Structural and functional alterations in the brain of patients exposed to childhood violence

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PART 1: The evidence base

Neuroimaging methods to assess brain structure and function

Neuroimaging measures provide direct insight into the structural and/or functional integrity of the brain, its connectivity and the timing of information processing. There are a number of different techniques to assess brain structure and function. In this essay we concentrate on those neuroimaging techniques that have been used most often in recent years.

Structural measures such as the size of specific brain regions or the volumes of grey and white matter are assessed using ***magnetic resonance imaging (MRI)*** while ***diffusion tensor imaging (DTI)*** is used to determine the integrity of the white matter tracts. ***Functional MRI (fMRI)*** measures changes in the blood oxygenation level as a consequence of neuronal activation and thus tracks the neuronal activity indirectly with excellent spatial resolution but a time delay of several seconds. ***Positron emission tomography (PET)*** uses the injection of radioactive tracers to measure changes in the blood flow and to determine active brain regions. Similar to fMRI, PET shows a good spatial resolution but a poor temporal resolution. ***Event-related potentials (ERPs)*** derived from ***electroencephalographic (EEG)*** recordings represent neuronal mass activation directly with high temporal but poor spatial resolution.

Patients are typically administered 1-2 functional MRI scans to measure brain activation during specific cognitive paradigms or during resting state. When recording fMRI data, usually a ***structural MR (sMRI)*** scan of the brain is also assessed.

Both, MRI and EEG are non-invasive neuroimaging techniques and well suited to be applied in patients and healthy controls from childhood to adulthood.

Alterations in neuroimaging measures of subjects who experienced childhood maltreatment

Neuroimaging studies in the past revealed major differences in the size, volume and function of specific brain structures in subjects who have experienced ***childhood maltreatment (CM)***. Child abuse probably acts as a severe stressor that induces a series of changes (Teicher et al., 2006) in physiology, neurochemistry and hormones. Such changes may critically affect brain development as reflected by alterations in brain structure and function (Hart and Rubia, 2012). A study by Carrion for example showed that cortisol levels and symptom severity of ***posttraumatic stress disorder (PTSD)*** predicted damage to the hippocampus over an ensuing 12-18 month period (Carrion et al., 2007).

The alterations seen in brain structure and function of subjects exposed to CM basically mirror behavioural consequences of childhood abuse such as for example deficits in memory (Raine et al., 2001; Teicher et al., 2012), cognitive control (Mueller et al., 2010), inhibition (Carrion et al., 2008) and emotion (Maheu et al., 2010).

There is a considerable number of neuroimaging studies examining the effect of CM and juvenile violence on structural and functional development of the brain. A majority of the studies available up to date concentrated on structural alterations related to CM but the number of cognitive activation studies is growing rapidly.

Most of the studies on CM, however, included patients suffering from CM-related PTSD. While a number of structural neuroimaging studies exist for children and adults, functional activation studies were almost exclusively done with adults and findings in paediatric populations are thus very sparse.

Typically, neuroimaging studies compared CM-related PTSD patients to healthy age and gender matched control groups (Andersen et al., 2008; Carrion et al., 2001; De Bellis and Keshavan, 2003; De Bellis et al., 1999b; De Bellis et al., 2002; De Bellis and Kuchibhatla, 2006; Hanson et al., 2010; Weniger et al., 2008). Some of these studies also looked at correlations between specific brain measures and onset of maltreatment, duration of maltreatment, symptoms or functional impairments (see (Hart and Rubia, 2012), e.g. Cohen, Grieve et al. 2006; Edmiston, Wang et al. 2011; Teicher, Anderson et al. 2012)).

Only four studies on structural imaging examined groups of mostly healthy subjects with CM history but without PTSD: The studies by Cohen et al. (Cohen et al., 2006) and Dannlowski et al. (Dannlowski et al., 2012) included extraordinary large samples and correlated the severity of CM, assessed with

adverse childhood experience (ACE) and/or ***childhood trauma questionnaires (CTQ)***, with structural (Cohen et al., 2006; Dannlowski et al., 2012) and/or functional neuroimaging measures in adults (Cohen et al., 2006). The regression analyses of both studies pointed to major impact of childhood trauma severity on fronto-striatal and limbic circuits. No significant correlations of neuroimaging measures with symptom ratings but with performance IQ was found in another study including healthy young adults (Tomoda et al., 2009). Finally there was only one study comparing healthy children with CM-history to control children (Hanson et al., 2010).

Summary of the neuroimaging literature on child maltreatment

Here, we shortly summarize major findings by first reviewing differences in brain structure followed by some evidence for functional differences as revealed with PET and fMRI. The ERP literature is summarized at the end of this chapter.

