



King's Research Portal

DOI: 10.1017/S0033291717002392

Document Version Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Lim, L., Hart, H., Mehta, M., Worker, A., Simmons, A., Mirza, K., & Rubia, K. (2017). Grey matter volume and thickness abnormalities in young people with a history of childhood abuse. *Psychological Medicine*, 1-13. Advance online publication. https://doi.org/10.1017/S0033291717002392

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

•Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research. •You may not further distribute the material or use it for any profit-making activity or commercial gain •You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Psychological Medicine

Grey Matter Volume and Thickness Abnormalities in Young People with a History of Childhood Abuse --Manuscript Draft--

| Manuscript Number: | PSM-D-17-00054R2 |
|--|---|
| Full Title: | Grey Matter Volume and Thickness Abnormalities in Young People with a History of Childhood Abuse |
| Article Type: | Original Article |
| Corresponding Author: | Lena Lim, Ph.D. Institute of Psychiatry, King's College London London, UNITED KINGDOM |
| Corresponding Author Secondary Information: | |
| Corresponding Author's Institution: | Institute of Psychiatry, King's College London |
| Corresponding Author's Secondary Institution: | |
| First Author: | Lena Lim, Ph.D. |
| First Author Secondary Information: | |
| Order of Authors: | Lena Lim, Ph.D. |
| | Heledd Hart, PhD |
| | Mitul Mehta, PhD |
| | Amanda Worker, MSc |
| | Andrew Simmons, PhD |
| | Kah Mirza, MBBS |
| | Katya Rubia, PhD |
| Order of Authors Secondary Information: | |
| Manuscript Region of Origin: | UNITED KINGDOM |
| Abstract: | Background: Childhood abuse is associated with abnormalities in brain structure and function. Few studies have investigated abuse-related brain abnormalities in medication-naïve, drug-free youth that also controlled for psychiatric comorbidities by inclusion of a psychiatric control group, which is crucial to disentangle the effects of abuse from those associated with the psychiatric conditions. |
| | Methods: Cortical volume (CV), cortical thickness (CT) and surface area (SA) were measured in 22 age-and gender-matched medication-naïve youth (aged 13-20) exposed to childhood abuse, 19 psychiatric controls matched for psychiatric diagnoses and 27 healthy controls. Both region-of-interest (ROI) and whole-brain analyses were conducted. |
| | Results: For the ROI analysis, the childhood abuse group compared to healthy controls only, had significantly reduced CV in bilateral cerebellum and reduced CT in left insula and right lateral orbitofrontal cortex (OFC). At the whole-brain level, relative to healthy controls, the childhood abuse group showed significantly reduced CV in left lingual, pericalcarine, precuneus and superior parietal gyri, and reduced CT in left pre- /postcentral and paracentral regions, which furthermore correlated with greater abuse severity. They also had increased CV in left inferior and middle temporal gyri relative to healthy controls. Abnormalities in the precuneus, temporal and precentral regions were abuse-specific relative to psychiatric controls, albeit at a more lenient level. Groups did not differ in SA. |

Conclusions: Childhood abuse is associated with widespread structural abnormalities in OFC-insular, cerebellar, occipital, parietal and temporal regions, which likely underlie the abnormal affective, motivational and cognitive functions typically observed in this population.

1

Word count Abstract: 244 Main text: 3998 Tables: 4 Figures: 3 Supplementary material: 1

Grey Matter Volume and Thickness Abnormalities in Young People with a History of Childhood Abuse

Lena Lim, PhD¹*; Heledd Hart, PhD¹*; Mitul Mehta, PhD²; Amanda Worker, MSc²; Andrew

Simmons, PhD²; Kah Mirza, MBBS¹; Katya Rubia, PhD¹

¹Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology &

Neuroscience, King's College London, London, United Kingdom, ²Department of Neuroimaging,

Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United

Kingdom

^{*} Dr. Lim and Dr. Hart share first authorship

Corresponding author:

Dr. Lena Lim Department of Child & Adolescent Psychiatry Institute of Psychiatry, Psychology & Neuroscience (IoPPN) King's College London De Crespigny Park London SE5 8AF United Kingdom Email: <u>lena.lim@kcl.ac.uk</u>

Abstract

Background: Childhood abuse is associated with abnormalities in brain structure and function. Few studies have investigated abuse-related brain abnormalities in medication-naïve, drug-free youth that also controlled for psychiatric comorbidities by inclusion of a psychiatric control group, which is crucial to disentangle the effects of abuse from those associated with the psychiatric conditions.

Methods: Cortical volume (CV), cortical thickness (CT) and surface area (SA) were measured in 22 age-and gender-matched medication-naïve youth (aged 13-20) exposed to childhood abuse, 19 psychiatric controls matched for psychiatric diagnoses and 27 healthy controls. Both region-of-interest (ROI) and whole-brain analyses were conducted.

Results: For the ROI analysis, the childhood abuse group compared to healthy controls only, had significantly reduced CV in bilateral cerebellum and reduced CT in left insula and right lateral orbitofrontal cortex (OFC). At the whole-brain level, relative to healthy controls, the childhood abuse group showed significantly reduced CV in left lingual, pericalcarine, precuneus and superior parietal gyri, and reduced CT in left pre-/postcentral and paracentral regions, which furthermore correlated with greater abuse severity. They also had increased CV in left inferior and middle temporal gyri relative to healthy controls. Abnormalities in the precuneus, temporal and precentral regions were abuse-specific relative to psychiatric controls, albeit at a more lenient level. Groups did not differ in SA.

Conclusions: Childhood abuse is associated with widespread structural abnormalities in OFCinsular, cerebellar, occipital, parietal and temporal regions, which likely underlie the abnormal affective, motivational and cognitive functions typically observed in this population.

Keywords: Childhood adversity, early-life stress, childhood maltreatment, cortical thickness, surface area, cortical volume, brain abnormalities

Introduction

Brain development is a complex process regulated by genes and sculpted by environmental experiences (Lenroot & Giedd, 2008). Although experiential influences affect brain structure and function throughout the lifespan, childhood experience is particularly crucial with early stress adversely affecting the nature and trajectory of normal brain development (Pechtel & Pizzagalli, 2011).

Childhood maltreatment, which includes physical, sexual and emotional abuse and neglect, is common in the UK with paediatric prevalence rates of 7-10% (NSPCC, 2011). It has been associated with a host of adverse consequences, such as low IQ, abnormal error processing (Lim *et al.* 2015), impaired attention, inhibition, emotion and reward processing (De Bellis & Zisk, 2014; Hart & Rubia, 2012; Pechtel & Pizzagalli, 2011). Large-scale epidemiological studies found that childhood maltreatment is significantly associated with first onsets of various psychiatric disorders, such as depression and post-traumatic stress disorder (PTSD) (Green *et al.* 2010).

The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of neural underpinnings (Bremner & Vermetten, 2001). Structural MRI studies show that, relative to non-maltreated controls, individuals exposed to childhood maltreatment have grey matter volume (GMV) abnormalities in several relatively late-developing brain regions, such as the orbitofrontal cortex (OFC) (De Brito *et al.* 2013; Edmiston *et al.* 2011; Hanson *et al.* 2010; Hodel *et al.* 2015; Thomaes *et al.* 2010), insula (Dannlowski *et al.* 2012; Edmiston *et al.* 2011; Lim *et al.* 2014), temporal lobes (Bremner *et al.* 1997; De Bellis *et al.* 2002; Tomoda *et al.* 2011) and cerebellum (Bauer *et al.* 2009; De Bellis & Kuchibhatla, 2006; Walsh *et al.* 2014). Volumetric abnormalities in subcortical regions such as the hippocampus and amygdala have been mainly observed in adults but not children/adolescents exposed to childhood maltreatment (Woon & Hedges, 2008). Recent studies also reported reduced visual cortex GMV in childhood maltreatment (Edmiston *et al.* 2011; Tomoda *et al.* 2009; Tomoda *et al.* 2012). Several reviews of childhood maltreatment have consistently reported structural deficits in several stress-susceptible brain regions including the OFC, limbic, insula and cerebellar regions (Hart & Rubia, 2012; Lim *et al.* 2014, McCrory *et al.* 2011a; Nemeroff, 2016; Teicher *et al.* 2016), with the late-developing OFC and cerebellum being particularly vulnerable to the effects of early stress (Hanson *et al.* 2010; Pechtel & Pizzagalli, 2011), and the insula is known to be involved in regulating the glucocorticoid effect (Fornari *et al.* 2012). Our meta-analysis also showed that childhood maltreatment is associated with GMV reduction in OFC-limbic-temporal regions and inferior frontal cortices that mediate top-down affect and cognitive control, respectively; and with GMV reduction in pre-/postcentral gyri that mediate sensory functions (Lim *et al.* 2014).

