which result in comparative outcomes in symptomatology between the males and females. A longitudinal study would be a viable approach to test whether sexually dimorphic grey matter volume within the postcentral gyrus represents a latent neurobiological risk factor for the development of psychiatric disorders and

whether it exerts influence on sexually divergent pathways from maltreatment to psychopathology.

Potentially confounding demographic and neural data was considered to increase the likelihood that the observed findings were associated with the experience of childhood maltreatment. First, males and females both within and across groups did not differ on age, sex, ethnicity, IQ and socio-economic status. Females both within and across the groups were more advanced in puberty compared to males; this was to be expected as females start puberty at an earlier stage and the males and females within this sample were matched on age. This relative advancement in puberty in the females compared to the males did not differ by group and there were no significant interaction between sex and group suggesting that both groups were matched on pubertal development. To further investigate the sexually dimorphic response to maltreatment, the statistical models were re-ran with pubertal status as a covariate. The previous pattern of grey matter differences between sex and group remained significant and therefore we can infer that the observed results are not related to variance in puberty development. The observation that the maltreated group, especially the females, were not more advanced in pubertal development than their non-maltreated peers stands in contrast to existing literature which has found that childhood maltreatment, especially sexual abuse within females, is affiliated with earlier timing of puberty (e.g. Bergevin, Bukowski, & Karavasilis, 2003; Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011; Wise, Palmer, Rothman, & Rosenberg, 2009). However such an association between childhood neglect and early pubertal development has not been found in males (Brown, Cohen, Chen, Smailes, & Johnson, 2004) and females (Mendle et al., 2011). The maltreatment profile of this sample show that childhood sexual abuse is the least common form of abuse (13%) while neglect is one of the most common (82%); hence it could be speculated that the differing patterns of pubertal development to previous literature may be partly due to the maltreatment demographics of this sample.

Second, both males and females within the maltreated group did not show any significant differences in the occurrence and severity of maltreatment experience, both across and within subtypes. This would suggest that both sexes experienced a similar level of maltreatment during childhood. Furthermore, the experience and severity of community violence did not differ by group or sex. Therefore we can infer that the differences captured by the interaction term are

likely due to sexually dimorphic responses to maltreatment rather than differences between the sexes in the experience of maltreatment or community violence.

Finally, in line with existing literature on sexually dimorphic cortical structure, males were found to exhibit larger overall grey matter, white matter, cerebrospinal fluid and total intracranial volume (Luders et al., 2009). There were no group differences relating to these global values. As the grey matter segments were only multiplied by the non-linear component of the registration during the normalisation procedure, the individual differences in brain size were accounted for. As a secondary check, standardised residuals of the grey matter values extracted from the significant postcentral were produced, covarying out the influence of total grey matter volume and separately total intracranial volume. The sexually dimorphic pattern of grey matter volume remained when re-running a 2x2 ANOVA investigating the interaction of group and sex on the standardised residuals.

Limitations and future directions

The present findings should be interpreted in light of a number of limitations, strengths and suggestions for future directions. First, although there were no significant differences between the two sexes in terms of maltreatment experience captured by official substantiated reports, this does not necessarily indicate lack of differences in the subjective experience of abuse. In **Chapter 2**, our findings showed that self-reported accounts of abuse severity were associated with grey matter volume within a number of cortical regions within the maltreated group, whereas substantiated official reports of maltreatment characteristics did not. Future investigations may consider using both self-report and official substantiated measures of trauma experience to better characterise an individual's past history of abuse and to explore sex differences in cortical structure related to the subjective experience of abuse.

Second, the intrinsic limitation of a purely structural investigation is that it does not allow us to concretely assign altered function to regions of abnormal grey matter volume. One can make inferences regarding the functional importance of an affected area based on existing literature and how this is understood within a plausible narrative. However, a systematic investigation into sexually dimorphic emotional processing of maltreated individuals would be needed to provide support

for the hypothesis that the postcentral gyrus could support divergent patterns of emotion processing, a potential precursor to risk of psychiatric disorder.

Third, the cross-sectional design of this study meant that we were unable to establish the causality of the results found or to support the suggestion that this area may support sexually divergent patterns of behaviour or symptomatology later in life. A follow-up of these individuals assessing behavioural functioning and structural change within a longitudinal project is needed to gain understanding on the predictive power of the cortical abnormalities on later behavioural functioning and risk for psychiatric disorders.

Fourth, findings presented here point to the importance of the need to consider and explore potential sex differences in the response to maltreatment behaviourally, functionally and structurally. In our study, females and males were found to represent divergent patterns of neural structure associated with maltreatment. These structural effects could have a cascade of currently unknown influences on neural functioning and behaviour that represent a fascinating and crucial route of future investigations. The implications of such research include potentially sexually distinct forms of intervention and therapy that serve maladaptive behaviours more prevalent within one sex than the other.

Lastly, to our knowledge this is the first time that the sexually dimorphic impact of maltreatment on cortical structure within a community sample of adolescents has been investigated. Additionally, previous studies recruiting adult samples have restricted analysis to a number of prescribed regions potentially limiting the detection of regions of interest. The current study used a whole brain analysis to allow for the sensitive detection of potential sex differences unrestricted to a-priori regions.

5.5. Conclusions

This chapter describes the first study of the sexually dimorphic impact of maltreatment on grey matter volume in a community sample of adolescents. Investigating whether regions of atypical structure within the maltreated group we observed that bilateral supramarginal gyrus reduction in GMV reported in Chapter 3 was primarily driven by females than males. The regions of reduced GMV in middle temporal lobe and medial orbitofrontal cortex appeared to be driven by both males and females. Furthermore, a disordinal interaction between sex and history of

childhood maltreatment was found within a region of the postcentral gyrus. Given the sexually distinct associations of the postcentral gyrus and supramarginal gyrus with emotion processing (Adolphs et al., 2000; Canli et al., 2002; Domes et al., 2010), a facet commonly found to be affected in maltreated individuals (Pollak, 2008), we hypothesise that structural abnormalities within these region may support sexually divergent patterns of emotion processing, a latent risk factor for the development of different patterns of psychiatric symptomatology in later life. Collectively, these findings indicate that males and females characterise the experience of maltreatment differently in grey matter volume, which may have potential consequences for behavioural functioning and risk for later maladaptive outcomes. Greater awareness to and investigation of sex differences in the impact of childhood maltreatment is needed, as it may have important implications for the detection and effective intervention of dysfunctional and negative behaviours.

CHAPTER 6: An investigation into the sexually dimorphic impact of maltreatment on cortical structure using surface-based measures.

6.1. Introduction

As detailed in Chapter 5, sex represents a key factor that may contribute to the heterogeneity in the developmental sequelae associated with childhood maltreatment. In Chapter 5, it was shown that although males and females show a similar pattern of GMV reduction in some regions, bilateral middle temporal lobes and left medial orbitofrontal cortex, they present with differences in GMV across a number of cortical regions, including bilateral supramarginal gyrus and left postcentral gyrus. No previous study, however, has examined sex differences in surface based measures in children exposed to maltreatment; as noted in Chapter 2, such discrete indices of cortical structure may provide more sensitive measures of changes in neural structure in response to adversity.

Sex differences are evident at many different levels of neurobiology and structure, from the structure of ion channels, to the molecular mechanism for apoptosis and to cognition and behaviour (Cahill, 2006; Jazin & Cahill, 2010; Li et al., 2005). It would therefore appear reasonable to hypothesize that a number of sex differences may be evident in the structural determinants of grey matter volume, including cortical thickness, surface area and local gyrification given that GMV differences have been associated with chronic environmental stressors, such as childhood maltreatment (Hart & Rubia, 2012; McCrory et al., 2010). The investigation of the sexually dimorphic impact of maltreatment on surface-based measures of cortical structure represents an important step in fully characterising the heterogeneous impact of maltreatment on the brain. This investigation may begin to provide valuable clues to potential sex-specific neuro-developmental pathways that may risk to maladaptive behaviours and psychiatric symptomatology typically associated with the experience of maltreatment.

Sex differences in cortical structure and developmental trajectories

Differences in cortical thickness across sexes have been observed in both post-mortem and in-vivo neuroimaging studies of humans (Lenroot & Giedd, 2010). Importantly, thinning of grey matter and changes in surface area and local gyrification are natural developmental processes that occur with age across the

cortex (Giedd, 1999; Raznahan et al., 2011; Sowell, 2004). Sex differences in cortical thickness have been reported in a number of regions of the cortex, as well as on a global cortical scale (Im et al., 2006; Luders et al., 2006; Luders et al., 2005; Lv et al., 2010; Sowell et al., 2007). In particular, women are found to have generally thicker cortices than men and regions including the parietal, occipital and motor areas, even when accounting for total brain volume (Im et al., 2006; Luders et al., 2006; Savic & Arver, 2014; Sowell et al., 2007). Within these areas of increase, testosterone has been found to play an important role in the structural integrity, negatively correlated with thickness values, suggesting that these differences may be driven by genetic and hormonal differences (Savic & Arver, 2014). The mechanism of cortical thinning, in particular, across sexes is believed to optimise computational processing as commonly used circuits are insulated and rarely used synapses are killed (Sowell et al., 2007). Recent investigations have reported that cortical thickness development follows an inverted-U cubic trajectory, however sex is found to have less of an influence of its tempo than other determinants of volume (Raznahan et al., 2011).

Cortical surface area also follows a pattern of female weighted local increases compared to men (Luders et al., 2006). Similar to cortical thickness, surface area follows an inverted-U cubic trajectory during adolescence, differing between sexes in the time to peak maturation, with females reaching peak surface area maturation earlier than males (Raznahan et al., 2011). The two determinants of surface area, convex hull area and local gyrification, also follow this cubic trajectory with sexually defined maturational peaks ((Raznahan et al., 2011).

Cortical folding, or gyrification, in females tends to be show patterns of highly localised increases compared to men, namely in aspects of the frontal, temporal and parietal lobes, such as the postcentral gyrus (Luders et al., 2006). Interestingly, males do not show any regions of significantly increased cortical folding compared to their female counterparts (Luders et al., 2006). Locally, in the exploration of cortical folding regions of right prefrontal cortex to display sex differences in maturation, where males displayed a steeper decrease in gyrification with age compared to females (Mutlu et al., 2013).

Other investigations have refined the analysis of sexually divergent trajectories in cortical structure to functionally defined regions. In a recent study of the structural development of regions associated with social behaviour, sex

differences in the development of grey matter volume and surface area but not in cortical thickness were observed (Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014). Interestingly, while in females, rapid volumetric expansion during childhood is equally driven by changes in thickness and surface area, in males approximately two-thirds of volume change is accounted for by area changes (Raznahan et al., 2011). Generally sex differences in surface area are responsible more to sex differences in grey matter volume across the age range than sex differences observed in cortical thickness (Raznahan et al., 2011). With these globally and locally diverse developmental trajectories, periods of environmental sensitivity to environmental stressors, such as adverse childhood experiences, may occur at differing developmental periods in males and females.

Sex differences in psychiatric disorders

With the onset of adolescence and puberty, there is a sexually divergent increase in the prevalence of adverse behaviours, including risk-taking behaviours and suicide in males and mood, anxiety and eating disorders in females (Costello, Copeland, & Angold, 2011; Lenroot & Giedd, 2010). As previously noted, adolescence represents a critical time in which many psychiatric disorders begin to emerge (Paus et al., 2008; Uhlhaas & Singer, 2011); a significant majority of these have differing rates of prevalence, age of onset and symptomatology between males and females (e.g. Crijnen et al., 1997; Leadbeater et al., 1999). While many studies have investigated GMV and sex differences across the range of psychiatric disorders, fewer studies have employed surface based indices. However a number of studies have been conducted in relation to with bipolar disorder (Fornito et al., 2009) and schizophrenia (Narr et al., 2005; Vogeley et al., 2000).

Sex differences in the neurobiological sequelae of maltreatment

To date, those studies investigating sex differences in cortical structure in individuals exposed to maltreatment have typically employed measures of GMV (De Bellis & Keshavan, 2003; De Bellis, Keshavan, et al., 1999; Teicher et al., 2004). One study, to our knowledge, has explored sexually dimorphic cortical thickness structure associated with early life experiences. Whittle and colleagues (2014) employed a longitudinal study to investigate the impact of positive parenting on cortical structure at 12 and 16 years of age. Cortical thinning within the anterior

cingulate across the two time points was associated with high maternal positive behaviour only within the male participants (Whittle et al., 2014). These findings suggest that cortical thickness is potentially sensitive, in a sex specific manner, to environmental influences in early life such as maternal care. It may be hypothesised that negative familial care and the experience of maltreatment would similarly exert influence on cortical thickness in a sex specific manner.

The current study

The current study aimed to build on the findings and theoretical framework of Chapters 4 and 5 by systematically investigating the sexually dimorphic impact of maltreatment experience on surface-based measures of cortical structure; cortical thickness, local gyrification and surface area. The present study endeavoured to address two main questions. First, are regions of atypical structure within the maltreated group compared to the non-maltreated group as reported in Chapter 4, driven more so by males and females? Second, is there an interaction between sex and group on the three separable measures of cortical structure using a whole brain analysis? We predicted that:

- (i)** in line with the findings of Chapter 5, maltreated females drive the findings of atypical structure in a number of the significant cortical regions described in Chapter 4; the right anterior cortex extending into superior frontal gyrus indicating cortical thickness decrease, the left superior parietal cortex displaying IGI increase and the exploratory investigation of the left inferior parietal cortex showing surface area decrease.
- (ii)** sex and maltreatment experience interact in all three of the surface-based cortical measures to provide differing patterns of atypical structure using a whole brain analysis; and
- (iii)** these regions of significant interaction will overlap with areas that represent sexually dimorphic GMV changes associated with maltreatment, potentially in regions associated with sexually divergent patterns of cognition and behaviour.