Of note, two very recent, excellent and comprehensive reviews on structural and functional differences related to CM and abuse nicely summarize the current literature. For a more detailed summary on neuroimaging literature, critical analyses and potential implications we thus refer to the following reviews (Hart and Rubia, 2012; McCrory et al., 2010) and especially to the summary tables in (Hart and Rubia, 2012).

Differences revealed by sMRI affected global measures such as the total size of the cerebral, cerebellar and ventricle volumes. But also more regional differences, usually in the form of reduced sizes or volumes, were found. **Fronto-limbic circuitries including the hippocampus, amygdala, the striatum as well as the *prefrontal cortex (PFC)*, the *anterior cingulate gyrus (ACC)* and the *orbitofrontal cortex (OFC)*** (Hart and Rubia, 2012) are especially affected by CM. But also specific white matter tracts such as the corpus callosum seem affected by CM.

Hippocampus: Several studies pointed to diminished hippocampal volume in adults with a history of CM (Andersen et al., 2008; Bremner et al., 1997; Dannlowski et al., 2012; Edmiston et al., 2011; Teicher et al., 2012; Weniger et al., 2008) but not yet in maltreated children (Carrion et al., 2001; De Bellis et al., 1999b; De Bellis et al., 2002; Hanson et al., 2010; Mehta et al., 2009). A very recent study could show that the childhood trauma score was negatively correlated with hippocampal grey matter volume in a large group of adults without psychiatric conditions (Dannlowski et al., 2012). The hippocampus is a brain structure that is crucially involved in learning and memory. Stress-induced high levels of glucocorticoids over prolonged periods may thus affect the hippocampal structure and subfield development (Teicher et al., 2012) through neurotoxicity (Carrion et al., 2007; McEwen and Magarinos, 1997) and cause associated cognitive deficits such as impaired memory (Bremner et al., 1995; Bremner et al., 1993; Navalta et al., 2006). The findings of altered volume in affected adults but not children suggests that CM may cause abnormal development of this structure that becomes only apparent in the mature brain, i.e. years after the insult, as supported by the meta-analysis of Woon et al. comparing studies of children and adults with PTSD following CM (Woon and Hedges, 2008).

Decreased metabolism in the hippocampus has been demonstrated for children who experienced early deprivation during resting state condition (Chugani et al., 2001) and in abused women when exposed to traumatic scripts (Bremner et al., 1999) or to emotionally valenced word pairs (Bremner et al., 2003). Increased activation was demonstrated when neglected adolescents viewed angry or fearful faces (Maheu et al., 2010) or when pain patients with childhood sexual abuse history performed an empathy-for-pain paradigm (Noll-Hussong et al., 2010). Finally altered activation of the hippocampus was also reported for olfactory stimulation (Croy et al., 2010) in women with history of CM.

Amygdala: Less clear are the findings regarding effects of CM on the amygdala. The amygdala has been implicated in fear conditioning, but also emotional learning and memory and in the modulation of memory and attentional systems (Phelps and LeDoux, 2005). A volume reduction has been reported for adults with CM related PTSD (Weniger et al., 2008) or adolescents who experienced CM. This effect was especially pronounced when looking at those adolescents who suffered from emotional neglect (Edmiston et al., 2011). But prolonged time of early deprivation was also related to increased right amygdala volume in another study (Mehta et al., 2009) or yielded no differences in size (Andersen et al., 2008; Bremner et al., 1997). Also a meta-analyses did not yield consistent differences in amygdala volume (Woon and Hedges, 2008) suggesting that this brain region might be less vulnerable to structural changes (McCrory et al., 2010).

The alterations in the functional activation of the amygdala depended on the task: Decreased metabolism in the amygdala was reported in a resting state PET study with deprived children (Chugani et al., 2001) while increased amygdala activation was found in patients with PTSD during a fear-conditioning paradigm (Bremner et al., 2005) and when youth with emotional neglect processed threatening faces (Maheu et al., 2010). Amygdala responsiveness to threat-related facial expressions

was furthermore strongly related to childhood trauma scores in healthy adults (Dannlowski et al., 2012).