Cortical volume (CV) is determined by two separable cortical indices, cortical thickness (CT) and surface area (SA), which are genetically (Panizzon *et al.* 2009) and phenotypically (Winkler *et al.*, 2010) independent with differing developmental trajectories (Panizzon *et al.* 2009). Studies examining CT, SA and CV may be more sensitive to individual differences than considering volume alone (Hutton *et al.* 2009). However, as most of the earlier structural studies on childhood maltreatment examined abuse-related volumetric abnormalities, examining group differences in volume in the current study thus allows for comparison with the existing literature. Also, volume measurements are useful for subcortical structures where CT/SA measurements are unavailable. Therefore, it is important to explore these brain measures to better understand the structural correlates of childhood maltreatment.

To date, few studies on childhood maltreatment examined whole-brain differences in CV, CT and SA within the same sample. Compared with healthy controls, maltreated young people had significantly reduced CT in right OFC (Gold *et al.* 2016; Kelly *et al.* 2016; Kelly *et al.* 2013), and reduced SA in left middle temporal and lingual regions (Kelly *et al.* 2013). Children who experienced psychosocial deprivation exhibited widespread CT reductions in lateral OFC, precuneus, insula, parietal and lingual gyri, which were furthermore associated with inattention and impulsivity (McLaughlin *et al.* 2014). In adults, childhood sexual abuse was associated with reduced CT in left somatosensory cortex, while emotional abuse was associated with reduced CT in bilateral precuneus and left somatosensory cortex (Heim *et al.* 2013). Individuals exposed to domestic violence during childhood had reduced CT in bilateral lingual (Tomoda *et al.* 2012).

Given that childhood maltreatment is associated with the development of psychiatric complications (Herrenkohl *et al.* 2013; MacMillan *et al.* 2013; Sugaya *et al.* 2012), it is crucial to control for these in order to disentangle the effects of maltreatment from the psychiatric comorbidities (Hart & Rubia, 2012; Lim *et al.* 2014; McCrory *et al.* 2011a). Only two prior structural studies in childhood maltreatment controlled for psychiatric disorders. However, they examined CV alone in specific disorders such as psychosis (Sheffield *et al.* 2013) and depression (Chaney *et al.* 2014), which limits the generalizability of their findings to other psychiatric comorbidities. Also, the majority of patients in the two studies were on psychotropic medications (e.g. Chlorpromazine, SSRIs), which are known to affect brain structure and function (Murphy, 2010).

Therefore, the aim of this study was to control for the limitations of earlier studies by conducting both ROI and whole-brain structural (CV, CT, SA) analyses in medication-naïve, drug-free youth exposed to documented childhood physical abuse and in healthy controls. To assess the specificity of the association with childhood abuse, we included a third group of psychiatric controls that was matched with the abuse group on psychiatric comorbidities. Sexual abuse was excluded because it has different effects on brain structure (Heim *et al.* 2013) and different behavioural and psychiatric consequences (Lewis *et al.* 2016; Lopez-Castroman *et al.* 2013; Teicher *et al.* 1997; Weierich & Nock, 2008). For instance, both childhood physical abuse and neglect, but

not sexual abuse, were associated with alterations in regional corpus callosum size (Teicher *et al.* 1997) and with GMV reduction in a distributed corticostriatal-limbic system (Edmiston *et al.* 2011). Furthermore, childhood sexual abuse is associated with experiences unique to sexual victimization relative to other abuse experiences; for example, traumatic sexualization, stigmatization, attributions of responsibility as well as feelings of guilt and shame may impact sexual abuse victims differently than victims of other abuse experiences (Feiring *et al.* 1996; Finkelhor & Browne, 1985). For these reasons, and in order to obtain a more homogenous group, we only included youth exposed to childhood physical abuse. Nevertheless, it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Claussen & Crittenden, 1991; Edwards *et al.* 2003) since psychological maltreatment would be present in *almost all* cases of physical maltreatment (Claussen & Crittenden, 1991).

Since childhood maltreatment is consistently associated with structural deficits in several stress-susceptible brain regions including the OFC, limbic, insula and cerebellar regions (Hart & Rubia, 2012; Lim *et al.* 2014; McCrory *et al.* 2011a; Nemeroff, 2016; Teicher *et al.* 2016), we hypothesized that the abuse group, relative to both healthy and psychiatric controls, would have structural abnormalities particularly in the OFC, insula and cerebellum. We also investigated abnormalities outside our priori defined ROIs with a whole-brain analysis.

Methods and Materials

Participants

Seventy (23 abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medicationnaïve, drug-free and age-and-gender matched youth (aged 13-20) were assessed by a child psychiatrist (KM) using the Development and Well-Being Assessment (DAWBA) (Goodman *et al.* 2000), which was designed to generate ICD-10 and DSM-IV psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ) (Goodman, 1997) and Beck's Depression Inventory (BDI) (Beck *et al.* 1988) were also used to provide symptom scores on psychopathology. IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) was used to measure the severity of childhood physical, sexual and emotional abuse, and physical and emotional neglect. Socioeconomic status (SES) was measured by two non-sensitive items (on housing tenure and room occupancy) from the Family Affluence Scale (FAS) (Currie *et al.* 1997).

Exclusion criteria for all participants were childhood sexual abuse, drug abuse, learning disability, neurological abnormalities, epilepsy, IQ < 70 and MRI contraindications. Urine screening for recent drug use was conducted with 10-panel urine drug test integrated cups (T-Cup; http://www.testfield.co.uk). All participants or their guardians if they were under the age of 18, provided written informed consent to participate in the study. The study was approved by the National Research Ethics Service Committee London-Fulham.

The 23 youth who experienced physical abuse before the age of 12 were first recruited through social services and psychiatric clinics. They or their guardians were first asked to provide signed permission to contact their social services for written confirmation of official records of physical abuse. The Childhood Experience of Care and Abuse (CECA) interview (Bifulco *et al.*, 1994) was used to corroborate the CTQ and provide information on the age of onset and duration of abuse. The participants scored \geq 13 (i.e. the cut-off for severe/extreme physical abuse) (Bernstein & Fink, 1998) on the CTQ physical abuse subscale and information from the CECA interview and the CTQ were consistent with the official records. The common psychiatric comorbidities included PTSD, depression, anxiety and conduct disorder (Table 1). One participant was excluded due to MRI motion artefacts, leaving a final sample of 22 participants. The 20 psychiatric patients that were matched with the abuse group on psychiatric comorbidities but with no history of childhood maltreatment (scoring below the cut-offs for the respective CTQ subscales) (Bernstein & Fink, 1998) were recruited through psychiatric clinics and social services (Table 1). PTSD patients experienced non-abuse related trauma (e.g. witnessed a murder, experienced a car accident or experienced the death of a loved one). One participant was excluded due to motion artefacts, leaving a final sample of 19 patients.

The 27 healthy controls with no history of psychiatric illness and childhood maltreatment (scoring below the same cut-offs as above) were recruited through advertisements in the same geographic areas of South London to ensure similar SES (Table 1).

MRI Acquisition and Analysis

The MRI acquisition procedures are described in the supplementary materials.

Image preprocessing and analyses were carried out using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvest.edu). After preprocessing (supplementary materials), whole-brain between-group differences in CV, CT and SA were investigated within the QDEC surface-based group analysis. For each hemisphere, the General Linear Model was computed vertex-by-vertex for analysis of each cortical morphometric measure (CV, CT and SA), with group as a between-subjects factor and IQ, age, and a total brain measure (total brain volume for CV, mean CT for CT, and total SA for SA) included as covariates. Although there were no significant group differences in age, it was included given the relatively wide age range of the current sample. Cortical maps were smoothed with a FWHM Gaussian kernel of 10 mm. Between-group differences were corrected for multiple comparisons with a Monte Carlo *z*-field simulation at p < 0.05 (two-tailed).

For group differences in the hypothesised ROIs (i.e. OFC, insula, cerebellum), ANOVA with group (Abuse vs Healthy controls; Abuse vs Psychiatric controls) as a between-subject factor

and covariates outlined above were used on the cortical measures of these regions generated during the automated segmentation and parcellation process (Fischl *et al.* 2004). Given that a limited number of studies have aimed at specifying surface-based brain indices in relation to abuse exposure (Kelly *et al.* 2016), the stringent Bonferroni multiple comparisons correction was not applied in this analysis to limit potential type II errors.

Tests for normality were conducted in SPSS using the Kolmogorov-Smirnov and Shapiro-Wilk tests. None of the volume measurement distributions deviated significantly from normality.