6.2. Methods

Please refer to Chapter 3 for information regarding the recruitment of participants, the measures administered and the structural scanning parameters. Table 5.1 and Table 5.2 in Chapter 5 provides information regarding the male ($n = 58$) and female ($n = 64$) participants in the maltreated ($n = 60$) and non-maltreated group ($n = 62$). The methods section of Chapter 2 describes the procedure for pre-processing the structural images using FreeSurfer (v5.3.0; <http://surfer.nmr.harvard.edu>).

Statistical analysis

The extracted mean structural values from within the significant regions of group analyses reported in Chapter 4 were imported into SPSS (IBM, Armonk, NY) to further explore the influence of sex within these group differences.

Group and sex were coded as between subject factors and contrast weighting within the QDEC (query, design, estimate, contrast) application of FreeSurfer was used to examine the interaction between group and sex. Significant clusters were converted to labels and projected from the mean surface onto the participant's individual surfaces, subsequently extracting the mean values from each participant to plot the direction of results. Cortical thickness measurements were smoothed with a full-width-at-half-maximum kernel of 15mm. Local gyrification index measurements were smoothed at 5mm and 0mm, due to IGI maps being inherently smooth (given that GI is calculated in a radius of 25mm). Excessive smoothing of the IGI data can contribute to the failure in computing Monte-Carlo null-z simulation to correct for multiple comparisons. Statistical comparisons within QDEC were corrected for multiple comparisons with a Monte Carlo z-field simulation at $p < 0.05$ (two-tailed).

Surface area was analysed at gyral level, based on the Desikan-Killiany parcellation atlas (Desikan et al., 2006), due to the surface area measure provided by FreeSurfer at a vertex level represents how much the brain has to be stretched in order to fit into common space and therefore not a genuine surface area measure. The area values provided in the parcellation statistics files represent true estimates of area at the gyral level rather than a measure of areal expansion. Surface area values were extracted at a gyral level and inputted into SPSS. A mixed-model Analysis of Variance (ANOVA) was used to assess sex by group interactions in gyral level surface area across the whole cortex.

The model was re-ran with the covariates of intracranial cortical volume, mean cortical thickness and mean local gyrification index across both hemisphere to ensure that differences in global values significantly influenced the differences observed on local values. Additionally, as cortical thickness, surface area, and local gyrification undergo dynamic changes during childhood and adolescence and are known to be influenced by IQ and age (Giedd & Rapoport, 2010; Raznahan et al., 2011; Shaw et al., 2006). Although there were no significant group differences in age and IQ, the models were re-ran with these variables and covariates of no interest and additional group comparisons were conducted within SPSS v.20 (IBM, Armonk, NY).

6.3. Results

Socio-demographic characteristics

As previously reported in Chapter 5, the maltreated group did not differ from the non-maltreated group in relation to sex, age, self-reported Tanner stage, handedness, IQ, SES and ethnicity (Table 5.1, Chapter 5). Socio-demographic characteristics between males and females are shown in Table 5.2, Chapter 5. There was a sex difference on pubertal development with the females showing more advanced pubertal development than males; however this pattern of relative pubertal maturity in females was similar across the two groups and there was no group x sex interaction ($F(1,118) = .098, P = .755$). A 2x2 ANOVA was used to explore whether there were group x sex interactions on the remaining socio-demographic variables. None of these dimensions were found to represent an interaction with group and gender and thus were not considered likely to confound the interpretation of the results.

Community violence did not differ significantly between males and females and there was no interaction between sex and group on total community violence ($F(1,118) = .561, p = .456$). Within the maltreated group occurrence of abuse across subtypes did not differ by sex and within those participants who experienced abuse, the severity did not differ by sex (Table 5.3, Chapter 5). Therefore any perceivable Group x Sex interactions are unlikely to be due to differences in the objective experience of maltreatment between males and females.

Analytic Strategy

As with the previous chapters, to aid in the clarity of the presentation of the results, an analytic strategy is described below:

- (i) Global measures of surface-based measures were assessed between groups and sex to ascertain whether there were any global differences in cortical structure.
- (ii) The group differences reported in Chapter 4 were further analysed to investigate whether the observable results were driven more so by males or females.
- (iii) The interaction between sex and group on distinct cortical indices were investigated on a whole brain scale using general linear models.

i. Group and sex differences: global measures of structure

Gender by group interactions were not significant for total intracranial volume ($F(1,118) = .74, p = .39$) mean cortical thickness ($F(1,118) = .03, p = .87$), mean local gyrification index ($F(1,118) = .46, p = .50$) and mean surface area ($F(1,118) = 1.34, p = .25$) across both hemispheres. Maltreated and non-maltreated groups did not show a significant difference in intracranial volume, however males displayed a significantly greater intracranial volume, mean local gyrification index and mean surface area compared to females (Table 6.1). The statistical models were re-run with mean global values across hemispheres included as covariates of no interest for the respective analyses due to the significant global differences between males and females.

Table 6.1. Global measures of cortical volume between the maltreated and non-maltreated groups, and between males and females. Values are in mm³.

By group					
	<i>Control (n = 60)</i>		<i>MT (n = 62)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Estimated ICV	1479214.0	122189.4	1446047.6	117034.3	0.13
Mean CT	2.65	0.09	2.65	0.10	0.86
Mean IGI	3.18	0.12	3.17	0.12	0.94
Mean SA	2646.82	233.75	2590.61	211.50	0.17

By sex					
	<i>Males (n = 37)</i>		<i>Females (n = 47)</i>		<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Estimated ICV	1512992.0	115087.5	1416473.0	106273.4	<0.001
Mean CT	2.65	0.10	2.65	0.10	0.86
Mean IGI	3.21	0.11	3.15	0.13	0.01
Mean SA	2704.03	203.55	2540.51	213.57	<0.001

ICV: Intracranial volume; CT: cortical thickness; IGI: local gyrification index; All values were computed across both hemispheres. All p values derived from t-tests.

ii. The influence of sex on structural differences associated with maltreatment

The regions of significant group differences across the structural indices of cortical thickness, local gyrification and surface area in Chapter 4 (Table 4.2) were explored to determine whether the observable differences between groups were driven more so by males or females. The extracted mean values were extracted and imported into SPSS. An Analysis of Variance (ANOVA) was applied to the data. Group and sex were coded as between subjects and the mean values within the significant cluster or region was coded as the within subject factor.

Cortical thickness

No significant interactions were found within the cluster of decreased cortical thickness in the rostral anterior cingulate cortex (ACC)/superior frontal cortex cluster ($F(1,118) = 0.19, p = .67$). Furthermore there was no significant main effect of sex ($F(1,118) = 2.56, p = .11$). Figure 6.1 plots the extracted mean cortical thickness values for sex and group within this region. The model was re-run including age and IQ as covariates and the same pattern of results remained, including a non-significant interaction between sex and group ($F(1,116) = 1.39, p = .24$).

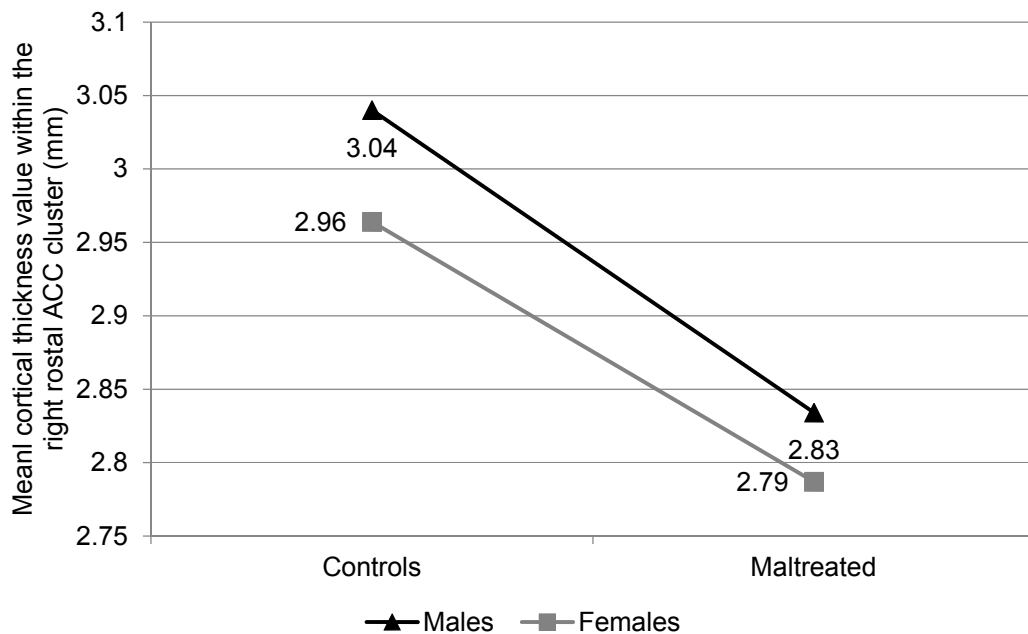


Figure 6.1. Line chart illustrating the mean cortical thickness values within the right rostral ACC cluster split by group and sex.

Notes: There was no significant effect of sex nor an interaction between group and sex. Cortical thickness values in mm.

Local gyrification

Within the superior frontal cluster that displayed a significantly increase local gyrification in the maltreated group, there was no significant interaction between sex and group ($F(1,118) = 1.00, p = .32$). Additionally there was no main effect of sex ($F(1,118) = 1.26, p = .26$). Figure 6.2 displays the mean local gyrification index values across the groups and sex. Re-running the model including age and IQ as covariates did not modify the pattern of results and the interaction remained not significant ($F(1,116) = .39, p = .53$).

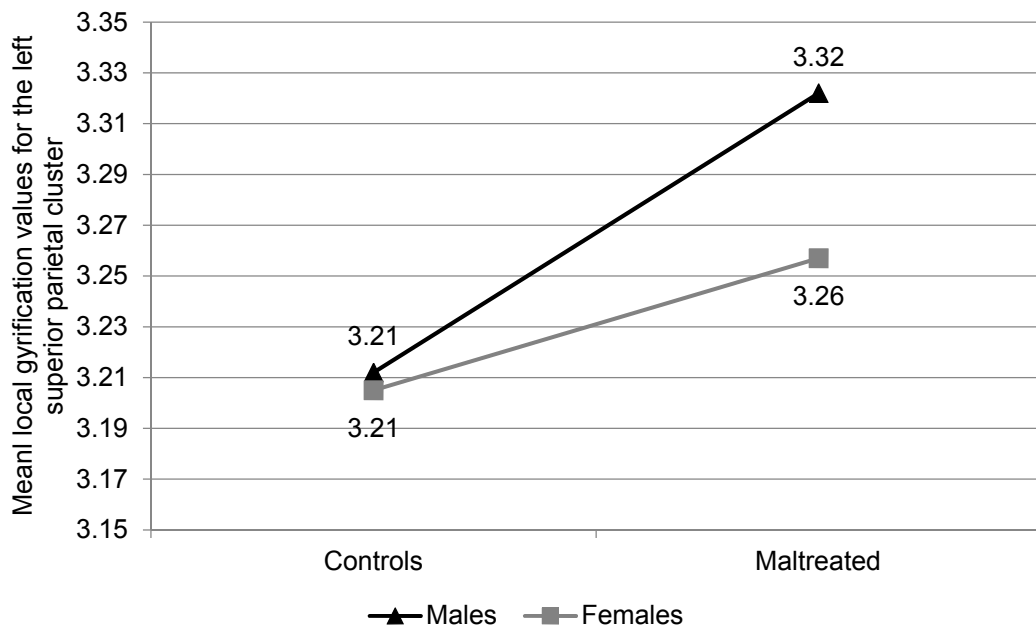


Figure 6.2. Line chart illustrating the mean local gyrification index values within the left superior parietal cluster split by group and sex.

Notes: There was no significant effect of sex or an interaction between group and sex.

Surface area

An exploratory analysis was undertaken to explore the mean surface area value within the right inferior parietal area, which was found to significantly differ between the maltreated and control groups when corrected for multiple comparisons at the lobar level only (see chapter 4). As with the previous two cortical indices, surface area values within this region were found not to display an interaction between group and sex ($F(1,118) = .65, p = .42$). Furthermore this region did not show a main effect of gender ($F(1,118) = .12, p = .73$). Similarly, this pattern of results

remained when including age and IQ as covariates into the model. Figure 6.3 displays the mean surface area value within the parcellated region of the inferior parietal region across the groups and sex.