Prefrontal and orbitofrontal cortex: Another brain structure potentially affected by CM which is important for planning, control and monitoring of behavioural outcome, cognition and emotion regulation is the PFC and especially the orbitofrontal part of the PFC. The PFC matures particularly late (Sowell et al., 2001; Toga et al., 2006) and may thus be especially vulnerable to early stress. Chronic stress as induced by CM may weaken the regulatory control exerted by the OFC (Hanson et al., 2010) and thus affect self regulation of social-emotional behaviour, inhibition and adaptation to changing environmental contigencies. The OFC exhibited smaller volumes in physically abused children in comparison to non-abused control children (Hanson et al., 2010). Grey matter volume negatively correlated with the severity of self-reported CM in adolescents (Edmiston et al., 2011) and adults (Dannlowski et al., 2012) without psychiatric diagnosis. These results also coincide with the recent finding of smaller OFC, insula and cingulate regions with increasing cumulative exposure to adverse life events in healthy adults (Ansell et al., 2012). Also adolescents (Andersen et al., 2008) or children with history of CM exhibited reduced PFC volumes (De Bellis et al., 2002). Abnormal PFC structure may thus put maltreated children at greater risk for a variety of behavioural problems emerging also later in life (Hanson et al., 2010) and mediate the development of stress-related disorders (Ansell et al., 2012).

In accordance with the structural alterations in subjects with history of CM, consistent alterations in functional activation of prefrontal brain regions were reported. Reduced activation was found during a working memory task (Raine et al., 2001) and during tasks testing inhibition/cognitive control (Carrion et al., 2008; Mueller et al., 2010) in dorsolateral and inferior PFC. When testing memory of childhood abuse and effects of emotion on attention (Bremner et al., 1999; Bremner et al., 2003; Schmahl et al., 2003; Schmahl et al., 2004), increased blood flow was found in the anterior PFC, OFC, medial PFC but also dorsolateral PFC. Non-traumatic olfactory cues were associated with increased activation of the PFC, inferior and middle frontal regions (Croy et al., 2010). Further also an empathy-inducing pain paradigm was associated with increased medial and lateral PFC activation in adults with sexual abuse history suffering from chronic functional pain syndromes (Noll-Hussong et al., 2010).

Anterior cingulate gyrus: Reductions in the volume of the ACC were found in subjects with CM history (Cohen et al., 2006; Dannlowski et al., 2012; Kitayama et al., 2006; Treadway et al., 2009) and also functional differences were found in abused subjects during tasks requiring executive control (Carrion et al., 2008; Mueller et al., 2010), interference in Stroop paradigms (Thomaes et al., 2012) and tasks testing memory, emotion, traumatic scripts and processing of olfactory cues (Bremner et al., 1999; Bremner et al., 2003; Croy et al., 2010; Schmahl et al., 2004).

Cerebellum: There is some evidence from structural and functional imaging studies that the cerebellum is affected by CM as revealed in children and adolescents with a history of maltreatment or socioemotional deprivation (De Bellis and Kuchibhatla, 2006). The cerebellum is involved in motor coordination, emotional and cognitive development and fear conditioning amongst others (Schmahmann and Sherman, 1998) and its function may be impaired by early trauma (Anderson et al., 2002).

White matter tracts: There are only few studies examining connectivity and integrity of white matter tracts in subjects with CM. Consistent alterations were detected in the corpus callosum (Andersen et al., 2008; De Bellis and Keshavan, 2003; De Bellis et al., 1999b; De Bellis et al., 2002; Jackowski et al., 2008; Kitayama et al., 2007; Teicher et al., 2004). But also the uncinate fasciculus connecting the OFC and the anterior temporal lobe (Eluvathingal et al., 2006) as well as the fornix, arcuate fasciculus and the cingulum bundle showed diminished white matter integrity in young adults that were exposed to parental verbal abuse in childhood (Choi et al., 2009). Finally, aberrant connectivity in fronto-striatal projections of children with early deprivation was found whereby increased connectivity was associated with increased externalizing behavioral problems (Behen et al., 2009).

Striatum: Altered striatal structure was reported in the studies of (Cohen et al., 2006; Dannlowski et al., 2012; Edmiston et al., 2011) and increased activation of the striatum in abused subjects was reported when examining inhibition and response control (Mueller et al., 2010).

Other areas: Further alterations were also seen in parieto-temporal regions (Hanson et al., 2010; Tomoda et al., 2010) and insula (Dannlowski et al., 2012; Edmiston et al., 2011; Thomaes et al., 2012).

***Event-related potential (ERP)** studies associated with CM:* There are only few studies that have studied subjects with history of CM using ERPs. Three studies examined alterations in ERPs evoked by processing emotional faces (Cicchetti and Curtis, 2005; Parker and Nelson, 2005; Pollak et al., 2001) one study used visual and auditory emotional cues *(Shackman et al., 2007)*. While the study by

Cicchetti looked at brain responses in abused and non-abused toddlers (Cicchetti and Curtis, 2005) the other groups examined children (Pollak et al., 2001; Shackman et al., 2007). Alterations in ERPs between abused and non-abused children were especially pronounced in the processing of angry and/or fearful faces/cues. The findings indicate that extreme emotional experiences may alter attention allocation regulation and sensitivity to emotional information (Pollak, 2008; Shackman et al., 2007).