Finally, we also conducted three preliminary analyses. First, we explored if gender influenced the impact of maltreatment on brain measures at the whole-brain level in QDEC with age, IQ and a total brain measure included as covariates. Second, the significant clusters were extracted for exploratory Pearson correlational analysis with the clinical measures *within* each group and with the abuse measures within the abuse group only. Lastly, we explored if the groups differed on hippocampus volume (supplementary materials).

Results

Subject Characteristics

The groups did not differ significantly on age, gender, ethnicity nor SES (p>0.05), but differed on IQ (p<0.001), which was expected as this is typical for the population (Geoffroy *et al.* 2016; Mills *et al.* 2011; Young & Widom, 2014) (Table 1). Although we selected participants with severe childhood physical abuse, they also experienced severe emotional abuse and neglect (Table 1), which typically co-occur with physical abuse; hence we consider this group representative of the childhood abuse population (Edwards *et al.* 2003; Trickett *et al.* 2011).

ROI Analysis

Relative to healthy controls only, the abuse group showed significantly reduced CV in left (F(1,44)=4.68, p=0.03) and right (F(1,44)=5.33, p=0.02) cerebellum, and reduced CT in left insula (F(1,44)=6.06, p=0.02) and right lateral OFC (F(1,44)=4.30, p=0.04). The abuse and psychiatric groups did not differ significantly (Table 2). There were no significant group differences on hippocampus volume (supplementary materials).

Whole-brain Analysis

Cortical volume

Compared to healthy controls, the abuse group had significantly reduced CV in a lefthemispheric posterior cluster comprising lingual, pericalcarine, precuneus, cuneus, isthmus cingulate and superior parietal gyri (Table 3, Figure 1; cluster-corrected p < 0.05). They had larger CV in two left-hemispheric clusters: inferior temporal gyrus, along with middle temporal and inferior parietal gyri (Table 3, Figure 2; cluster-corrected p < 0.05). Two of these regional differences, reduced CV in left precuneus (t = -2.36, p < 0.05) and larger CV in left middle temporal gyrus (t = 2.38, p < 0.05), were also significant relative to psychiatric controls at an uncorrected level; suggesting that the CV abnormalities in these two regions could be abusespecific. Healthy and psychiatric controls did not differ significantly from each other. There was no significant maltreatment by gender interaction.

Cortical thickness

The abuse group had significantly reduced CT in left precentral, postcentral and paracentral gyri (Table 4, Figure 3; cluster-corrected p < 0.05) relative to healthy controls, and significantly reduced left precentral CT (t = -2.18, p < 0.05) relative to psychiatric controls at an uncorrected level, suggesting that the precentral deficit could be abuse-specific. Healthy and psychiatric controls

did not differ significantly from each other. There was no significant maltreatment by gender interaction.

Surface area

There were no significant group differences or maltreatment by gender interaction in SA.

Correlational Analysis

The significant clusters were correlated with the SDQ and abuse measures within each group, controlling for IQ and age. Lower CV in the lingual-pericalcarine-precuneus cluster was significantly associated with higher CTQ physical abuse (r = -0.45, p < 0.05) and total score (r = -0.46, p < 0.05) in the abuse group, and with higher SDQ total score (r = -0.49, p < 0.05) and peer problems (r = -0.56, p < 0.05) in the healthy controls. Reduced CT in the pre-/postcentral cluster was also significantly associated with higher CTQ total score (r = -0.46, p < 0.05) in the abuse group.

Discussion

To our knowledge, this is the first structural study on childhood abuse that examined group differences in CV, CT and SA within the same sample in a group of medication-naïve, drug-free youth that also controlled for psychiatric comorbidities by inclusion of a psychiatric control group. Both are crucial to elucidate the effects of abuse independent from effects associated with psychiatric comorbid conditions or medication and drug abuse (Hart & Rubia, 2012; Lim *et al.* 2014; McCrory *et al.* 2011a).

For the ROI, the abuse group had significantly reduced CV in bilateral cerebellum and reduced CT in left insula and right lateral OFC, compared to healthy controls only. At the whole-brain level, relative to healthy controls, the abuse group showed significantly reduced CV in a

cluster comprising left lingual, pericalcarine, precuneus and superior parietal regions, along with reduced CT in left pre-/postcentral and paracentral regions, which were furthermore significantly associated with greater abuse severity. Lower lingual-pericalcarine-precuneus CV was associated with greater SDQ total score and peer problems in the healthy controls, thereby suggesting possibly detrimental effects particularly in terms of peer problems, at least in the general healthy population. The abuse group also had increased CV in left inferior and middle temporal regions compared to healthy controls. Abnormalities in the precuneus, middle temporal and precentral regions were abuse-specific relative to psychiatric controls, albeit at a more lenient level.

The OFC receives strong inputs from the limbic system and is involved in emotion regulation, social behaviour and reward-related decision making (O'Doherty *et al.* 2001; Rempel-Clower, 2007). It also receives inputs from the visual and somatosensory regions, and the lateral OFC is activated when viewing aversive pictures (Nitschke *et al.* 2006) and experiencing unpleasant touch (Rolls *et al.* 2003). The current finding of a thinner right lateral OFC is consistent with previous studies that found thinner right (lateral) OFC in children who experienced severe early-life deprivation and childhood abuse (Gold *et al.* 2016; Kelly *et al.* 2013; McLaughlin *et al.* 2014), and extends findings of our meta-analysis (Lim *et al.* 2014) and other volumetric studies that found significantly reduced OFC CV in children (De Brito *et al.* 2013; Edmiston *et al.* 2011; Hanson *et al.* 2010; Hodel *et al.* 2015) and adults (Thomaes *et al.* 2010) exposed to childhood maltreatment.

The insula plays a key role in interoceptive-awareness and emotion regulation (Carlson *et al.* 2011; Goldin *et al.* 2008) and together with the somatosensory, motor and prefrontal cortices, forms part of the neural circuitry of pain (Tracey & Mantyh, 2007). It is also part of the salience network that detects threat (Pichon *et al.* 2012), where it integrates information about salience into perceptual decisions about pain (Wiech *et al.* 2010). Previous structural studies have found thinner

insula in children who experienced severe early-life derivation (McLaughlin *et al.* 2014), as well as reduced insula CV in children (Edmiston *et al.* 2011) and adults (Dannlowski *et al.* 2012) exposed to physical abuse and childhood maltreatment, respectively.

The cerebellum is vulnerable to the effects of early stress (Pechtel & Pizzagalli, 2011). It plays a crucial role in emotion processing and fear conditioning via its connection with limbic structures and the HPA axis (Schutter & van Honk, 2005), and is a key region in many cognitive processes, particularly attention and timing functions (Arnsten & Rubia, 2012; Stoodley & Schmahmann, 2009). Cerebellar deficit has also been reported in previous studies of childhood abuse (Bauer *et al.* 2009; De Bellis & Kuchibhatla, 2006; Edmiston *et al.* 2011), and may possibly underlie the affective and cognitive deficits in this population.

Childhood maltreatment has been associated with abnormal development of the sensory systems that relay adverse sensory experiences. For instance, studies reported reduced lingual CV in women who experienced childhood sexual and physical abuse (Tomoda *et al.* 2009), reduced lingual CT in children who experienced psychosocial deprivation (McLaughlin *et al.* 2014) and in young adults who witnessed domestic violence during childhood (Tomoda *et al.* 2012), as well as reduced lingual SA in maltreated children (Kelly *et al.* 2013). Also, women exposed to childhood sexual and emotional abuse had reduced CT in left somatosensory cortex (Heim *et al.* 2013). Thus, the current findings of reduced left lingual CV and motor-somatosensory CT in the abuse group are consistent with these earlier studies and our meta-analysis finding of a smaller left motor-somatosensory CV in childhood maltreatment (Lim *et al.* 2014). Together, these findings support the suggestion that the sensory systems that process and interpret adverse sensory inputs may be altered by the abuse experience, reflecting an adaptive response of the developing brain to protect the child from highly hostile environmental conditions by gating sensory experiences and processing related to the abuse (Heim *et al.* 2013). Given that painful stimulation decreases blood

flow in the somatosensory cortex (Tommerdahl *et al.* 1996), severe and painful punishments during the critical time of synapse formation and development in childhood may possibly reduce the number of synapses leading to a thinner somatosensory cortex. Moreover, the association between abuse and deficits in the sensory regions is further underpinned by the current findings of significant negative correlations between them.