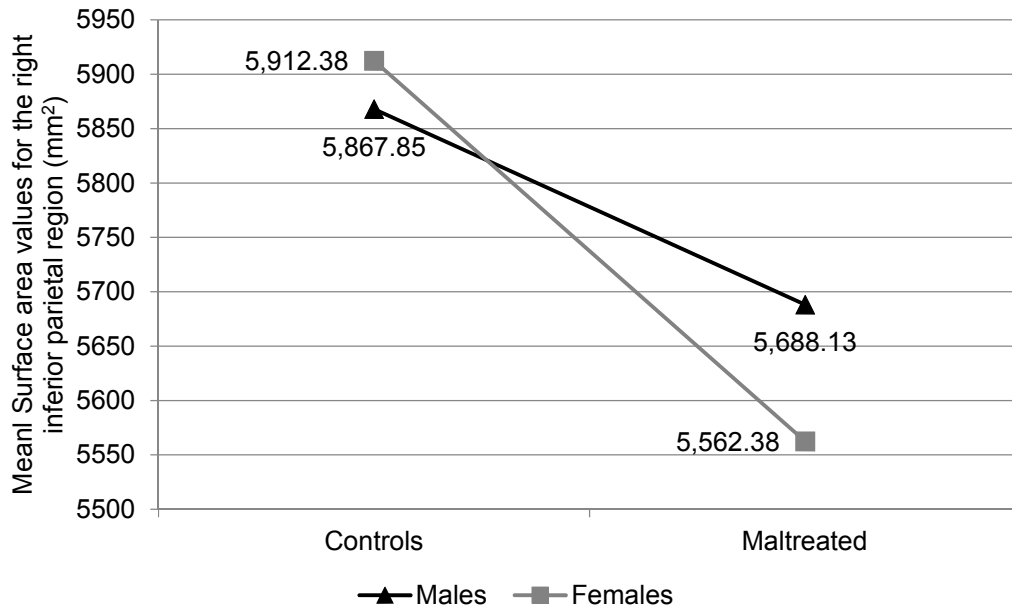


Figure 6.3. Line chart illustrating the mean surface area values within the right inferior parietal cluster split by group and sex.

Notes: There was no significant effect of sex nor an interaction between group and sex. Surface area values in mm³.

iii. Sex differences following maltreatment on discrete surface-based cortical indices

A general linear model analysis was applied to the data to investigate interactions between sex and group. Sex and group were coded as discrete variables, and demeaned and normalised intracranial volume was included as a nuisance factor.

Cortical thickness

No sex by group interactions were observed for cortical thickness in both left and right hemisphere. The model was re-run including age and gender as nuisance factors with the same pattern of no significant regions of interaction being observed.

Local gyrification

The local gyrification analysis identified two significant clusters showing an interaction between sex and group; one in the left hemisphere and one in the right hemisphere. The left hemisphere cluster had its peak within the precentral gyrus (Table 6.2, Cluster 1; $x=-37$, $y=-18$, $z=65$; $p_{\text{cluster}} < .001$) with the cluster extending into post and paracentral cortices and more medially into superior frontal, and post and caudal cingulate cortices (Figure 6.4, Cluster 1). Inspection of the means indicate that the maltreated females show less gyrification in this region than in the maltreated males. Within the right hemisphere a larger significant cluster was identified with its peak located in the inferior parietal cortex (Table 6.2, Cluster 2; $x=44$, $y=-68$, $z=7$; $p_{\text{cluster}} < .001$) and the cluster extending into aspects of the temporal lobe, the precuneus, lateral occipital lobe and lingual gyrus (Figure 6.4, Cluster 2). Figure 6.4 highlights the extent of these clusters on the inflated average surface. The mean local gyrification values for each of these clusters within the model excluding age and IQ as covariates were extracted, plotted (Figure 6.5 and Figure 6.6) and post-hoc multiple comparisons were implemented.

The model was re-run including age and IQ as nuisance factors in the same manner as the analysis in Chapter 5. Within the left hemisphere the cluster peak remained within the precentral gyrus ($X=-37$, $Y=-18$, $Z=65$; Area = 1402.7mm²; $\max\text{-log}_{10} = -4.00$; $p_{\text{cluster}} < .001$), however the cluster extent was reduced and did not extend into aspects of the superior frontal and cingulate cortex. This same pattern of cluster extent reduction was observed in the significant right hemisphere cluster. The peak coordinate remained within the bank superior temporal sulcus ($X=46$, $Y=-72$, $Z=14$; Area = 5075.9mm²; $\max\text{-log}_{10} = -4.00$; $p_{\text{cluster}} < .001$), however the cluster did not extend into aspects of the inferior parietal and supramarginal regions.

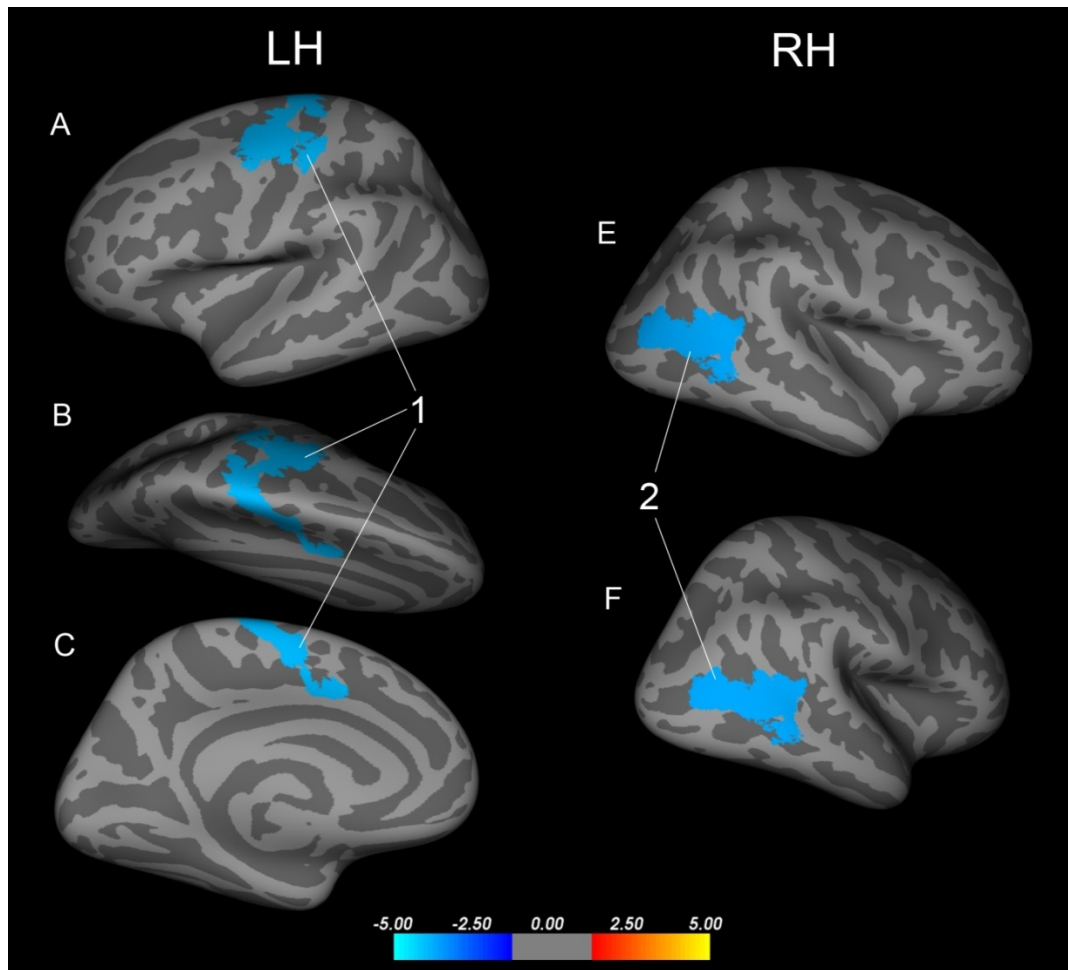


Figure 6.4. Clusters of a significant interaction between group and sex in local gyrification index.

Notes: Significant clusters reflecting group by sex interaction in local gyrification across both hemispheres projected onto an inflated average surface. In the left hemisphere, the cluster peak lies in the precentral gyrus ($x = -37, y = -18, z = 65$) and extends medially into superior frontal and cingulate cortex. In the right hemisphere the cluster peak lies within the inferior parietal gyrus and extended into aspects of the temporal lobe ($x = 46, y = -72, z = 14$). LH=left hemisphere; RH=right hemisphere. The colour bar visualises the \log_{10} significance value of the clusters ($5 = p < .00001$). Cluster statistics are shown in **Table 6.2**.

Table 6.2. Significant clusters for the interaction of sex and group in local gyrification.

Cluster no.	Anatomical regions	Cluster no.	L/R	max- \log_{10}	P_{cluster}^a	Area (mm ²)	Local Maxima (X, Y, Z)		
1	precentral gyrus/ superior frontal	1	L	-4.00	<0.001	2825.77	-37	-18	65
2	Inferior parietal gyrus / temporal lobe	2	R	-4.00	<0.001	1692.26	44	-68	7

L=left; R=right; ^a Cluster probability

As shown in Figure 6.5, the males and females in the maltreated group differed significantly in local gyrification within the left precentral cluster ($p < .005$), whereas there was no significant difference between the males and females in the control group ($p = .99$). Moreover, this pattern of results was mirrored when running post-hoc multiple comparison tests on the right hemisphere superior frontal cluster where there was a significant difference in local gyrification between the males and females within the maltreated group ($p = .024$). This pattern for the right inferior parietal cluster is illustrated in Figure 6.6. All other comparisons between sex and group combinations were non-significant.

The model for the right inferior cluster was re-run including age and IQ as covariates and the interaction remained significant ($F(3,116) = 6.434$, $p = .013$), while the main effect of group ($F(3,116) = .28$, $p = .60$) and sex ($F(3,116) = 2.16$, $p = .14$) remained non-significant. This pattern remained when pubertal stage was included as a covariate with a significant interaction showing the same relationship between group and sex ($F(2,117) = 10.46$, $p = .002$).

This pattern was replicated within the left precentral cluster when age and IQ were added as covariates ($F(3,116) = 4.36$, $p = .039$). Including pubertal status as a covariate also did not affect the significance of the interaction ($F(2,117) = 5.59$, $p = .020$).

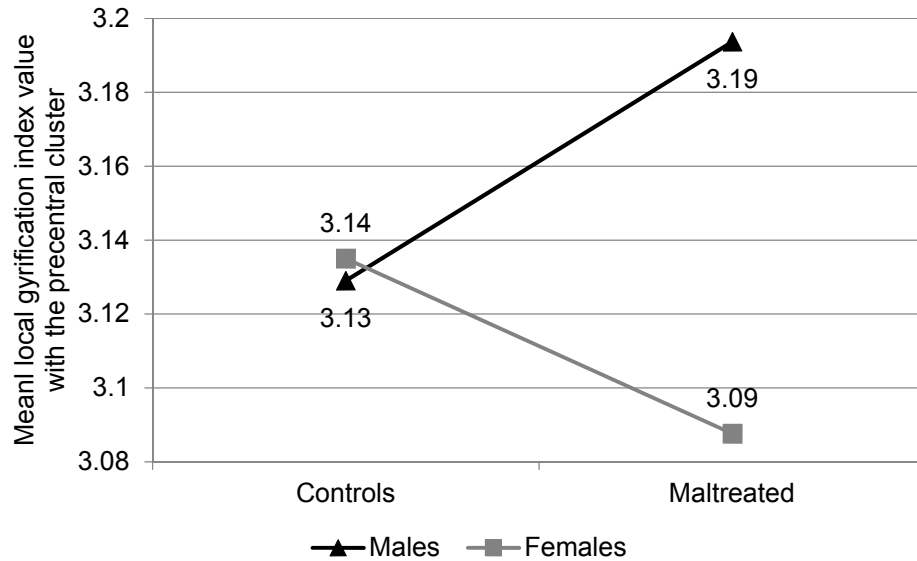


Figure 6.5. Plot of the mean local gyrification values within the left precentral cluster (Figure 6.4, Cluster 1) split by group and sex.

Notes: A significant group difference between the males and females is observed between the males and females within the maltreated group ($p < .005$). There was no significant main effect of group and no significant difference between males and females in the control group.

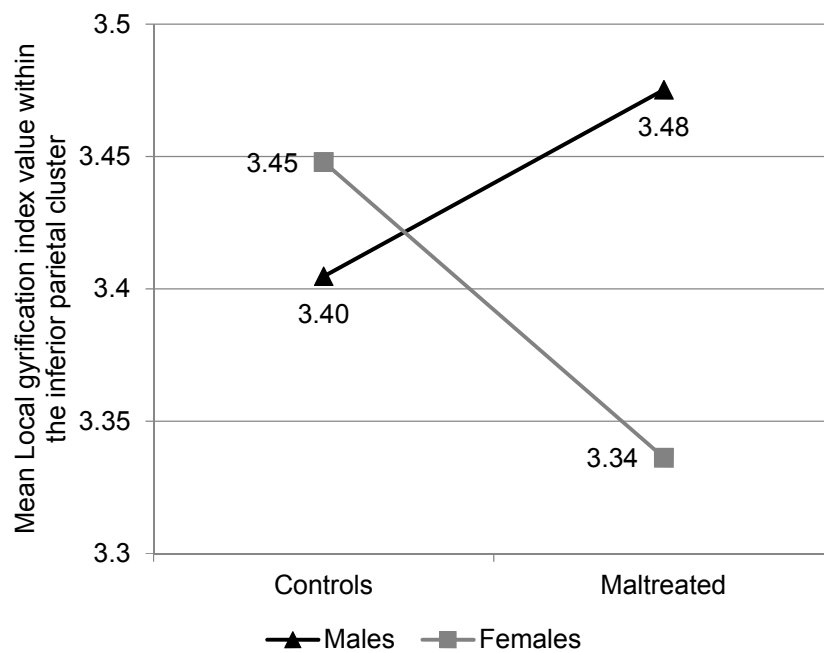


Figure 6.6. Plot of mean local gyrification values within the right inferior parietal cluster (Figure 6.4, Cluster 2) split by group and sex.