The finding of a possibly abuse-specific reduced precuneus CV corroborates earlier findings of a negative association between precuneus CV and abuse severity (Dannlowski *et al.* 2012), as well as reduced CT (Heim *et al.* 2013; McLaughlin *et al.* 2014) and network centrality of the precuneus (Teicher *et al.* 2014) in individuals exposed to childhood maltreatment. The precuneus plays a critical role in self-referential processing (Cavanna & Trimble, 2006). Childhood maltreatment has been associated with an increase in negative self-associations, which are postulated to further enhance negative bias when engaged in new situations, leading to the development and maintenance of affective disorders after exposure to childhood maltreatment (van Harmelen *et al.* 2010). Hence, the abuse-specific deficit in the precuneus may possibly be related to disturbances in self-referential processing in victims of childhood abuse, making them more vulnerable to the development and maintenance of psychopathology.

The possibly abuse-specific increased middle temporal CV is also novel. The middle temporal lobe is involved in moral function and intention attributions, and its dysfunction is often implicated in violent psychopathy (Fumagalli & Priori, 2012; Sommer *et al.* 2010). Boys with callous-unemotional conduct problems had greater middle temporal CV than healthy controls (De Brito *et al.* 2009), while thicker middle temporal cortex correlated with higher concurrent psychopathic traits and psychopathic tendencies in adolescents (Yang *et al.* 2015). Thus, the abuse-specific increase in middle temporal CV may possibly serve as a biomarker for the development of psychopathic propensity in later life.

The OFC-limbic-cerebellar structural deficits may possibly underlie the neuropsychological deficits in emotion and reward processing (Pine *et al.* 2005; Weller & Fisher, 2013) and attention (Pollak *et al.* 2010) observed in childhood maltreatment. This relationship is further supported by findings of fMRI studies of childhood maltreatment of abnormal OFC-limbic-cerebellar activation during emotion processing. For instance, increased activation in the insula (Garrett *et al.* 2012; McCrory *et al.* 2011b) and cerebellum (McCrory *et al.* 2013) relative to controls to angry faces has been reported in maltreated children; together with lower OFC activation to angry faces in severely deprived children (Tottenham *et al.* 2011) and healthy adults exposed to childhood physical abuse (Taylor *et al.* 2006), suggesting a deficit in their emotion-regulation abilities.

Finally, although there were no significant differences in the ROIs between the abuse group and psychiatric controls or between the psychiatric and healthy controls, the brain measurements of the psychiatric controls were in between those of the abuse group and healthy controls. This suggests that the abuse group, by nature of the abuse experience *and* the psychiatric comorbidities, was more adversely impaired than the psychiatric controls.

Among the strengths of this study are that all participants were medication-naïve and drugfree, and their abuse experience was carefully assessed and corroborated by social service records. Also, we included a psychiatric control group to determine the specificity of childhood abuse in our findings. The inclusion of a childhood abuse group without any psychiatric disorders would have provided a more robust means of determining abuse-specific abnormalities; however, such a "pure" group would not be representative of the general childhood abuse populations, as large-scale epidemiological and longitudinal studies have consistently reported that childhood maltreatment is linked developmentally to psychiatric disorders (Herrenkohl *et al.* 2013; MacMillan *et al.* 2013; Sugaya *et al.* 2012), and a meta-analysis further reported a causal relationship between non-sexual childhood maltreatment and a range of mental disorders (Norman *et al.* 2012). It is unclear to what extent pubertal development, malnutrition, prenatal drug exposure and presence of current life stressors may have influenced the findings. The SES measure used is limited, as it does not provide information on parents' income and education; however, youth often have difficulties in reporting this information (Currie *et al.* 1997). Although we recruited participants exposed to childhood physical abuse, it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards *et al.* 2003; Trickett *et al.* 2011).

In summary, using medication-naïve, drug-free, carefully assessed age-and-gender-matched groups of youth exposed to childhood abuse and psychiatric controls matched on psychiatric comorbidities, we found that childhood abuse is associated with widespread structural abnormalities in the OFC-limbic, cerebellar, parietal, temporal and sensory regions; which likely underlie the abnormal affective, motivational and cognitive functions typically observed in this population.

Acknowledgments

This study, LL and HH were supported by the Reta Lila Weston Trust for Medical Research and the Kids Company. LL was also supported by the National Medical Research Council. AS and KR were supported by the UK Department of Health via the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) for Mental Health at South London and the Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

We thank all the individuals and their families who participated in this study. We also thank the staff of Kids Company London for their help with recruitment.

Financial Disclosure/Conflict of Interest

KR has received speaker's honoraria from Lilly and Shire. MM has acted as a consultant for Cambridge Cognition and Lundbeck and has received fees from Shire for contribution towards education. KM has received research and educational grants from Glaxo Smith Kline and Shire pharmaceuticals and has served on the advisory boards of Janssen, Eli Lily and Shire pharmaceuticals. KM has also received honoraria for speaking at conferences organized by Janssen, Eli Lilly and Shire pharmaceuticals. LL, HH, AW, CC, XX, GB and AS reported no financial interests or potential conflicts of interest.

References

Arnsten AF, Rubia K (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of American Academy of Child Adolescent Psychiatry* **51**, 356-367.

Bauer PM, Hanson JL, Pierson RK, Davidson RJ, Pollak SD (2009). Cerebellar volume and cognitive functioning in children who experienced early deprivation. *Biological Psychiatry* **66**, 1100-1106.

Beck AT, Steer RA, Carbin MG (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review* **8**, 77-100.

Bernstein DP, Fink L (1998). *Childhood Trauma Questionnaire: A retrospective self-report manual San Antonio, TX: The Psychological Corporation.*

Bifulco A, Brown GW, Harris TO (1994). Childhood Experience of Care and Abuse (CECA): a retrospective interview measure. *Journal of Child Psychology and Psychiatry* **35**, 1419-1435.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--A preliminary report. *Biological Psychiatry* **41**, 23-32.

Bremner JD, Vermetten E (2001). Stress and development: behavioral and biological consequences. *Devlopment and Psychopathology* **13**, 473-489.

Buckholtz JW, Meyer-Lindenberg A (2008). MAOA and the neurogenetic architecture of human aggression. *Trends in Neurosciences* **31**, 120-129.

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002). Role of genotype in the cycle of violence in maltreated children. *Science* **297**, 851-854.

Cavanna AE, Trimble MR (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* **129**, 564-583.

Cerasa A, Quattrone A, Gioia MC, Magariello A, Muglia M, Assogna F, Bernardini S, Caltagirone C, Bossù PSpalletta G (2011). MAO A VNTR polymorphism and amygdala volume in healthy subjects. *Psychiatry Ressearch* **191**, 87-91.

Chaney A, Carballedo A, Amico F, Fagan A, Skokauskas N, Meaney JFrodl T (2014). Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *Journal of Psychiatry and Neuroscience* **39**, 50-59.

Charney DS (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *American Journal of Psychiatry* **161**, 195-216.

Chipman P, Jorm AF, Prior M, Sanson A, Smart D, Tan X, Easteal S (2007). No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: results from two community surveys. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 144B, 561-565.

Chorbov VM, Lobos EA, Todorov AA, Heath AC, Botteron KN, Todd RD (2007). Relationship of 5-HTTLPR genotypes and depression risk in the presence of trauma in a female twin sample. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **144B**, 830-833.

Cicchetti D, Rogosch FA, Sturge-Apple ML (2007). Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: depressive symptomatology among adolescents from low socioeconomic status backgrounds. *Development and Psychopathology* **19**, 1161-1180.

Claussen AH, Crittenden PM (1991). Physical and psychological maltreatment: relations among types of maltreatment. *Child Abuse and Neglect* **15**, 5-18.

Currie CE, Elton RA, Todd J, Platt S (1997). Indicators of socioeconomic status for adolescents: the WHO Health Behaviour in School-aged Children Survey. *Health Education Research* **12**, 385-397.

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T, Kugel H (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry* **71**, 286-293.

De Bellis MD, Keshavan MS, Frustaci K, Shifflett H, Iyengar S, Beers SR, Hall J (2002). Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biological Psychiatry* **51**, 544-552.

De Bellis MD, Kuchibhatla M (2006). Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biological Psychiatry* **60**, 697-703.

De Bellis MD, Zisk A (2014). The biological effects of childhood trauma. *Child and Adolescent Psychiatric Clinics of North America* **23**, 185-222, vii.

De Brito SA, Mechelli A, Wilke M, Laurens KR, Jones AP, Barker GJ, Hodgins S, Viding E (2009). Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain* **132**, 843-852.

De Brito SA, Viding E, Sebastian CL, Kelly PA, Mechelli A, Maris H, McCrory EJ (2013). Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. *Journal of Child Psychology and Psychiatry* **54**, 105-112.

Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha, R, Mayes LC, Blumberg HP (2011). Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics and Adolescent Medicine* **165**, 1069-1077.

Edwards VJ, Holden GW, Felitti VJ, Anda RF (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. *American Journal of Psychiatry* **160**, 1453-1460.

Feiring C, Taska L, Lewis M (1996). A process model for understanding adaptation to sexual abuse: the role of shame in defining stigmatization. *Child Abuse and Neglect* **20**, 767-782.

Finkelhor, DBrowne, A (1985). The traumatic impact of child sexual abuse: A conceptualization. *American Journal of Orthopsychiatry* **55**, 530-541.

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004). Automatically parcellating the human cerebral cortex. *Cerebal Cortex* 14, 11-22.

Fornari RV, Wichmann R, Atucha E, Desprez T, Eggens-Meijer E, Roozendaal B (2012). Involvement of the insular cortex in regulating glucocorticoid effects on memory consolidation of inhibitory avoidance training. *Frontiers in Behavioral Neuroscience* **6**, 10.

Fumagalli M, Priori A (2012). Functional and clinical neuroanatomy of morality. *Brain* **135**, 2006-2021.

Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A (2012). Brain activation to facial expressions in youth with PTSD symptoms. *Depression and Anxiety* **29**, 449-459.

Geoffroy MC, Pinto Pereira S, Li L, Power C (2016). Child neglect and maltreatment and childhood-to-adulthood cognition and mental health in a prospective birth cohort. *Journal of the American Academy of Child and Adolescent Psychiatry* **55**, 33-40.e3.

Gold AL, Sheridan MA, Peverill M, Busso DS, Lambert HK, Alves S, Pine DS, McLaughlin KA (2016). Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. *Journal of Child Psychology and Psychiatry* 57, 1154-1164.

Goldin PR, McRae K, Ramel W, Gross JJ (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biological Psychiatry* **63**, 577-586.

Goodman R (1997). The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology and Psychiatry* **38**, 581-586.

Goodman R, Ford T, Richards H, Gatward R, Meltzer H (2000). The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry* **41**, 645-655.

Green J, McLaughlin KA, Berglund PA (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication i: Associations with first onset of dsm-iv disorders. *Archives of General Psychiatry* **67**, 113-123.

Hanson J, Chung M, Avants B, Shirtcliff EA, Gee J, Davidson R, Pollak S (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *Journal of Neuroscience* **30**, 7466-7472.

Hart H, Rubia K (2012). Neuroimaging of child abuse: a critical review. *Frontiers in Human Neuroscience* **6**, 52.

Heim CM, Mayberg HS, Mletzko T, Nemeroff CB, Pruessner JC (2013). Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *American Journal of Psychiatry* **170**, 616-623.

Herrenkohl TI, Hong S, Klika JB, Herrenkohl RCRusso MJ (2013). Developmental impacts of child abuse and neglect related to adult mental health, substance use, and physical health. *J ournal of Family Violence* **28**, 10.1007/s10896-012-9474-9.

Hodel AS, Hunt RH, Cowell RA, Van Den Heuvel SE, Gunnar MR, Thomas KM (2015). Duration of early adversity and structural brain development in post-institutionalized adolescents. *Neuroimage* **105**, 112-119.

Holmes A (2008). Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. *Neuroscience and Biobehavioural Reviews* **32**, 1293-1314.

Huang YY, Cate SP, Battistuzzi C, Oquendo MA, Brent D, Mann JJ (2004). An association between a functional polymorphism in the monoamine oxidase a gene promoter, impulsive traits and early abuse experiences. *Neuropsychopharmacology* **29**, 1498-1505.

Hutton C, Draganski B, Ashburner J, Weiskopf N (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage* **48**, 371-380.

Jabbi M, Korf J, Kema IP, Hartman C, van der Pompe G, Minderaa RB, Ormel Jden Boer JA (2007). Convergent genetic modulation of the endocrine stress response involves polymorphic variations of 5-HTT, COMT and MAOA. *Molecular Psychiatry* **12**, 483-490.

Kelly PA, Viding E, Wallace GL, Schaer M, De Brito SA, Robustelli B, McCrory EJ (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biological Psychiatry* **74**, 845-852.

Kelly PA, Viding E, Puetz VB, Palmer AL, Samuel S, McCrory EJ (2016). The sexually dimorphic impact of maltreatment on cortical thickenss, surface area and gyrification. *Journal of Neural Transmisson* **123**, 1069-1083.

Kim-Cohen, J, Caspi, A, Taylor, A, Williams, B, Newcombe, R, Craig, IWMoffitt, TE (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. *Molecular Psychiatry* **11**, 903-913.

Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmid B, Becker K, Zimmermann US, Schmidt MH, Esser G, Rietschel M, Banaschewski T (2009). Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: evidence from a high-risk community sample of young adults. *International Journal of Neuropsychopharmacology* **12**, 737-747.

Lenroot RK, Giedd JN (2008). The changing impact of genes and environment on brain development during childhood and adolescence: initial findings from a neuroimaging study of pediatric twins. *Devlopment and Psychopathology* **20**, 1161-1175.

Lewis T, McElroy E, Harlaar N, Runyan D (2016). Does the impact of child sexual abuse differ from maltreated but non-sexually abused children? A prospective examination of the impact of child sexual abuse on internalizing and externalizing behavior problems. *Child Abuse and Neglect* **51**, 31-40.

Lim L, Hart H, Mehta MA, Simmons A, Mirza K, Rubia K (2015). Neural Correlates of Error Processing in Young People With a History of Severe Childhood Abuse: An fMRI Study. *American Journal of Psychiatry* **172**, 892-900. Lim L, Radua J, Rubia K (2014). Gray Matter Abnormalities in Childhood Maltreatment: A Voxel-Wise Meta-Analysis. *Am J Psychiatry* **171**, 854-863.

Lopez-Castroman J, Melhem N, Birmaher B, Greenhill L, Kolko D, Stanley B, Zelazny J, Brodsky B, Garcia-Nieto R, Burke AK, Mann JJ, Brent DA, Oquendo MA (2013). Early childhood sexual abuse increases suicidal intent. *World Psychiatry* **12**, 149-154.

MacMillan HL, Tanaka M, Duku E, Vaillancourt T, Boyle MH (2013). Child physical and sexual abuse in a community sample of young adults: Results from the Ontario Child Health Study. *Child Abuse and Neglect* **37**, 14-21.

McCrory EJ, De Brito SA, Viding E (2011a). The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Frontiers in Psychiatry* **2**, 48.

McCrory EJ, De Brito SA, Kelly PA, Bird G, Sebastian CL, Mechelli A, Samuel S, Viding E (2013). Amygdala activation in maltreated children during pre-attentive emotional processing. *British Journal of Psychiatry* **202**, 269-276.

McCrory EJ, De Brito SA, Sebastian CL, Mechelli A, Bird G, Kelly PA, Viding E (2011b). Heightened neural reactivity to threat in child victims of family violence. *Current Biol*ogy **21**, R947-948.

McLaughlin KA, Sheridan MA, Winter W, Fox NA, Zeanah CH, Nelson CA (2014). Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to ADHD. *Biological Psychiatry* **76**, 629-638.

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri AR, Pezawas L, Blasi G, Wabnitz A, Honea R, Verchinski B, Callicott JH, Egan M, Mattay V, Weinberger DR (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the United States of America* 103, 6269-6274.

Mills R, Alati R, O'Callaghan M, Najman JM, Williams GM, Bor W, Strathearn L (2011). Child abuse and neglect and cognitive function at 14 years of age: findings from a birth cohort. *Pediatrics* **127**, 4-10.

Murphy SE (2010). Using functional neuroimaging to investigate the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs). *Current Pharmaceutical Design* **16**, 1990-1997.

Nemeroff CB (2016). Paradise Lost: The neurobiological and clinical consequences of child abuse and neglect. *Neuron* **89**, 892-909.

Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006). Functional neuroanatomy of aversion and its anticipation. *Neuroimage* **29**, 106-116.

Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and metaanalysis. *PLoS Medicine* 9, e1001349.

NSPCC (2011). Child abuse and neglect in the UK today. September 2011.

Nugent NR, Tyrka AR, Carpenter LL, Price LH (2011). Gene–environment interactions: early life stress and risk for depressive and anxiety disorders. *Psychopharmacology* **214**, 175-196.

Olsson CA, Byrnes GB, Lotfi-Miri M, Collins V, Williamson R, Patton C, Anney RJL (2005). Association between 5-HTTLPR genotypes and persisting patterns of anxiety and alcohol use: results from a 10-year longitudinal study of adolescent mental health. *Molecular Psychiatry* **10**, 868-876.

Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, Jacobson K, Lyons MJ, Grant MD, Franz CE, Xian H, Tsuang M, Fischl B, Seidman L, Dale A, Kremen WS (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebal Cortex* **19**, 2728-2735.

Pechtel P, Pizzagalli DA (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* **214**, 55-70.

Pichon S, de Gelder B, Grezes J (2012). Threat prompts defensive brain responses independently of attentional control. *Cereal Cortex* 22, 274-285.

Pine DS, Mogg K, Bradley BP, Montgomery L, Monk CS, McClure E, Guyer AE, Ernst M, Charney DS, Kaufman J (2005). Attention bias to threat in maltreated children: implications for vulnerability to stress-related psychopathology. *American Journal of Psychiatry* **162**, 291-296.

Pollak SD, Nelson CA, Schlaak MF, Roeber BJ, Wewerka SS, Wiik KL, Frenn KA, Loman MM, Gunnar MR (2010). Neurodevelopmental effects of early deprivation in postinstitutionalized children. *Child Development* **81**, 224-236.

Rempel-Clower NL (2007). Role of orbitofrontal cortex connections in emotion. *Annals of the New York Academy of Sciences* **1121**, 72-86.

Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F (2003). Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cerebal Cortex* **13**, 308-317.

Schutter DJ, van Honk J (2005). The cerebellum on the rise in human emotion. *Cerebellum* 4, 290-294.

Sheffield JM, Williams LE, Woodward, ND, Heckers S (2013). Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. *Schizophrenia Research* **143**, 185-191.

Shih JC, Chen K, Ridd MJ (1999). MONOAMINE OXIDASE: From Genes to Behavior. *Annual Review of Neuroscience* 22, 197-217.

Sommer M, Sodian B, Döhnel K, Schwerdtner J, Meinhardt J, Hajak G (2010). In psychopathic patients emotion attribution modulates activity in outcome-related brain areas. *Psychiatry Research* **182**, 88-95.

StoodleyCJ, Schmahmann JD (2009). Functional topography in the human cerebellum: a metaanalysis of neuroimaging studies. *Neuroimage* **44**, 489-501.

Sugaya L, Hasin DS, Olfson M, Lin KH, Grant BF, Blanco C (2012). Child physical abuse and adult mental health: a national study. *Journal of Traumatic Stress* **25**, 384-392.

Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J (2006). Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biological Psychiatry* **59**, 224-229.

Taylor A, Kim-Cohen J (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Development and Psychopathology* **19**, 1029-1037.

Taylor SE, Eisenberger NI, Saxbe D, Lehman BJ, Lieberman MD (2006). Neural responses to emotional stimuli are associated with childhood family stress. *Biological Psychiatry* **60**, 296-301.

Teicher MH, Anderson CM, Ohashi K, Polcari A (2014). Childhood maltreatment: altered network centrality of cingulate, precuneus, temporal pole and insula. *Biological Psychiatry* **76**, 297-305.

Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E (1997). Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Annals of the New York Academy of Sciences* **821**, 160-175.

Teicher MH, Samson JA, Anderson CM, Ohashi K (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews Neuroscience* **17**, 652-666.

Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, van Balkom AJ, Smit JH, Veltman DJ (2010). Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *Journal of Clinical Psychiatry* **71**, 1636-1644.

Tommerdahl M, Delemos KA, Vierck CJ, Favorov OV, Whitsel BL (1996). Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. *Journal of Neurophysiology* **75**, 2662.

Tomoda A, Navalta CP, Polcari A, Sadato N, Teicher MH (2009). Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. *Biological Psychiatry* **66**, 642-648.

Tomoda A, Polcari A, Anderson CM, Teicher MH (2012). Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. *PLoS One* **7**, e52528.

Tomoda A, Sheu YS, Rabi K, Suzuki H, Navalta CP, Polcari A, Teicher MH (2011). Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. *Neuroimage* 54 Suppl 1, S280-286.

Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ (2011). Elevated amygdala response to faces following early deprivation. *Developmental Sci*ence **14**, 190-204.

Tracey I, Mantyh PW (2007). The cerebral signature for pain perception and its modulation. *Neuron* **55**, 377-391.

Trickett PK, Kim K, Prindle J (2011). Variations in emotional abuse experiences among multiply maltreated young adolescents and relations with developmental outcomes. *Child Abuse and Neglect* **35**, 876-886.

van Harmelen AL, de Jong PJ, Glashouwer KA, Spinhoven P, Penninx BW, Elzinga BM (2010). Child abuse and negative explicit and automatic self-associations: the cognitive scars of emotional maltreatment. *Behaviour Research Therapy* **48**, 486-494.

Viding E, Frith U (2006). Genes for susceptibility to violence lurk in the brain. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 6085-6086.

Walsh ND, Dalgleish T, Lombardo MV, Dunn VJ, Van Harmelen A-L, Ban M, Goodyer IM (2014). General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. *NeuroImage: Clinical* **4**, 308-318.

Wechsler D (1999). *Wechsler Abbreviated Scale of Intelligence*. The Psychological Corporation: San Antonio, Texas.

Weder N, Yang BZ, Douglas-Palumberi H, Massey J, Krystal JH, Gelernter J, Kaufman J (2009). MAOA genotype, maltreatment, and aggressive behavior: the changing impact of genotype at varying levels of trauma. *Biological Psychiatry* **65**, 417-424.

Weierich MR, Nock MK (2008). Posttraumatic stress symptoms mediate the relation between childhood sexual abuse and nonsuicidal self-injury. *Journal of Consulting and Clinical Psychology* **76**, 39-44.

Weller JA, Fisher PA (2013). Decision-making deficits among maltreated children. *Child Maltreatment* **18**, 184-194.

Wiech K, Lin CS, Brodersen KH, Bingel U, Ploner M, Tracey I (2010). Anterior insula integrates information about salience into perceptual decisions about pain. *Journal of Neurosci* ence **30**, 16324-16331.

Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, Duggirala R, Glahn DC (2010). Cortical Thickness or Grey Matter Volume? The Importance of Selecting the Phenotype for Imaging Genetics Studies. *NeuroImage* **53**, 1135-1146.

Woon FL, Hedges DW (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* **18**, 729-736.

Yang Y, Wang P, Baker LA, Narr KL, Joshi SH, Hafzalla G, Raine A, Thompson PM (2015). Thicker Temporal Cortex Associates with a Developmental Trajectory for Psychopathic Traits in Adolescents. *PLoS ONE* **10**, e0127025.

Young JC, Widom CS (2014). Long-term effects of child abuse and neglect on emotion processing in adulthood. *Child Abuse and Neglect* **38**, 1369-1381.

| | Childhood | | Psychi | atric | Heal | thy | | | |
|--|-----------|-------|--------|-------|----------|------|----------|------------------|----------------|
| | Abu | Abuse | | rols | Controls | | Ana | alysis | |
| | (N=22) | | (N=19) | | (N=27) | | | | |
| | Mean | SD | Mean | SD | Mean | SD | F(2, 65) | <i>p</i> (corr.) | Between Groups |
| Age (years) [age range:13-20] | 17.6 | 2.31 | 16.8 | 2.59 | 17.5 | 1.63 | 0.80 | ns | • |
| Socioeconomic status | 2.77 | 0.69 | 2.94 | 0.66 | 3.22 | 0.75 | 2.53 | ns | - |
| IQ | 89.5 | 12.5 | 93.5 | 12.8 | 105.4 | 10.1 | 12.3 | < 0.001 | CA, PC < HC |
| Strengths and Difficulties Questionnaire: | | | | | | | | | |
| Emotional problems | 4.68 | 2.72 | 4.89 | 2.98 | 1.92 | 1.61 | 10.7 | < 0.001 | CA, PC > HC |
| Conduct problems | 4.36 | 1.99 | 2.21 | 2.20 | 1.68 | 1.60 | 12.4 | < 0.001 | CA > PC, HC |
| Hyperactivity | 5.41 | 2.34 | 4.68 | 2.65 | 2.84 | 2.14 | 7.4 | 0.001 | CA, PC > HC |
| Peer problems | 3.77 | 1.51 | 2.53 | 1.95 | 1.16 | 1.72 | 13.4 | < 0.001 | CA > PC, HC |
| Prosocial | 7.36 | 1.76 | 8.58 | 1.78 | 8.08 | 1.41 | 2.87 | ns | - |
| Total difficulties score | 18.2 | 6.05 | 14.3 | 6.31 | 7.60 | 5.73 | 18.9 | < 0.001 | CA, PC > HC |
| Beck's Depression Inventory | 16.4 | 10.4 | 19.4 | 10.2 | 5.92 | 6.09 | 8.17 | 0.001 | CA, PC > HC |
| Childhood Trauma Questionnaire: | | | | | | | | | |
| Physical abuse | 20.9 | 4.97 | 6.00 | 1.45 | 5.52 | 0.94 | 126.6 | < 0.001 | CA > PC, HC |
| Emotional abuse | 17.9 | 4.30 | 7.00 | 1.86 | 6.04 | 1.13 | 98.1 | < 0.001 | CA > PC, HC |
| Sexual abuse | 5.14 | 0.64 | 5.15 | 1.07 | 5.11 | 0.42 | 1.49 | ns | - |
| Physical neglect | 14.1 | 4.97 | 6.63 | 3.69 | 5.59 | 1.22 | 40.4 | < 0.001 | CA > PC, HC |