Notes: A significant group difference between the males and females is observed between the males and females within the maltreated group ($p = .024$). There was no significant main effect of group and no significant difference between males and females in the control group.

Surface area

A mixed-model Analysis of Variance (ANOVA) was used to assess sex differences in gyral level surface area across the whole cortex. Group and Sex were coded as between subject factors and both hemisphere and region were coded as within subject factors. Follow up ANOVAs were used to examine group and sex interactions in surface area within gyral regions. As indicated in Chapter 4, due to the relatively large number of follow-up ANOVAs, a false discovery-rate correction (Benjamini & Hochberg, 1995) was performed per hemisphere and per lobe to control for multiple comparisons. There was a main effect of Sex ($F(1,118) = 21.31$, $p < .001$) and a main effect of Group ($F(1,118) = 4.36$, $p = .04$) on surface area. However there was no significant group by sex interaction ($F(1,118) = 1.34$, $p = .25$) in cortical surface area. There was both a significant sex by gyral region ($F(33,88) = 8.36$, $p < .001$) and group by gyral region ($F(33,88) = 2.68$, $p = .012$) interaction, however there was no significant three way interaction between group, gender and gyral region ($F(33,88) = 1.58$, $p = .144$).

Follow-up one way ANOVAs were used to examine group differences in gyral level surface area. Applying FDR correction for multiple comparisons by lobar region, we observed that left pars triangularis was the only gyral region of surface area to represent an interaction between sex and group ($F(1,118) = 10.58$, $p = .001$). This region did not survive multiple corrections across the 34 gyral regions by hemisphere.

Correlations

As previously reported in Chapter 4, a 2x2 ANOVA exploring sex by group interactions for trauma symptomatology found that there was no main effect of sex and no sex by group interaction for internalising problems and externalising problems. A main effect of group was observed for both internalising and externalising problems. No correlations were observed between extracted grey matter values and psychiatric symptomatology within either the maltreated male or females.

6.4. Discussion

The present chapter sought to systematically investigate the sexually dimorphic impact of maltreatment experience on surface-based measures of cortical structure; cortical thickness, local gyrification and surface area. We examined whether structural group differences, as reported in Chapter 4, between maltreated and non-maltreated groups were driven more so by females or males. We additionally examined whether sex and childhood maltreatment experience interacted to exhibit atypical structure using surface-based methods. First, we found that the surface based differences in cortical thickness, local gyrification and surface area between maltreated and non-maltreated groups (as reported in Chapter 4) were not differentially driven by males or females. Rather, the pattern of atypical structure was similar across both maltreated males and females. Second, in our whole brain analysis no significant interactions between sex and maltreatment were found in relation to cortical thickness and surface area. However, sex and experience of childhood maltreatment interacted in two bilateral clusters with females showing reduced gyrification: the left precentral extending into paracentral and cingulate cortex and the right temporal lobe extending in to the lateral occipital lobe.

Our first step was to investigate whether the regions found to display group differences between the maltreated and non-maltreated groups, reported in Chapter 4, were driven more so by females or males. Our results suggested that within these clusters of significant atypical structure associated with the experience of childhood maltreatment, that maltreated male and female individuals exhibited similar patterns of change compared to the control group. These findings stand in contrast with the GMV findings reported in Chapter 5, which identified two significant clusters which were only significant in the female individuals and contributed to the main effect of group. Independently exploring the cortical determinants of volume may not uncover structural differences between groups or sexes that survive statistical thresholding and controls, however the cumulative impact of these cortical indices may be observable as a significant pattern of GMV decrease, as observed within bilateral supramarginal gyrus in **Chapters 4 & 5**.

Cortical thickness and surface area were found to show similar patterns across the groups and sexes indicating that sex did not influence the impact of

maltreatment on the brain in these cortical indices. The differences in gyrification representing an interaction between group and sex may potentially illustrate a downstream consequence of an aberrant developmental trajectory of cortical growth in response to the experience of maltreatment. These two significant clusters extend over a number of cortical regions, therefore these findings will be considered in light of the collective function of these areas.

The first significant cluster was located in the left hemisphere, broadly spanning across the regions of precentral cortex into paracentral cortex and aspects of posterior cingulate and superior frontal cortex. The pattern of interaction between sex and maltreatment experience indicated that males and females in the control group did not differ in local gyrification index, however in individuals who had experienced childhood maltreatment there was a divergent pattern of difference. While maltreated males displayed an increase in IGI compared to control males, maltreated females displayed a relative decrease in IGI to the control females. Males and females within the maltreated sample significantly differed in the IGI within this region, indicating that exposure to abuse and neglect was partly characterised by distinct patterns of atypical IGI within this pre/paracentral region.

While these regions have traditionally been attributed to motor abilities (Havel et al., 2006), they have also been implicated in diverse cognitive and affective functions. Importantly, sex differences in the function of this region of paracentral cortex have been noted in previous investigations exploring cognitive control of affective states in normative samples (Domes et al., 2010). Furthermore, it has been suggested that this region has a general role in the cognitive reappraisal of affect (Eippert et al., 2007; Ochsner et al., 2004). In addition, the regions of posterior cingulate and superior frontal cortex have been associated with the processing of emotionally valenced stimuli (Fischer, Wik, & Fredrikson, 1996; Maddock, 1999; Maddock & Buonocore, 1997) and the retrieval of emotional knowledge (Ochsner et al., 2004) respectively. Adults with PTSD and childhood histories of abuse, shows increased BOLD response during traumatic memory recall in both the posterior cingulate and the motor cortex (Bremner et al., 1999). The authors of this particular investigation suggested that increased activation in this region represents an important component for coping with physical threat (Bremner et al., 1999), potentially via the cognitive control of emotional states. However aspects of this current cluster has also been found to show neurally distinct patterns of activity during olfactory processing in women with a history of childhood

maltreatment (Croy et al., 2010) and in cognitive control tasks using non-emotionally valenced stimuli in maltreated adolescents (Mueller et al., 2010), which may suggest that atypical neural activity in this region is not limited to associated trauma or emotional state and these regions may represent a more general role in cognitive control processes. Importantly, a recent investigation exploring cognitive and emotional processing in maltreated youth with PTSD using an emotional oddball task, found that maltreated males and females displayed differential neural activity within a region of the post and precentral gyrus (Crozier, Wang, Huettel, & De Bellis, 2014). Such neural differences were believed to underlie dysfunction in cognitive control during emotional processing; therefore we propose that structural variation within these regions may sub-serve similar differences within this domain. The sexually divergent structural differences reported in this current chapter, taken alongside the common finding of atypical structure within the rostral anterior cingulate/OFC as reported in Chapter 3, which we proposed may underlie deficits in emotional regulation, could suggest that both males and females may display deficits in the cognitive control of emotion, however there may be particular neural and behavioural characteristics that characterise deficits between the sexes.

The second cluster indicating an interaction between sex and maltreatment experience was located in the right hemisphere, extending across the middle temporal and inferior parietal regions, an area commonly referred to as the tempo-parietal junction. In the control group males and females did not differ in local gyrification index. However in individuals who had a childhood experience of maltreatment, maltreated males were found to display increased local gyrification index compared to male controls and maltreated females were found to show decreased local gyrification index compared to control females.

Broadly speaking, the bilateral middle temporal gyrus has been found consistently to be involved in theory of mind (Völlm et al., 2006) as well as in autobiographical memory processing (Holland et al., 2011). Both domains proposed to have similar neural underpinnings (Corcoran & Frith, 2003; Markowitsch & Staniloiu, 2011; Rabin, Gilboa, Stuss, Mar, & Rosenbaum, 2010; Spreng, Mar, & Kim, 2009). Similarly, the right parietal region is believed to have a vital role in self-representation (Keenan, Nelson, O'Connor, & Pascual-Leone, 2001) and perception of one's own body (Berlucchi & Aglioti, 2010). Collectively, this tempo-parietal junction has been consistently been shown to be activated during the selective attribution of mental states and theory of mind (Saxe & Kanwisher, 2003; Saxe &

Wexler, 2005). Furthermore, sex differences within these domains are apparent in normative samples (Baron-Cohen, 2000; Brown, Donelan-McCall, & Dunn, 1996). Divergent cortical structure between the two sexes is of interest as it may underlie similarly divergent patterns of behaviour associated to these functional domains. Certainly, impairments in concepts of self and emotional regulation are apparent in maltreated samples of children and adults (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003; Classen, Field, Atkinson, & Spiegel, 1998; Rogosch, Cicchetti, & Aber, 1995), suggested to be a delay in the typical development of theory of mind (Cicchetti et al., 2003). In particular, women with PTSD attributed to childhood trauma, display divergent abilities in theory of mind compared to non-maltreated controls (Nazarov et al., 2014), potentially highlighting that atypical function in this domain may be associated with the emergence of a psychiatric disorder.

Theory of mind deficits are seen within a number of psychiatric disorders, such as depression (Huprich, Pouliot, & Bruner, 2012; Shestyuk & Deldin, 2014), anxiety disorders (Hezel & McNally, 2014), and psychotic disorders (Bora, Yucel, & Pantelis, 2009; Langdon et al., 1997; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007), all of which have been shown to have a higher preponderance in individuals who have experienced maltreatment (e.g. Fisher et al., 2013; Green et al., 2010; Kessler et al., 2010; Toth et al., 1992). Structurally, within these disorders we find that the region of middle temporal into inferior parietal cortex displays volumetric and cortical thickness decreases in samples of depressive patients (Jaworska et al., 2014; Wagner et al., 2012) and local gyrification index reductions in individuals with schizophrenia (Nesvåg et al., 2014; Palaniyappan & Liddle, 2012a). Interestingly, Nesvåg and colleagues also reported IGI reductions in a similar left paracentral/precentral region within a sample of schizophrenic patients as we have previously described in our sample (Nesvåg et al., 2014), potentially indicating similar patterns of effected behaviour. As discussed in the discussion, the prevalence and phenotype of these disorders differs between the sexes (Leadbeater et al., 1999; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012) and based on this collective information, we hypothesise that sexually divergent patterns of local gyrification index associated with the experience of maltreatment, may possibly underlie sexually distinct patterns of atypical theory of mind, which may act as latent vulnerabilities for the emergence of psychiatric disorders later in life.

Limitations

The present findings should be interpreted in light of a number of limitations, strengths and suggestions for future directions. First, the use of a cross-sectional study restricts our ability to make causal inferences about the experience of childhood maltreatment and the observed differences in the males and females of the maltreated group.

Second, as grey matter volume is determined by cortical thickness and surface area, it was surprising not to observe differences in similar precentral clusters displayed in the sex by group interaction in Chapter 5. Why were sex differences in the structural determinants of grey matter volume (cortical thickness and surface area) not exhibited in the same region as the GMV interaction described in Chapter 5? One possibility is that the volumetric interaction was born from a cumulative effect of surface area and cortical thickness, too weak independently to have been detected whole brain within the current chapter. Differences in the analysis techniques may have intrinsically introduced variations that may have confounded the results. While this is something that cannot be fully controlled, significant quality checks were undertaken at every step of the processing pipeline in both analysis techniques to ensure that the findings were not confounded by normalisation and intra-subject alignment discrepancies.

Third, we are limited in our interpretation of the results as a similar interactions between sex and maltreatment experience were not observe in psychiatric symptomatology implying that there isn't an association between the atypical structure and current psychiatric symptoms. It may be that these structural differences underlie aspects of behavioural that have not become maladaptive to an extent that the emergence of psychiatric symptomatology has become apparent. Similarly these differences may represent latent biomarkers for atypical behaviour in later life. Likewise, a more prosaic explanation may be that these structural differences are, in a sense, normalised by other neuro-physiological processes which translates to ostensibly similar behaviour or function.

6.5. Conclusion

This current chapter has shown that while sex and childhood maltreatment interact to produce differential patterns of local gyrification in males and females, but that males and females who experience maltreatment are remarkably similar in relation

to cortical thickness and surface area. This suggests that the experience of maltreatment may have a generic effect irrespective of sex on the latter two structural indices. The two bilateral clusters showing reduced gyrification in females were a left hemisphere cluster extending across region of pre- and para-central cortex into posterior cingulate and superior frontal cortex and a right hemisphere cluster primarily situated in the tempo-parietal junction. These regions have been implicated in emotion regulation and theory of mind processes respectively, both commonly found to be affected in maltreated populations (Rogosch et al., 1995).

We propose that sexually dimorphic patterns of atypical structure within these two clusters may contribute to differences in latent neural risk factors for psychiatric symptomatology in later life across males and females. Furthermore, these findings emphasize the potential importance of sex in understanding the differential outcomes for males and females following maltreatment, and indicate the need to consider sex in future investigations.