 TABLE 1. Demographic Characteristics of 22 Young People Exposed to Childhood Abuse, 19 Psychiatric Controls and 27 Healthy Controls

| Emotional neglect | 18.3 | 3.84 | 8.79 | 3.69 | 7.93 | 3.35 | 53.0 | < 0.001 | CA > PC, HC |
|---|------|------|------|------|------|------|----------|---------|--|
| Age at onset of (physical) abuse (years) | 4.00 | 2.76 | - | - | - | - | - | - | - |
| Duration of (physical) abuse (years) | 8.27 | 3.12 | - | - | - | - | - | - | - |
| | Ν | % | Ν | % | Ν | % | χ^2 | р | Between Groups |
| Gender (Males) | 15 | 68 | 9 | 47 | 21 | 77 | 4.67 | ns | CA vs HC (χ^2 =0.57, ns); CA vs PC (χ^2 =1.82, ns); HC vs PC (χ^2 =4.55, p=0.03) |
| Ethnicity: | | | | | | | 7.98 | ns | - |
| Caucasian | 10 | 45 | 3 | 16 | 13 | 48 | | | |
| Afro-Caribbean | 9 | 41 | 10 | 52 | 12 | 44 | | | |
| Others (Asian/mixed) | 3 | 14 | 6 | 32 | 2 | 8 | | | |
| Psychiatric diagnosis: | | | | | | | | | |
| PTSD | 13 | 59 | 12 | 63 | - | | | | |
| Depression | 6 | 27 | 6 | 32 | - | | | | |
| Anxiety disorders | 5 | 23 | 5 | 26 | - | | | | |
| Social phobia | 1 | 5 | 1 | 5 | - | | | | |
| ADHD | 1 | 5 | 1 | 5 | | | | | |
| ODD/CD/Other disruptive behaviours | 5 | 23 | 4 | 21 | - | | | | |

Abbreviations: CA=Childhood Abuse group; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroni corrected; ADHD=Attention Deficit Hyperactivity Disorder; PTSD=Post-Traumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; ns=non-significant

| Brain regions | Childhood Abuse (N=22) | | ChildhoodPsychiatricAbuse (N=22)Controls (N=19) | | Healthy (N= | Healthy Controls (N=27) | | vs HC com | parisons | CA vs PC comparisons | | |
|---------------|---------------------------|------|---|------|----------------|----------------------------|-----------------|-----------|--|----------------------|---------|---|
| | Mean | SD | Mean | SD | Mean | SD | F (1,44) | p value | | F(1,36) | p value | |
| Cerebellum | | | | | | | | | | | | |
| Left CV | 54314 | 5158 | 56358 | 6854 | 57463 | 4992 | 4.68 | 0.03 | CA <hc< td=""><td>0.24</td><td>ns</td><td>-</td></hc<> | 0.24 | ns | - |
| Right CV | 55308 | 5038 | 55408 | 6799 | 58392 | 4318 | 5.33 | 0.02 | CA <hc< td=""><td>1.27</td><td>ns</td><td>-</td></hc<> | 1.27 | ns | - |
| Insula | | | | | | | | | | | | |
| Left CV | 6959 | 812 | 6806 | 762 | 7025 | 708 | 0.53 | ns | - | 0.11 | ns | - |
| Left CT | 3.13 | 0.13 | 3.19 | 0.17 | 3.23 | 0.14 | 6.06 | 0.02 | CA <hc< td=""><td>0.28</td><td>ns</td><td>-</td></hc<> | 0.28 | ns | - |
| Left SA | 2154 | 279 | 2083 | 223 | 2121 | 174 | 0.51 | ns | - | 0.02 | ns | - |
| Right CV | 7101 | 922 | 7041 | 1020 | 7200 | 766 | 0.19 | ns | - | 0.17 | ns | - |
| Right CT | 3.12 | 0.12 | 3.21 | 0.15 | 3.17 | 0.15 | 2.02 | ns | - | 3.19 | ns | - |
| Right SA | 2221 | 280 | 2168 | 340 | 2228 | 234 | 0.29 | ns | - | 0.36 | ns | - |
| Lateral OFC | | | | | | | | | | | | |
| Left CV | 8556 | 998 | 8464 | 1099 | 8649 | 903 | 0.20 | ns | - | 0.15 | ns | - |
| Left CT | 2.79 | 0.14 | 2.86 | 0.23 | 2.83 | 0.18 | 0.69 | ns | - | 0.22 | ns | - |
| Left SA | 2624 | 319 | 2562 | 324 | 2636 | 287 | 0.35 | ns | - | 0.86 | ns | - |
| Right CV | 8673 | 1222 | 8489 | 1117 | 8609 | 696 | 0.17 | ns | - | 0.18 | ns | - |
| Right CT | 2.80 | 0.17 | 2.90 | 0.15 | 2.91 | 0.20 | 4.30 | 0.04 | CA <hc< td=""><td>2.55</td><td>ns</td><td>-</td></hc<> | 2.55 | ns | - |
| Right SA | 2747 | 358 | 2565 | 368 | 2624 | 252 | 1.74 | ns | - | 1.79 | ns | - |

TABLE 2. Group Differences in the Cortical Measures of the Regions of Interest among 22 Young People Exposed to Childhood Abuse, 19Psychiatric Controls and 27 Healthy Controls

Abbreviations: CA=Childhood Abuse group; HC=Healthy Controls; PC=Psychiatric Controls; OFC=Orbitofrontal Cortex; CV=Cortical Volume (mm³); CT=Cortical Thickness (mm); SA=Surface Area (mm²); ns=non-significant; SD=Standard Deviation

TABLE 3. Regions with Significant Group Differences in Cortical Volume among 22 Young People Exposed to Childhood Abuse, 19 PsychiatricControls and 27 Healthy Controls

| Comparison | Brain regions | Talairach Coordinates (x,y,z) | Brodmann's Area | <i>t</i> value | p value | Cluster size (mm ³) |
|------------|--|----------------------------------|--------------------|--------------------|---------|---------------------------------|
| CA < HC | Left pericalcarine/precuneus/cuneus/ isthmus cingulate/lingual/superior parietal gyrus | -19.0, -72.7, 10.4 | 18/17/19/29/7 | -3.16 ^a | 0.003 | 3368.05 |
| CA < PC | Left precuneus | -11.4, -64.2, 23.8 | 31 | -2.36 ^b | 0.02 | 220.11 |
| CA > HC | Left inferior temporal gyrus | -48.1, -23.9, -23.4 | 20 | 2.99 ^a | 0.02 | 1301.33 |
| | Left middle temporal/inferior parietal gyrus | -48.0, -58.1, 5.5 | 21/39 | 2.82 ^a | 0.03 | 1231.88 |
| CA > PC | Left middle temporal gyrus | -54.5, -45.5, -1.5 | 21 | 2.38 ^b | 0.02 | 188.29 |

Abbreviations: CA, Childhood Abuse group; HC, Healthy Controls; PC, Psychiatric Controls

^a The *t* value at which the test statistic is significant at p < 0.05, corrected for multiple comparisons with a Monte Carlo z-field simulation.

^b The *t* value at which the test statistic is significant at p < 0.05, uncorrected for multiple comparisons.

TABLE 4. Regions with Significant Group Differences in Cortical Thickness among 22 Young People Exposed to Childhood Abuse, 19Psychiatric Controls and 27 Healthy Controls

| Comparison | Brain regions | Talairach Coordinates (x,y,z) | Brodmann's Area | <i>t</i> value | p value | Cluster size (mm) |
|------------|---|----------------------------------|--------------------|--------------------|---------|-------------------|
| CA < HC | Left precentral/postcentral/ paracentral | -38.8, -13.0, 55.4 | 4/1/2/3 | -3.05 ^a | 0.004 | 1029.25 |
| CA < PC | Left precentral | -28.6, -22.7, 60.9 | 4 | -2.18 ^b | 0.04 | 207.44 |

Abbreviations: CA=Childhood Abuse group; HC=Healthy Controls; PC=Psychiatric Controls

^a The *t* value at which the test statistic is significant at p < 0.05, corrected for multiple comparisons with a Monte Carlo z-field simulation.

^b The *t* value at which the test statistic is significant at p < 0.05, uncorrected for multiple comparisons.

Figure Legend

Figure 1. Significant cortical volume cluster projected onto the inflated surface of the left hemisphere in (A) medial and (B) tilted anterior views. The significant cluster shows reduced cortical volume in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, p < 0.05.

Figure 2. Significant cortical volume clusters projected onto the inflated surface of the left hemisphere in lateral view. The significant clusters show increased cortical volume in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, p < 0.05.

Figure 3. Significant cortical thickness cluster projected onto the inflated surface of the left hemisphere in (A) lateral and (B) medial views. The significant cluster shows reduced cortical thickness in the childhood abuse group compared with healthy controls, and survived cluster correction for multiple comparisons using Monte Carlo simulation, p < 0.05.







A)



B)



Figure 1

A)

B)





Figure 2





A)

B)





1

±

Supplementary Materials

MRI Image Acquisition

Images were acquired using a 3-T GE Signa HDx system (General Electric, USA) at the Centre for Neuroimaging Sciences, King's College London, UK. The body coil was used for radio frequency (RF) transmission and an eight-channel head coil for RF reception. High-resolution structural three-dimensional (3D) T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) images were acquired. 166 contiguous slices, 1.2 mm thickness, a 256 x 256 x 166 matrix and a repetition time/echo time of 7/2.8 ms (field of view 260 mm). Full brain and skull coverage was required for each subject and detailed quality control was carried out on all MR images according to previously published quality control criteria (Simmons *et al.* 2011).

MRI Image Processing

The surface-based analysis was carried out using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvest.edu). Technical details of this well-validated and fully automated procedure have been extensively described elsewhere (Fischl *et al* 2002; Fischl *et al* 2004a; Fischl *et al* 2004b; Segonne *et al*. 2004). Briefly, the FreeSurfer pipeline performs cortical reconstruction and subcortical volumetric segmentation including the removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne *et al*. 2004). Automated Talairach (Talairach & Tournoux, 1988) transformation is performed, followed by segmentation of the subcortical white matter (WM) and deep grey matter (GM) volumetric structures (including hippocampus, amygdala, caudate, putamen, thalamus and ventricles) (Fischl *et al*. 2002; Fischl *et al* 2004a). This is followed by intensity normalization (Sled *et al*. 1998), tessellation of the GM-WM boundary and the GM-cerebrospinal fluid (CSF) boundary, automated topology correction (Fischl *et al*. 2001; Segonne *et al*. 2007) and surface deformation following intensity gradients to optimally place the GM/WM and GM/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Fischl & Dale, 2000). On completion of the cortical models, individual cortical

folding patterns are then registered to a spherical atlas based on folding patterns, to match cortical geometry across subjects (Fischl *et al.* 1999). Cortical thickness can be calculated at each location of the cortex as the distance between the white and pial surface (Fischl & Dale, 2000). The cerebral cortex is then parcellated into units based on gyral and sulcal structure allowing local curvature and surface area measures to be computed (Fischl *et al.* 2004b). Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas *et al.* 2002) and manual measurements (Salat *et al.* 2004).

| | Childhood Abuse (N=22) | | Psychiatric Controls (N=19) | | Healthy Controls (N=27) | | Analysis | | |
|---|---------------------------|-----|--------------------------------|-----|----------------------------|-----|----------|---------|----------------|
| | Mean | SD | Mean | SD | Mean | SD | F (2,62) | p value | Between Groups |
| Left hippocampus volume (mm ³) | 4405 | 447 | 4286 | 435 | 4481 | 369 | 0.61 | ns | - |
| Right hippocampus volume (mm ³) | 4293 | 465 | 4371 | 348 | 4520 | 354 | 0.46 | ns | - |

Table S1. Group Differences in Hippocampus Volume among 22 Young People Exposed to Childhood Abuse, 19 Psychiatric Controls and 27Healthy Controls

Abbreviations: SD=Standard Deviation; ns=non-significant

Figure S1. Associations between (**a**) left lingual-pericalcarine-precuneus CV and CTQ total score, (**b**) left lingual-pericalcarine-precuneus CV and CTQ physical abuse score, (**c**) left pre-/postcentral CT and CTQ total score within the abuse group



Figure S2. Associations between (a) left lingual-pericalcarine-precuneus CV and SDQ total score (b) left lingual-pericalcarine-precuneus CV and SDQ peer problem score within the healthy control group



- Fischl B, Sereno MI, Tootell RB, Dale AM (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapping* **8**, 272-284.
- Fischl B, Dale AM (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proceedings of the National Academy of Sciences of the United States of America 97, 11050-11055.
- Fischl B, Liu A, Dale AM (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Transactions* on Medical Imaging 20, 70-80.
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002). Whole brain segmentation: automated labelling of neuroanatomical structures in the human brain. *Neuron* 33, 341-355.
- Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, Dale AM (2004a). Sequence-independent segmentation of magnetic resonance images. *Neuroimage* 23, S69-84.
- Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004b). Automatically parcellating the human cerebral cortex. *Cerebral Cortex* 14, 11-22.
- Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 58, 695-701.
- Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex* 14, 721-730.
- Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B (2004). A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 22, 1060-1075.

- Segonne F, Pacheco J, Fischl B (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Transactions on Medical Imaging* **26**, 518-529.
- Simmons A,Westman E, Muehlboeck S, Mecocci P, Vellas B, Tsolaki M, Kloszewska I,Wahlund LO, Soininen H, Lovestone S, Evans A, Spenger C (2011). TheAddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease: experience from the first 24 months. *International Journal of Geriatric Psychiatry* 26, 75– 82.
- Talairach, J, Tournoux P (1988). Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System - an Approach to Cerebral Imaging, Thieme Medical Publishers, New York, NY.

<u>Reply to Editorial office</u>

1) Amend the abstract (both in the abstract text box and the main document) to use only our standard subheadings of Background, Methods, Results, Conclusions.

Thank you. We have now used the standard subheadings for the abstract (in both the abstract text box and main document).

2) You also need to amend the reference list to our usual style (see instructions for authors).

Thank you. We have now amended the references accordingly.

3) Although Figure 2 clearly requires colour, I think that Figures 1 and 3 would still be completely meaningful if printed in black and white. You may therefore wish to eliminate the unnecessary use of colour from those figures. You will be asked to pay for unnecessary colour printing (\pounds 200 per figure). If you wish you may have colour online and black-and-white in print at no charge, in which case you should submit two copies of the figures, identical in every respect other than the colour.

Thank you. We have now included 2 versions of Figures 1-3 for print and online: Figure 1_online colour Figure 1_print BW Figure 2_online colour Figure 2_print colour Figure 3_online colour Figure 3_print BW

PLEASE NOTE THE FOLLOWING: A REVISION WILL ONLY BE ACCEPTED IF THE FOLLOWING POINTS ARE OBSERVED. FAILURE TO COMPLY WITH THESE REQUIREMENTS WILL ONLY LEAD TO DELAY.

A) Figures, which should be uploaded as a separate file, should be produced using size 8 point Arial font for the legend. Any wording within a figure should ideally be in Arial - 8 point size is standard, but this may vary depending on space limitations within individual figures. Wherever possible figures for print should be monochrome although colour figures are acceptable for online. Figures should NOT be embedded or included in the main text tile.

Thank you. We have now changed the wordings within the figures to Arial size 8, and included 2 versions of Figures 1-3 for print and online: Figure 1_online colour Figure 1_print BW Figure 2_online colour Figure 2_print colour Figure 3_online colour Figure 3_print BW

B) References should be in the Harvard format, listing all authors, date, article title, journal title in full, volume, page numbers.

We have now amended the references accordingly.

C) Appendices and supplementary material also should be submitted as a separate file from the main text. These will be published online exactly as they are received, so a clean version without

track changes showing, etc, must be submitted. Authors may upload two *clearly labelled* versions of supplementary material, one clean and one showing changes if they feel this appropriate.

We have now uploaded the final version of the supplementary material without any track changes.

D) Text files (and tables) should be uploaded in editable form (ie word processor files, not pdf).

The text files and tables were previously and are now uploaded as Word .doc files.

E) If you decide to submit both a clean copy and a tracked changes copy of your manuscript, please be sure to classify the tracked version as "response to reviewers" and not as supplementary or any other designation. (if submitting only a tracked version then that should be classified as the main document or "manuscript")

We have now submitted a clean copy of our manuscript.