CHAPTER 7: General discussion

7.1. Overview

Childhood maltreatment remains a major public health and social-welfare concern. The impact of maltreatment is protracted and far-reaching, associated with negative outcomes in multiple functional domains of cognition, affect, and behaviour (Cicchetti & Toth, 2005; Gilbert, Widom, et al., 2009). Importantly there is an increasingly large body of literature indicating that maltreatment increases the risk towards the emergence of a range of psychiatric disorders. In many instances these disorders may only arise well into an individual's adult years (Pechtel & Pizzagalli, 2011). The broad spectrum of associated psychiatric disorders range from depression, anxiety disorders and PTSD to conduct disorder and schizophrenia (Anda et al., 2006; Read, Os, Morrison, & Ross, 2005; Scott et al., 2010; Widom & Maxfield, 2001). More broadly, maltreatment has been associated with negative outcomes in physical health, economic productivity and academic attainment (Gilbert et al, 2009). In recent years, a wealth of structural imaging investigations have illustrated cortical regions central to the neural characterisation of childhood abuse and neglect, in a bid to understand how early stress might become 'biologically embedded' in the brain. The findings from both animal and human literature of atypical structural development associated with chronic stress in early life provide strong support for the role of maltreatment in the emergence of subsequent psychiatric disorder in adolescence and adulthood (Hart & Rubia, 2012; McCrory et al., 2010).

Despite the considerable progress in the field of structural neuroimaging of childhood maltreatment there are still areas that necessitate further research to improve our understanding of how maltreatment exposure may heighten developmental vulnerability to psychiatric disorders through neurodevelopmental pathways. Furthermore, a number of factors limit our interpretation of existing findings. This discussion will first revisit these limitations that characterise much of the existing literature, as these served to provide the rationale for the research questions that have motivated the current thesis. These research questions will then be restated, followed by a summary and discussion of the current findings as they pertain to each question. Research then clinical implications of the findings will be considered, before a discussion of the strengths and limitations of this thesis.

7.2. Limitations of extant research

A series of limitations have characterised much of the extant research in relation to the study of atypical neural structure associated with maltreatment. First, the majority of samples of maltreated individuals studied to date have limited in that they have presented with comorbid psychiatric disorder. Recruitment of individuals with concurrent psychiatric disorder presents a limitation to the interpretation of findings in structural and functional research as one cannot confidently separate the influence of maltreatment experience from that of the psychiatric disorder. Many psychiatric disorders are characterised themselves by differences in cortical structure compared to normative samples. Only a handful of extant studies have recruited samples without a concurrent diagnosis of psychiatric disorders (De Brito et al., 2013; Hanson et al., 2010; McCrory et al., 2013; McCrory et al., 2011). By recruiting a community sample of maltreated individuals without a diagnosis of psychiatric disorders we may go some way in understanding how maltreatment impacts brain structure separable from the influence of psychopathology.

Second, most existing studies have failed to adequately control for influential demographic variables. Cortical development is sensitive to a number of demographic variables such as IQ, pubertal status and SES (Brito & Noble, 2014; Shaw et al., 2006; Shaw et al., 2008). These prominent factors are routinely neglected when controlling or covarying potentially confounding variables in group analyses.

Third, the dimensions that characterise maltreatment, including subtype, severity and chronicity of abuse, have been consistently found to influence behavioural outcomes (e.g. English, Graham, et al., 2005), yet relatively little research has systematically explored how these dimensions influence atypical structure associated with maltreatment (see (Andersen et al., 2008; Edmiston et al., 2011) as an exception).

Fourth, males and females show markedly different neural environments; from the structure of ion channels and hormonal milieu to neurodevelopmental trajectories of cortical structure (Cahill, 2006; Raznahan et al., 2010). There are observable differences in how males and females respond to stressful environments, particularly early maltreatment, reflected in distinct patterns of hormonal and behavioural response (Del Giudice et al., 2011; Doom et al., 2013).

Furthermore there are differences in socialisation and access to social support between males and females which may impact the trajectory of psychopathological development. Epidemiological and clinical studies have consistently reported sex differences in the prevalence and symptomatology of psychiatric disorders associated with maltreatment (e.g. Leadbeater et al., 1999). However, there is a considerable paucity of knowledge reflecting sex differences in the neural representation of maltreatment exposure.

Fifth, the majority of structural studies in maltreatment have employed volumetric techniques to quantify structural differences within maltreated samples (McCrorry et al., 2010). While volumetric techniques have been widely used over the past decade and are well validated, it has been suggested that volume is a rather blunt measure of the underlying cortical structure (Hutton et al., 2009). Grey matter volume is determined by number of separable cortical properties, including cortical thickness, surface area and in turn, local gyrification that have differing neurodevelopmental pathways and genetic influences (Panizzon et al., 2009; Schaer et al., 2008). Such differences provide a convincing rationale for the investigation of these properties as independent indices of brain structure impacted by childhood maltreatment.

7.3. Research questions

The current thesis set out to address these gaps in the current understanding of the impact of maltreatment using the T1-weighted structural images of two samples of maltreated adolescents and children and well-matched control peers. The combined sample of a sixty-two maltreated individuals and sixty well-matched non-maltreated peers serves as one of the largest community samples of maltreated individuals in an investigation of the neural impact of maltreatment. A T1-weighted structural MRI scan was obtained for all of the participants alongside an extensive battery of behavioural questionnaires collected from the participants and their primary caregiver as part of a larger longitudinal study. Official substantiated reports of childhood maltreatment were collected for all of the maltreated participants, including self-report trauma histories on a subset of participants (Sample 2). As a result, the samples were well-suited for the systematic investigation of the impact of maltreatment on brain structure within this thesis. I endeavoured to empirically address five outstanding research questions:

1. Is the experience of childhood maltreatment associated with alterations in the structural determinants of grey matter volume?
2. Do the characteristics of the maltreatment experience (i.e. subtype, severity and chronicity) influence any observed grey matter volume differences?
3. Do the characteristics of the maltreatment experience (i.e. subtype, severity and chronicity) influence any surface-based differences of cortical structure (i.e. cortical thickness, surface area and gyrification)?
4. Is there a sexually dimorphic impact of maltreatment on grey matter volume?
5. Is there a sexually dimorphic impact of maltreatment on surface-based measures of cortical structure?

I will concisely provide a summary of the findings of the empirical chapters that sought to address these questions and then discuss the implications of these findings for maltreatment research, before exploring a number of clinical implications of the thesis findings.

Chapter 2: Is the experience of childhood maltreatment associated with alterations in the structural determinants of grey matter volume?

In **Chapter 2**, we presented a study that investigated the impact of maltreatment on the structural determinants of grey matter volume, cortical thickness, surface area and local gyrification. Overall, maltreatment was associated with a pattern of reduction in these structural indices compared to the non-maltreated peers. We reported a decrease in cortical thickness within the maltreated group compared to the non-maltreated peers within a region that extended across aspects of the rostral anterior cingulate cortex, orbitofrontal cortex and the superior frontal cortex. Furthermore we found that local gyrification reductions in the maltreated group were evident in the lingual gyrus and in a cluster extending across the anterior insula and the pars opercularis. Last, we reported reductions in surface area with the left middle temporal lobe and in the lingual gyrus. The two groups were well-matched on a number of demographic variables, including age, pubertal status, SES and IQ and no participant had a diagnosis of psychiatric disorder, therefore we are confident that these structural differences are likely to be attributed to an experience of childhood maltreatment. Of interest was the finding of reduced cortical thickness

within a frontal cluster, including the anterior cingulate. GMV reductions in the anterior cingulate have been observed in maltreated adults but not within maltreated children (Hart & Rubia, 2012; Lim et al., 2014). We suggested that variations in cortical thickness within this region may have a cumulative impact alongside other indices of brain structure that is only observable as a reduction in GMV later in life. Importantly, these findings indicated atypical structure in maltreated individuals in a number of regions not previously reported in studies of grey matter volume, suggesting that investigating structural determinants of GMV alongside volumetric techniques may allow for a more sensitive detection and representation of cortical regions associated with maltreatment exposure.

Chapter 3: Do the characteristics of the maltreatment experience (i.e. subtype, severity and chronicity) influence any observed grey matter volume differences?

In **Chapter 3**, we investigated the associations between a number of maltreatment characteristics, psychiatric symptomatology and atypical grey matter volume. Our initial group analysis identified regions of atypical structure associated with maltreatment exposure. Notably reductions in GMV were found in the right supramarginal gyrus and the right middle temporal gyrus within Sample 2. The combined sample group analysis also identified GMV reductions in the maltreated group relative to controls within bilateral supramarginal gyrus, bilateral middle temporal gyrus and left medial orbitofrontal cortex. Investigation into the associations between GMV in these regions and maltreatment characteristics indicated that total maltreatment severity derived from a self-report measure was negatively associated with grey matter volume within the right supramarginal gyrus of the maltreated group. Furthermore, self-report physical abuse scores were negatively associated with GMV within the region of right supramarginal gyrus. No significant associations were found between neural structure and indices of maltreatment, as derived from the child's social services records (i.e. in relation to maltreatment subtype, severity, or chronicity).

In relation to psychiatric symptomatology, GMV within the right supramarginal gyrus was found to be significantly and negatively associated with both externalising and internalising behaviour scores derived from a parent-rated measure of psychiatric symptom severity. Of particular note was the finding that

GMV within this region of right supramarginal gyrus in the maltreated group significantly mediated the relationship between childhood maltreatment and externalising symptoms, suggesting one possible way by which early maltreatment and psychiatric symptomatology may be linked at the neural level.

Chapter 4: Do the characteristics of the maltreatment experience (i.e. subtype, severity and chronicity) influence any surface-based differences of cortical structure (i.e. cortical thickness, surface area and gyrification)?

In **Chapter 4**, we extended the theoretical aims of **Chapter 3** to explore the influence of maltreatment characteristics on surface-based measures of cortical structure. The findings of Sample 1 in **Chapter 2** guided regions of interest for the analysis of group differences in Sample 2. A trend effect for a decrease in the region of the rostral anterior cingulate extending into the superior frontal was observed, however an increase in local gyrification was noted within the ROI of the pars opercularis and anterior insula. Employing a whole brain analysis, we found that cortical thickness was increased in a region of lateral occipital into superior frontal gyrus within the maltreated group compared to the non-maltreated peers. Furthermore local gyrification increase within the maltreated group were detected in a region covering the fusiform and parahippocampal gyrus accompanying the aforementioned region of the insula. To our surprise, this pattern of findings differed from what we observed in **Chapter 2** and were contrary to our predictions.

Our second step in the analysis procedure, combining Sample 1 and Sample 2, was to identify regions of atypical structure in a large sample, with a diverse history of maltreatment experience. In regards to cortical thickness we observed a decrease within the right rostral anterior cingulate into superior frontal cortex within the maltreated group compared to controls, mirroring the findings of decreased cortical thickness within a similar cluster reported in **Chapter 2**. The decrease in cortical thickness within this ACC cluster may represent the most reliable finding within the thesis. By contrast, analysis of group differences local gyrification index, indicated increases within the left superior parietal cortex of the maltreated group compared to non-maltreated peers. No group differences in cortical surface area reached significance after correcting for multiple comparisons.

Surprisingly, no regions of atypical structure were found to be associated with the maltreatment characteristics as derived from the child's social services records or in relation to the child's self-report. (However, local gyrification index values within the insula were positively associated with self-reported scores of emotional neglect in the maltreated group of Sample 2). Similarly, no regions of atypical structure were significantly associated with psychiatric symptomatology.

Chapter 5: Is there a sexually dimorphic impact of maltreatment on grey matter volume?

In **Chapter 5** we presented a study investigating the sexually dimorphic impact of childhood maltreatment on grey matter volume. This investigation sought to address two questions, whether: i) the previously described group GMV differences in the maltreated group (**Chapter 3**) were driven more by males or females?; and ii) if there was an interaction between sex and the experience of maltreatment on grey matter volume?

Our findings in relation to the first question indicated that the decrease in grey matter volume reported within the bilateral supramarginal gyrus of the maltreated group compared to the non-maltreated peers was driven by the female participants. In bilateral supramarginal gyrus it was found that males in the control and maltreated groups displayed similar levels of grey matter volume, however the maltreated females displayed a significantly reduced level of GMV within both of these regions, suggesting that the females were driving the observed GMV group differences within this region reported in **Chapter 3**.

To address the second question regarding whether sex and maltreatment experienced interact on grey matter volume, we employed a flexible factorial model across the whole brain. Our findings indicated that there was a disordinal interaction between sex and maltreatment experience within a region of the postcentral gyrus. This interaction represented a pattern of greater grey matter volume within the control females compared to the control males, however those who had experienced childhood maltreatment displayed an inverted pattern of grey matter decrease between males and females, in other words, maltreated females had less GMV within the postcentral gyrus compared to maltreated males. Interactions between sex and maltreatment experience were not found for any of the measures of psychiatric symptomatology suggesting that there is not an isomorphic relation

between the pattern of GMV differences and current ostensible psychiatric symptoms in the sample participants.

Chapter 6: Is there a sexually dimorphic impact of maltreatment on surface-based measures of cortical structure?

In **Chapter 6** we presented a study investigating the sexually dimorphic impact of childhood maltreatment on surface based measures of cortical structure. This investigation sought to address two questions, whether: i) the previously described group surface based differences in the maltreated group (**Chapter 4**) were driven more by males or females?; and ii) if there was an interaction between sex and the experience of maltreatment in relation to surfaces based indices?

Interestingly we found that all of the previously reported group differences in **Chapter 4**, showing atypical structure in the maltreated group compared to the non-maltreated peers, were similar across male and female participants. When we explored the interaction between sex and maltreatment experience on local gyrification index across each hemisphere, we found two significant clusters, a left hemisphere cluster extending across pre and paracentral cortices into superior frontal and cingulate cortex, and a right hemisphere cluster extending across inferior parietal and middle temporal regions. The pattern of interaction for both of these regions was that of similar local gyrification index between male and female control participants and an increase of IGI in the male maltreated group and a decrease in IGI in female participants. Both groups and sexes were matched on all demographic variables, except for pubertal status, where female participants showed greater pubertal development compared to their male counterparts in both groups. We ran the models again with pubertal status included as a covariate of no interest and the significant interaction and pattern of relative IGI remained, suggesting that these significant results were not the result of variations in pubertal status. No interactions between sex and maltreatment exposure were observed within the measures of cortical thickness and surface area.

7.4. Research implications

As stated previously, the findings of these empirical chapters have implications on a number of theoretical and methodological areas of maltreatment research. I will succinctly discuss these topics below; including the current understanding of

atypical structure associated with maltreatment, the utility of investigating the structural determinants of GMV, the associations between brain structure and maltreatment characteristics and psychiatric symptomatology, and the influence of sex in the impact of maltreatment on brain structure.

While the significant regions of each empirical chapter has been discussed in depth within their respective empirical chapter discussion sections, I will briefly highlight a couple of cortical regions that represent important implications for the domain of maltreatment research and provide a focus for future studies. The cortical regions of the anterior cingulate cortex and the middle temporal gyrus have been consistently reported in structural imaging studies of childhood maltreatment (Lim et al, 2014) and represent potentially important areas in the underlying structure of behavioural and psychiatric functioning associated with maltreatment.

The anterior cingulate cortex

As detailed in the introduction to the thesis, the anterior cingulate cortex has extensive connections with cortical, limbic and paralimbic regions. Of importance are its dense interconnections with neighbouring regions of the frontal cortex as well as the amygdala and the anterior insula, areas involved in modulating vigilance to emotionally salient information in the environment and interoceptive awareness, respectively (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Davis & Whalen, 2001; Devinsky et al., 1995). Early lesion studies in humans note that ablations to this region produced a lack of distress, apathy and emotional instability (Corkin, Twitchell, & Sullivan, 1979). More recently, neuroimaging investigations have proposed a central role for the anterior cingulate cortex in emotional regulation through its top-down modulation of limbic and endocrine systems (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Ochsner & Gross, 2005; Quirk & Beer, 2006; Schiller & Delgado, 2010; Vogt, Finch, & Olson, 1992). It has been proposed that functional activation within the ACC and associated amygdala reflect behavioural patterns of emotional conflict (Etkin et al., 2006). The ACC's functional relationship to the amygdala has been of great interest in the investigation of emotional regulation and the neural characterisation of individuals with PTSD (Bremner, 2002; Bryant et al., 2008; Liberzon & Martis, 2006; Shin & Liberzon, 2010). Specifically, in structural studies smaller GMV in the right anterior cingulate cortex was found to characterise a sample of individuals with abuse-related PTSD compared to control subjects (Kitayama et al., 2006; Thomaes et al., 2011). Furthermore, the existing

maltreatment literature has consistently reported GMV reductions within samples of maltreated adults (Cohen et al., 2006; Hart & Rubia, 2012; Lim et al., 2014; Treadway et al., 2009) see Lim et al, 2014 for a meta-analytic review). Deficits in effective emotional regulation have been proposed to be likely due to the disruption in development of fronto-limbic neural circuits involved in emotion, including the amygdala, orbito-frontal cortex and the ACC (Ochsner & Gross, 2005). The findings of the **Chapters 2, 3 & 4** indicated that while there was an absence of GMV differences within the right ACC, reductions in cortical thickness within this region were evident in the maltreated group compared to the non-maltreated peers. These findings viewed alongside the previously described functional and structural literature, may suggest that atypical structure within this region may underlie differing patterns of emotional regulation between the maltreated and non-maltreated peers. Certainly, robust associations have been made between maltreatment exposure and under controlled and ambivalent emotion regulation patterns (Maughan & Cicchetti, 2002). However, as an emotional regulation paradigm was not available for these participants we cannot infer that these structural differences reflect behavioural differences within this domain. It would be of interest in future studies to investigate the role of the anterior cingulate in emotional regulation using functional neuroimaging task such as the Stroop task with emotionally salient task-irrelevant stimuli (Etkin et al., 2006).

As suggested in **Chapter 2**, GMV is determined by surface area and cortical thickness. It is therefore possible that prolonged exposure to maltreatment may have a cumulative impact on cortical thickness, particularly within the ACC, across development that is only observable as a reduction in GMV by adulthood. It would be of interest to determine whether GMV differences reported in adult samples are a product of variations in surface area, cortical thickness or a cumulative impact of the two. Structural differences within the ACC may be subtle early in development, and possibly due to functional differences, atypical structure becomes more pervasive over time, emerging as a region of volumetric difference detectable via VBM. Further longitudinal investigations incorporating functional or behavioural measures of emotion regulation would be useful in determining what role reductions in cortical thickness play within this affective process. Furthermore whether these differences confer risk for psychiatric disorder later in life and whether certain protective factors 'normalise' these differences.

Temporal regions

The middle temporal region houses a collection of anatomically related structures that play a vital role in autobiographical memory (Holland et al., 2011; Squire, Stark, & Clark, 2004). With connections to limbic-related regions, the temporal lobe has been proposed to play a crucial role in mediating emotional processes such as retrieving information about emotional content in salient stimuli (Adolphs et al., 2003; Davidson, 2004). In particular, functional connections between the middle temporal lobe and the amygdala have been found to predict performance on memory retrieval for emotional events (Dolcos, LaBar, & Cabeza, 2004). The middle temporal lobe has been reported as supporting lateralised characteristics of affective processing; the left MTL is closely implicated with the processing of local and fine-grained aspects of emotional cues (Fusar-Poli et al., 2009; Kim & Hamann, 2007). Whereas, the right MTL is reportedly involved in automatic processing of global aspects of emotional stimuli ((Fusar-Poli et al., 2009; Kim & Hamann, 2007). Deficits within these domains characterise a variety of psychiatric disorders (Kleim & Ehlers, 2008; Stuhmann et al., 2011). Animal studies have established a causal relationship between experiences of early stress and reduced grey matter in temporal regions (Jackowski et al., 2011). Furthermore, early human studies identified structural reductions in the middle temporal lobe associated with maltreatment exposure (De Bellis et al., 2002) and subsequent investigations in adolescence and adults samples support this pattern of reduced volume (Hanson et al., 2010; Lim et al., 2014; Tomoda et al., 2011). Collectively, these findings are consistent with atypical structure within the left and right middle temporal lobe observed within the maltreated group of this thesis, as reported in **Chapter 2 & 3**. Given the existing literature on these region's functions and the causal relationship between stress and reductions in GMV, our findings may represent compromised abilities in these domains of affective functioning within our maltreated sample. These findings may be especially relevant for studies investigating the impact of maltreatment on autobiographical memory, particularly for emotional events.

The utility of surface-based techniques in maltreatment research

One of the important overarching findings of this thesis was the value in investigating surface-based measures of cortical structure associated with maltreatment exposure. **Chapter 2** concisely demonstrated two main points. First that surface-based investigation may uncover regions of atypical structure within maltreated populations previously undetected by volumetric techniques. Second, atypical structure captured by these surface-based indices of brain structure may

represent developmental precursors to GMV differences, observable in samples of maltreated adults but unseen in studies of maltreated children and adolescents. The first point was further supported when comparing the findings of **Chapters 3 and 4**, which indicated distinctive patterns of atypical structure within the maltreated group compared to the non-maltreated peers across the volumetric and surface-based analyses. Recent neuroimaging studies are concurrently employing volumetric and surface-based techniques to provide integrated characterisations of cortical structure and its association with clinical disorders (e.g. Cerasa et al., 2013; Colloby et al., 2011; Kühn, Schubert, & Gallinat, 2011); it therefore remains an important methodological factor to consider for the future studies of maltreatment. Primarily, it may help to provide clarification for the heterogeneity in findings of neural structure associated with maltreatment, by identifying regions that may be more subtly impacted by maltreatment, identified by structural determinants of GMV, than regions that may represent greater targets to the impact of early life stress and consistently identified via VBM. However, it may also serve to resolve discrepancies between findings in maltreated adult and child studies by potentially identifying structural precursors, in the form of cortical thickness for instance, to volumetric differences observed in adult samples but not within child samples. An understanding of these factors may provide further clues to the importance of cortical structure variations in the neural pathways from maltreatment to psychiatric disorder.

The influence of maltreatment characteristics on brain structure

One central drive of this thesis was to further understand the importance of dimensions characterising maltreatment on brain structure. Systematic investigations within **Chapters 3 and 4** sought to determine how chronicity, severity and subtype influenced atypical cortical structure associated with maltreatment recruiting one of the largest community samples of children and adolescents with documented histories of childhood maltreatment.

Our findings indicated that maltreatment characteristics derived from official substantiated reports were not significantly associated with any of the cortical indices in the regions representing atypical structure in the maltreated individuals, while self-report derived scales showed selective significant negative associations. In particular, GMV in the right SMG was negatively associated with total severity

across all subtypes and independently with physical abuse, while IGI in the left Insula was positively associated with emotional neglect alone.

These findings have two important implications. First, cortical structure represents a dose-response relationship with maltreatment exposure in specific regions, supporting previous structural findings indicating associations between trauma severity and grey matter volume (Edmiston et al., 2011; Teicher et al., 2012). Second, self-report measures of maltreatment may capture the impact of maltreatment on neural structure more sensitively than reports obtained from official substantiated sources. It may be that these two forms of maltreatment assessment are tapping into markedly different constructs of maltreatment that of subjective perception and objectively verifiable record of the childhood trauma. Subjective reports might therefore capture an aspect of resiliency and adaptation specific to an individual, represented as minimisation of self-report abuse severity, which may be closely related to the degree of stress that the maltreatment experience will have produced over time, and resulted in individual differences in its impact on cortical structure. Alternatively, because official reports are restricted to verifiable incidents of abuse and neglect, they are unlikely to capture the total incidence and severity of abuse (Hardt & Rutter, 2004) and therefore may not provide a sensitive index to capture the variance in maltreatment experience, and the subsequent associations with neural structure. The findings from this thesis underscore the importance of carefully selecting measures of maltreatment in clinical and research applications (Bremner, Bolus, & Mayer, 2007), especially when seeking to tease apart the impact of distinct aspects of maltreatment history on cortical structure.

Associations between brain structure and psychiatric symptomatology

The systematic investigations of **Chapters 3 and 4** also sought to explore the association between atypical structure in maltreated individuals and current psychiatric symptomatology. Due to differences in the questionnaire data between Samples 1 and 2, parent rated trauma symptomatology (CASI) were only available for Sample 2 participants. It was consistently found across both of the chapters that self-report trauma symptomatology (TSCC) was not significantly associated with atypical structure. However symptom scores for a range of disorders and internalising and externalising composite scores were found to reflect a significant negative association with GMV within the SMG.

These findings firstly highlight a discrepancy between two scales which attempt to capture similar behaviour patterns. It may be possible that subtle variance in participant's behaviour is captured by the more extensive parent-rated questionnaire (CASI) than the comparatively brief child-rated measure (TSCC). Further research should make use of multiple sources of both maltreatment exposure and psychiatric symptomatology to gain an understanding of the sensitivity and relevance of these sources to the neural embedding of maltreatment on cortical structure.

Nonetheless, the finding that structure is associated with current psychiatric symptomatology has important implications for maltreatment research. Primarily, it illustrates that abuse-related psychiatric symptomatology may be partly captured by variations in atypical structure, specifically the right supramarginal gyrus. Given that this region was also reported to have a significant negative association with maltreatment history we undertook an exploratory mediation analysis. Interestingly, GMV within the right supramarginal gyrus significantly mediated the relationship between total childhood trauma severity score and externalising symptom scores within the maltreated group. These findings add to the emerging evidence which has illustrated the mediating role of cortical structure in the relationship between maltreatment and psychiatric symptomatology (Gorka et al., 2014; Whittle et al., 2013). These findings therefore underline the critical importance in the investigation of cortical structure in understanding the embedding of chronic stress in early life and its impact on the development of maladaptive functioning across the life span.

However as we did not observe associations between psychiatric symptomatology and cortical structure in the majority of regions of atypical structure, it is harder to interpret the importance of atypical structure to current mental health. One possibility is that atypical structure within these regions represent differing patterns of cognition or behaviour that are not considered to be symptomatic of a psychiatric disorder. Consistent with the theory of latent vulnerabilities, these behaviours may only emerge as problematic to the individual under certain conditions or demands of a subsequent developmental period (McCrory & Viding, *in press*). As we recruited a non-clinical sample, we may have been underpowered to detect relationships between atypical structure and psychiatric symptomatology due to a restricted range of symptom severity below the clinical cut-off. While this is also a strength of the thesis as it allows us to attribute the observed group differences to maltreatment exposure rather than psychopathology, it would be of great interest to

see whether in time more severe pathology emerges and how it may relate to currently observed atypical structure in the maltreated group. The clinical implications of these findings within the focus of the theory of latent vulnerabilities will be further considered in the subsequent section.

Sex differences in the impact of maltreatment on brain structure

Another central theme to the thesis was the investigation of sex differences in the impact of maltreatment exposure on cortical structure. As discussed in **Chapters 5 and 6**, males and females display markedly different neural makeups at multiple stages of structure and function (e.g. Cosgrove et al., 2007; Fusar-Poli et al., 2009; Luders et al., 2009). The systematic investigations presented in **Chapters 5 & 6** examining the sexually dimorphic impact of childhood maltreatment on brain structure highlighted a number of significant implications for maltreatment research.

Importantly, we found that previously reported atypical structure within the maltreated group compared to the non-maltreated peers in within the bilateral supramarginal gyrus, in **Chapter 4**, was primarily driven by females, whereas males did not show any change in structural value between the control and maltreated groups. This finding underscore a vital challenge to researchers, determining whether atypical structure associated with maltreatment is representative of both males and females or whether it a unique neural characterisation of maltreatment in just one of the sexes. Furthermore, while there are observable cortical differences associated with maltreatment between the sexes, males and females share similarities in atypical structure associated with maltreatment. Researchers should be mindful that while there are many factors that suggest that males and females react differently to chronic stressful environments, there are equally, if not more, factors that show similarities between them.

Furthermore, our findings of **Chapters 5 and 6** indicate that there are regions of the brain that structurally represent an interaction between sex and maltreatment. Within these regions, we observed two patterns of interaction. Within the post central gyrus (**Chapter 5**) we saw that female control participants had greater GMV compared to their male counterparts, however in the maltreated individuals this relation was inverted so that the maltreated male participants had greater GMV compared to their female counterparts. The second pattern we observed in **Chapter 6**, indicated that non-maltreated male and female individuals did not display significantly difference IGI within the two reported regions, however

in the maltreated individuals females displayed a significantly decreased IGI compared to maltreated males. These findings underline the importance of sex as a variable of interest in maltreatment research in three ways. First, it indicates that the recruitment of mixed sex samples, without appropriate controls for the influence of sex, may potentially occlude the observation of atypical structure associated with maltreatment. Specifically structural differences within males associated with maltreatment exposure may be 'cancelled out' by opposing differences associated with maltreatment within females. Second, findings from investigations restricted to one sex with a history of maltreatment (e.g. Pederson et al., 2004; Tomoda, Navalta, et al., 2009; Vythilingam et al., 2002) may not appropriate to generalise to mixed samples of maltreated individuals. These two points present sex as a crucial dimension of interest for further investigations of maltreatment research, so as to not inappropriately occlude or inflate results common or distinct to maltreated populations.

The next step to take is to understand the functional significance of the sexually dimorphic impact of maltreatment on cortical structure. Functional neuroimaging studies of maltreatment are relatively sparse and in their infancy, however it would be of great importance to understand whether these structural differences in **Chapters 5 & 6** may confer differences in behavioural and neural patterns, particularly in domains previously assign to these cortical regions. The findings from this thesis may serve as way to direct and inform hypotheses about the potential cognitive and affective domains to pursue in future functional neuroimaging studies of sex differences in maltreatment. Furthermore, it would be of great value to determine whether these structural differences indicate distinct atypical neurodevelopmental trajectories in males and females. Longitudinal investigations measuring multiple levels of functions may be able to determine whether these differences are protracted across adolescence and into adulthood and if there are representative of isomorphic behavioural changes or signify latent vulnerabilities to the emergence of psychiatric disorders.

7.5. Clinical implications

The findings of this thesis have a number of important clinical implications, which I will discuss briefly. First, the findings of this thesis indicate that maltreated individuals show a diverse pattern of atypical structure compared to non-maltreated peers. While we investigated how these differences relate to specific psychiatric symptomatology, it is unclear the functional significance of these regions and how

they may represent atypical patterns of cognition, affect or behaviour. As we have noted throughout the thesis, similar atypical structural patterns has been observed in a number of psychiatric disorders, for example anterior cingulate anomalies in PTSD (Kitayama et al., 2006; Thomaes et al., 2011). Furthermore, neuroimaging studies have been able to associate distinct cytoarchitectural regions with particular functions; the middle temporal regions with autobiographical memory (Holland et al., 2011; Squire, 2004; Squire et al., 2004) or the insula with interoceptive awareness (Critchley et al., 2004). By using inference to the best explanation, we propose that atypical structure in these regions may partly underlie atypical patterns of behaviour within these domains. However we must be cautious as to the extent we can infer from these findings; the proposed mechanisms by which structure influences these behaviours are not clearly defined and represent a vital consideration for clinicians. These findings represent the early stages of our understanding of how cortical structure may inform our understanding, and conceptual models, of how maltreatment confers risk to psychiatric disorder through neural pathways. Systematic longitudinal studies are needed to investigate what role these atypical patterns of structure may play in behavioural outcomes associated with maltreatment.

Second, It is of clinical interest to understand to what extent these structural differences persist across the lifespan and whether, in supportive and nurturing environments and through effective therapeutic interventions, these structural alterations may be 'reversed' or diverted towards a normative developmental trajectory. The next step would be the use of longitudinal investigations to ascertain how positive factors, such as social support and a stable family dynamics, may mediate change in cortical structure across adolescence.

Third, within this thesis sex was found to be an important factor in how maltreatment exposure was associated with brain structure, representing partially different ways in how early life stress biologically embeds within the brain. We hypothesised that these sex differences in atypical structure may potentially underlie functional and behavioural differences. While it is unknown to what extent these structural differences contribute to divergent neurodevelopmental trajectories and maladaptive behaviours, it represent an important way in which we understand the heterogeneity in response to maltreatment. These findings underscore the need for increased awareness of sex differences in behavioural outcomes and risk to psychiatric outcomes associated with maltreatment in policy and clinical practice.

For instance, effective intervention programs may emphasise the detection and focus of certain behaviours or psychiatric symptomatology previously shown to have greater prevalence in males or females. Furthermore, we know that maltreated individuals show different phenotypic expression of psychopathology compared to non-maltreated patients with the same diagnosis (Teicher & Samson, 2013). It would be of interest to clinicians to understand whether males and females display ecophenotypic variation within the same diagnostic boundaries, potentially reflected in sexually dimorphic atypical structure that may provide clues to effective interventions.

Last, the theory of latent vulnerability captures the way in which changes in a range of neurocognitive systems reflect adaptation or altered calibration to early stressful environments, but may confer increased risk to the emergence of psychiatric disorders in later life (McCrory & Viding, *in press*). The current findings may represent one factor within a system that spans multiple neurocognitive domains that represent latent vulnerability to the emergence of maladaptive behaviours or psychiatric symptomatology. While these latent vulnerabilities may not pose a problem to the individual's current functioning; navigation of subsequent developmental periods or environmental challenges may cause these vulnerabilities to develop into ostensible behavioural, cognitive or affective difficulties. Equally, given favourable and supportive environmental conditions these vulnerabilities may never develop into difficulties. The challenge for clinicians is to operationalise latent vulnerabilities at multiple levels of neurocognitive systems for targeted and preventative intervention. Gordons (1983) framework for disease prevention considers three different levels in which clinicians can focus prevention strategies(Gordon Jr, 1983). Of these, a proposal for indicated prevention strategies, which target individuals who have increased vulnerability for a disorder but are currently asymptomatic, such as maltreated populations, benefits from pre-emptive control of new cases compared to symptomatic treatment. However, by operationalising latent vulnerabilities, clinicians may be able to identify individuals within these maltreated populations who may represent the greatest risk of developing negative outcomes. While it would be impractical and scientifically unsound to employ structural neuroimaging to identify potential latent vulnerabilities reflected in cortical structure, these findings inform clinicians and researchers on focussed routes to take to develop behavioural and experimental tasks that capture altered neurocognitive functioning (McCrory & Viding, *in press*).

7.6. Limitations and future directions

The findings of this thesis contribute to the growing knowledge of the impact of childhood maltreatment on brain structure and the heterogeneity in existing findings. Nonetheless, as noted in the empirical chapters, the findings should be interpreted in light of a number of limitations that future studies should endeavour to address.

First, data within the empirical chapters was obtained from a cross-sectional design. While there were many consistencies with our findings and established investigations and meta-analyses on the structural impact of childhood maltreatment, cross-sectional designs preclude the establishment of directionality of effects. As discussed throughout the empirical chapters, the future use of longitudinal investigations will allow for the clarification of the proposal that these structural impacts are associated with childhood maltreatment, and whether they represent markers for current or future atypical functioning and risk of psychiatric disorder. Longitudinal research would also shine a light on whether the reported findings of sexually dimorphic impact of maltreatment on cortical structure (**Chapters 5 & 6**) represent sexually divergent patterns of behaviour and if they are representative of a temporal snapshot of distinctive neurodevelopmental trajectories, or rather other physiological processes normalise the impact of these structural differences on behaviour between the sexes (Cahill, 2006; De Vries, 2004).

Second, there are intrinsic limitations to the analysis of cortical structure within the focus of psychological functioning. The main aim of neuroimaging research is to infer the mental processes that are associated with, for instance, a functional task or a clinical state. However, it is still not fully known how differences in cortical structure influence behaviour nor how local variations in, say, volume may contribute to a wider neural network relating to cognitive function. Reverse inference refers to the use of reasoning from activation or structural differences to cognitive and affective functions (Aguirre, Feinberg, & Farah, 2003; Poldrack, 2006). Much debate has taken place in relation to the erroneous and inflated claims some researchers have made using reverse inference on functional and structural literature to infer cognitive processes (e.g. Iacoboni et al., 2007; Lindstrom, 2011). However, reverse inference is not intrinsically weak (Poldrack, 2011) and can serve as an important tool in formulating focussed hypotheses for future research. Throughout this thesis, care has been made not to inflate the inferences we can make from atypical structure within these maltreated populations. We have

attempted to adopt adductive inference, or inference to the best explanation (Peirce, 1998; Poldrack, 2011). Future investigations using functional imaging within a longitudinal design will help to clarify the inferences made about the findings of the empirical chapters.

Third, the empirical chapters within this thesis have primarily focussed on the associations between atypical cortical structure and psychiatric symptomatology, while we did not specify or investigate protective factors. While some maltreated individuals go on to develop psychiatric disorders, some do not. The sequelae of maltreatment depends on a complex interaction between risk and protective factors at both neurobiological and environmental levels (Bolger & Patterson, 2003; Cicchetti & Toth, 2005). A certain amount of variance in the association between maltreatment experience and atypical structure may be attributable to protective factors that minimise the atypical cortical development. In future investigations it would be important to examine whether protective factors, such as social support or strength and numbers of placement, may moderate the impact of maltreatment on cortical structure.

Fourth, our sample of maltreated adolescents did not display a broad variance in maltreatment experience and severity. Both the self-report CTQ and the Kaufman scale derived from official substantiated reports indicated that the abuse was classed as low to moderate, with no participants classed as severely maltreated. Inability to detect associations between maltreatment characteristics and atypical structure may have been due in part to limited variation in maltreatment experience, both in subtype and severity. While this was an inherent limitation in recruiting a community sample of maltreated children adolescents, as selection was based on a broad requirement of exposure to child maltreatment regardless of subtype or severity, future studies may want to selectively recruit participants that characterise a full range of maltreatment experiences and dimensions. As a result, it is unknown whether these findings are generalizable to wider populations of maltreated individuals who have experienced severe forms of abuse and neglect. For instance, severe maltreatment may exert differing patterns of atypical structure rather than a linear impact in areas of atypical structure reported in this thesis. In future, longitudinal investigations are necessary to make inferences regarding the causal influence of maltreatment on cortical structure and in what ways variations in cortical structure fit in with theories of neurodevelopmental pathways.

7.7. Conclusions

The present thesis set out to systematically investigate the impact of maltreatment on brain structure. Our findings indicated that atypical structure across a number of cortical regions is associated with the experience of childhood abuse and neglect. Consistent with the existing literature we found atypical structural across separable cortical indices within frontal regions of the anterior cingulate, orbitofrontal cortex and superior frontal gyrus, middle temporal regions and insula cortex in maltreated participants compared to well-matched non-maltreated peers. Interestingly we observed that the maltreated individuals displayed atypical structure, in less commonly reported regions of the lingual gyrus, supramarginal gyrus and occipito-parietal cortex. The detection of a number of these significant clusters of atypical structure were possible through the use of surface-based techniques, rarely used within the maltreatment literature, and may provide for the better characterisation of the biological embedding of early life stress on the brain. Furthermore, use of such techniques may allow for the clues towards the route of discrepancies between adult and child structural maltreatment research. Within these regions of atypical structure, maltreatment severity is selectively associated with cortical structure, suggesting a dose-response relationship with early life stress. Additionally psychiatric symptomatology was found to negatively correlate with GMV within a localised region of right supramarginal gyrus. GMV within this region was additionally found to mediate the relationship between maltreatment exposure and externalising symptomatology, suggesting an influential role of cortical structure in the neural pathways that confer risk from childhood maltreatment to psychopathology. Importantly we found that sex represents a crucial factor in the characterisation of maltreatment on cortical structure. Group analysis which indicated GMV reductions within bilateral supramarginal gyrus of maltreated participants compared to non-maltreated peers were found to be driven by females. It was also found that males and females partially show divergent patterns of atypical structure in pre and post central regions and tempo-parietal areas in the wake of maltreatment. Together these findings suggest that the biological embedding of early life stress within the brain may show differences, as well as similarities, between males and females. A consideration of sex as an important contributory variable in future studies and clinical framework for effective prevention and intervention would be of great value. The data reported in this thesis contribute to an expanding evidence base, which details the impact of maltreatment on brain structure and how diverse contributory factors influence how this is characterised.

The next step is to use systematic longitudinal studies, which seek to link atypical structure with future behavioural, cognitive and affective functioning. This will help to clarify the importance of cortical structure in the neural pathways that lead from maltreatment to negative outcomes across the lifespan.

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Appendices

Supplemental Experimental Procedures

Chapter 2

Further exploratory analyses were conducted to explore associations between the cortical indices and psychiatric symptoms. No significant associations were found in the maltreated group between significant cortical clusters and the Trauma Symptom Checklist for Children, the Strengths and Difficulties Questionnaire (SDQ) or the 'State/Trait Inventory for Children.

Additional analyses were conducted to explore associations between regions showing structural differences between groups and neuropsychological functioning using the Behaviour Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000) a parent report measure assessing executive function behaviours in adolescents and children. No significant correlations were found ($p > .15$).

No children met clinical cut-off for anxiety, depression or posttraumatic stress disorder (PTSD). A total of 8 children fell in the category requiring clinical evaluation on the SDQ for conduct disorder and/or hyperactivity. When our analyses were conducted without these participants (Maltreatment group, $n = 11$), a cortical thickness whole brain analysis with cluster correction ($p < 0.05$) detected a significant cluster comparable to the originally reported cluster within the anterior cingulate cortex (ACC), superior frontal gyrus and extending into the anterior aspects of the orbitofrontal cortex (OFC) with a relocated maxima ($x = 27.7, y = 57.8, z = -9.5$; area = 5104.02 mm²; $p < 0.05$). In relation to surface area, a similar pattern of findings was obtained (middle temporal gyrus, $p < 0.05$; lingual gyrus $p < 0.05$). Finally in relation to gyrification, we found similar patterns of reduced gyrification within the lingual gyrus ($x = -19.5, y = -64.2, z = -9.6$; area = 3422.55 mm²; $p < 0.05$) and insula ($x = -35.7, y = -19.2, z = -5.3$; area = 47.92 mm²; $p < 0.05$); however the insula cluster did not survive the conservative multiple comparisons correction of Monte Carlo null z simulation, most likely due to a relatively small sample size. Overall, these findings suggest that the reported pattern of results across all structural parameters are not being driven by a subgroup of children with conduct and attention-deficit/hyperactivity disorder scores in the clinical range, but characterize the whole sample.

Supplemental Figures

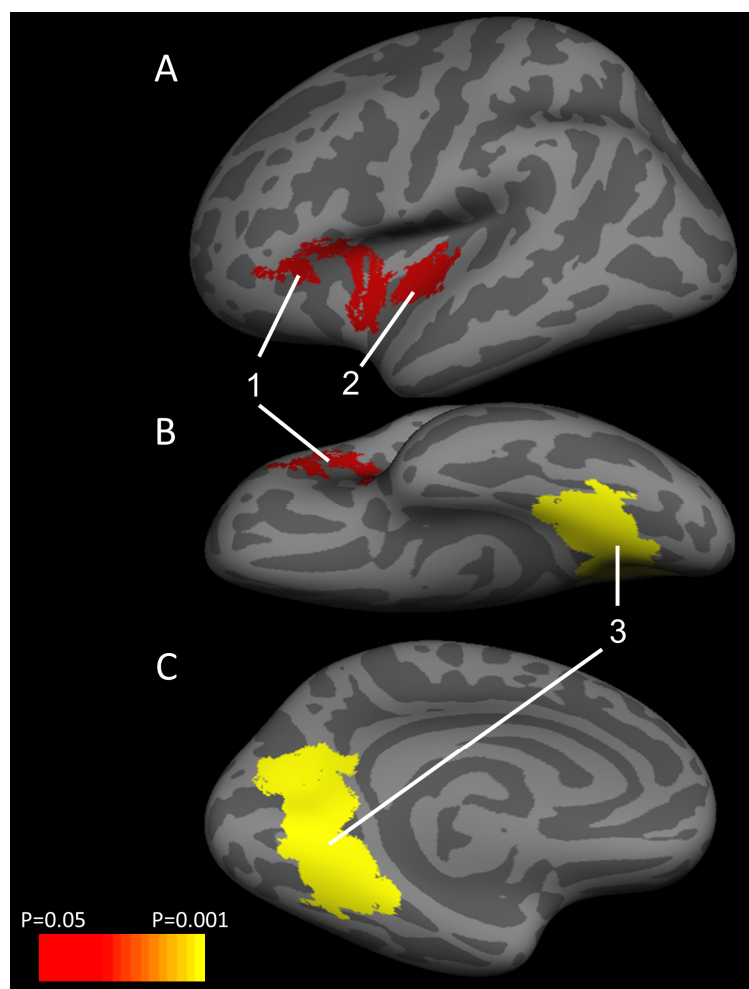


Figure A.1. Significant clusters of local gyrification decrease in the maltreated group without smoothing.

*Notes: The significant local gyrification index clusters without smoothing are projected onto the inflated left hemisphere in (A) lateral (B) inferior and (C) tilted inferior medial view. The three significant clusters show decreased gyrification in maltreated children compared to controls. Cluster 1 was identified as pars opercularis, Cluster 2 as insula and cumulatively reflected the cluster described in **Figure 2.3**, Chapter 2. The peak of Cluster 3 was identified as lingual gyrus and represented a similar cluster described in Chapter 2, **Figure 2.3**. All clusters survived cluster correction of $p < 0.05$*

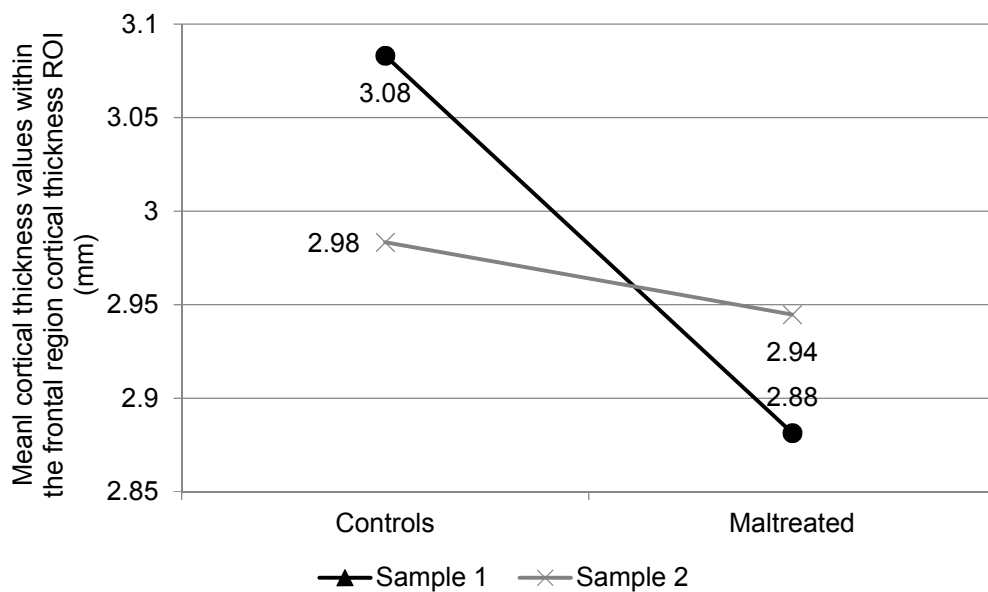


Figure A.2. Plot of the mean cortical thickness values extracted from the frontal region of interest.

Notes: The region of interest was determined by the cluster extent of the significantly decreased cortical thickness finding in the maltreated group compare to the non-maltreated group in sample 1 and described in Chapter 2. Mean cortical thickness values between the maltreated and non-maltreated group and split by sample.

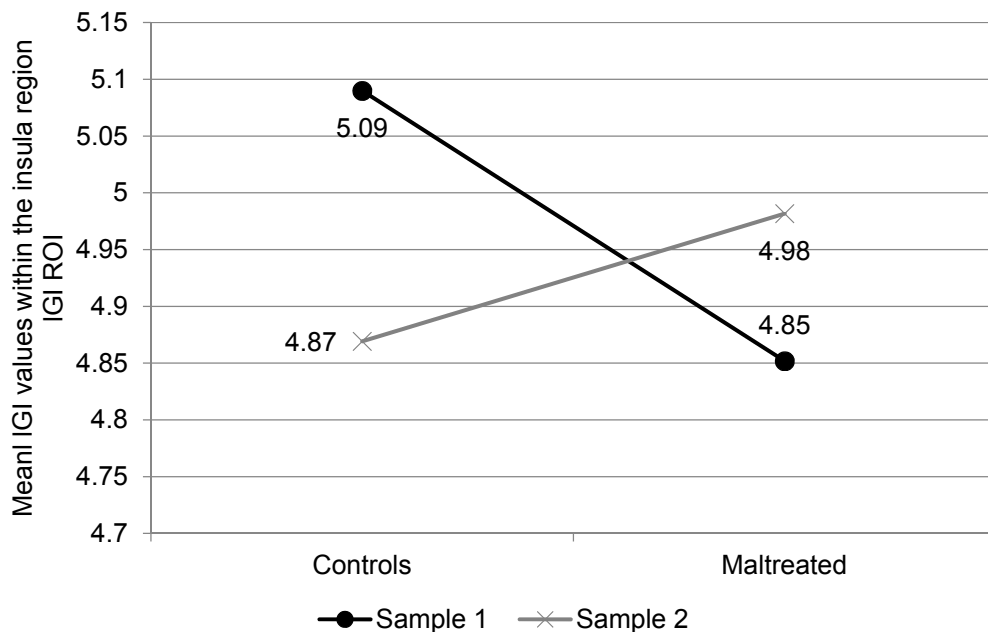


Figure A.3. Plot of the mean cortical thickness values extracted from the insula of interest.

Notes: The region of interest was determined by the cluster extent of the significantly decreased local gyrification index finding within the insula in the maltreated group compare to the non-maltreated group in sample 1 and described in Chapter 2. Mean IGI values between the maltreated and non-maltreated group and split by sample.

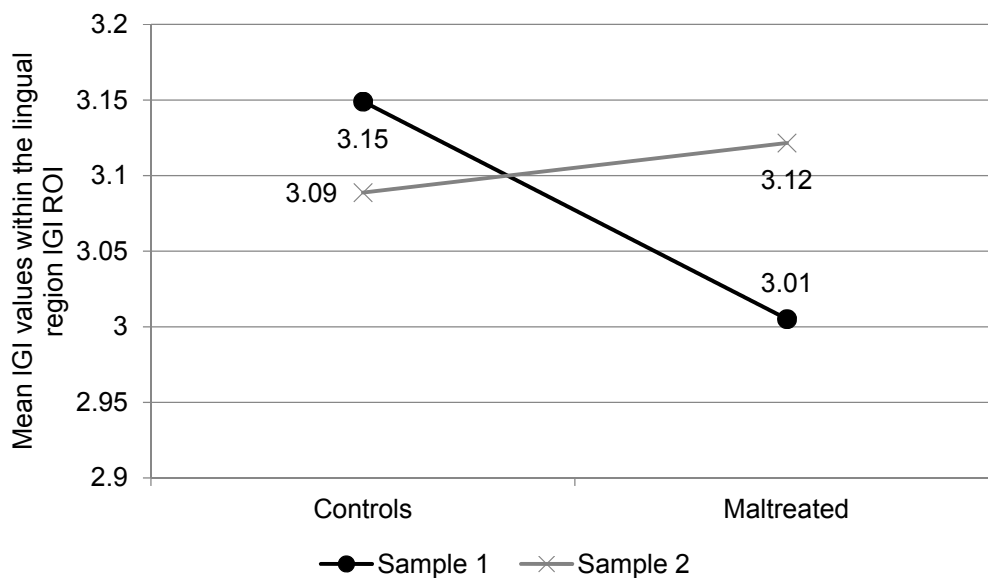


Figure A.4. Plot of the mean cortical thickness values extracted from the lingual gyrus region of interest.

Notes: The region of interest was determined by the cluster extent of the significantly decreased local gyrification index finding within the lingual gyrus in the maltreated group compare to the non-maltreated group in sample 1 and described in Chapter 2. Mean IGI values between the maltreated and non-maltreated group and split by sample.

Supplemental Tables

Table A.1. The estimated total intracranial volume for maltreated and non-maltreated children

	Non-maltreated (<i>n</i> = 21)		Maltreated (<i>n</i> = 22)		<i>p</i>
	Mean	SD	Mean	SD	
eTIV ^a	1459433.57	123784.18	1427930.00	104603.36	0.37

^a estimated total intracranial volume. mm³

Table A.2. Abuse subtype severity scores, estimated mean age of onset and duration in years of abuse of maltreated children

	Mean	SD
Physical abuse (<i>n</i> = 8)		
Kaufman score ^a	1.50	0.54
Estimated mean age of onset	3.29	2.06
Estimated mean duration ^b	5.00	3.16
Neglect (<i>n</i> = 19)		
Kaufman score ^a	2.53	1.12
Estimated mean age of onset	3.94	3.27
Estimated mean duration ^b	7.31	3.26
Sexual abuse (<i>n</i> = 5)		
Kaufman score ^a	2.00	1.87
Estimated mean age of onset	5.00	0.00
Estimated mean duration ^b	2.67	2.08
Emotional abuse (<i>n</i> = 18)		
Kaufman score ^a	2.94	1.06
Estimated mean age of onset	2.73	3.15
Estimated mean duration ^b	6.62	3.65

^a Kaufman scores are rated on a four point scale rated from 0 (no abuse present) to 4 (evidence of severe abuse).

^b in years.