Establishing causality between abnormal brain measures and juvenile victimization is difficult

Most of the studies examining neuroimaging measures in subjects with a history of childhood abuse have mixed subjects with and without psychiatric conditions and did not control for substance abuse and/or medication intake. Often, the studies included only, or a majority of cases suffering from CM-related PTSD. And these patients often suffered from additional comorbidities such as MDD[i], ODD[ii], BPD[iii], GAD[iv] and others (for details, see review by (Hart and Rubia, 2012)).

Therefore, it is very difficult to decide on whether changes in the brain are due to childhood abuse, the psychiatric conditions, medication or an interaction of these factors (Hart and Rubia, 2012; Tomoda et al., 2009). Moreover, confounding factors that are commonly present in maltreating families such as low ***socio-economic status (SES)***, low educational level, poor parenting skills, substance abuse or others (De Bellis et al., 2002) have to be considered as well. According to the systematic summary list in the review of Hart and Rubya (2012), only very few studies concentrated on healthy subjects without psychiatric conditions or on groups of mostly un-medicated cases without comorbidities (Cohen et al., 2006; Hanson et al., 2010; Tomoda et al., 2009).

Correlational analyses yielded relations between the age of trauma and/or duration of abuse with the cerebellar volume (De Bellis and Kuchibhatla, 2006), total brain volume (De Bellis et al., 2002) or volume of specific structures such as amygdala, hippocampus, striatum or anterior cingulate gyrus (Cohen et al., 2006; Mehta et al., 2009) and also between severity of experienced maltreatment with grey matter volume of PFC, amygdala, striatum, cerebellum and sensory association cortices (Edmiston et al., 2011). Furthermore there is some evidence for sensitive periods in which specific brain structures are especially vulnerable to maltreatment (Andersen et al., 2008).

Effect of moderation and mediation

There is some evidence for gender differences in brain imaging measures in subjects with a history of CM. The fact that grey and white matter development shows gender differences (Giedd et al., 1999) would also support the working hypothesis that CM may have different effects on boys and girls, also depending on the age of the trauma: Sex differences have been reported for example in sMRI studies on CM and concerned the total cerebral volumes and parts of the corpus callosum, lateral ventricular volumes as well as grey matter volume in fronto-striatal, limbic, temporo-parietal, temporo-occiptal lobes and cerebellum (De Bellis et al., 1999a; De Bellis and Keshavan, 2003; Edmiston et al., 2011).

In the meta-analyses of Woon indicates that the higher prevalence of PTSD in women does not correspond to more pronounced hippocampal volume reductions in females. The authors thus conclude that gender may not be a protective factor for hippocampal structure deficits in adults with PTSD (Woon and Hedges, 2011).

There is some evidence that specific brain structures are more affected by adverse events during certain critical developmental windows of high vulnerability: The frontal cortex e.g. seems especially vulnerable between the age of 14-16yrs whereas the hippocampus was maximally affected between age 3-5yrs and 11-13yrs and the corpus callosum by insult at the age 9-10yrs (Andersen et al., 2008).

Finally, the effect on brain structure most likely also depends on the type of CM (e.g. physical/emotional neglect/ abuse, sexual abuse (Edmiston et al., 2011)).

[i] MDD major depressive disorder
[ii] ODD oppositional defiant disorder
[iii] BPD borderline personality disorder
[iv] GAD generalized anxiety disorder

PART 2: Implications for prevention and intervention

There is some evidence for a normalisation of functional brain activation after intervention in subjects with CM history

To our knowledge there is only one neuroimaging study (Thomaes et al., 2012) examining the effects of intervention/therapy in subjects suffering from CM on brain function. This recently published study compared the effects of usual treatment with the effects of psycho-educational and cognitive behavioural stabilizing group treatment in addition to usual treatment. They examined the neuronal correlates of these treatments in two groups of CM related PTSD patients with fMRI. Successful treatment induced changes in the activation of the ACC and insula in a Stroop interference task. The "normalisation" of activation in these brain regions has been suggested to reflect increased selective attention and lower emotional arousal after treatment (Thomaes et al., 2012).
There is also evidence from many other brain imaging studies that treatment of PTSD induces changes in brain function. FMRI studies e.g. reported marked changes of functional activation in subjects with PTSD related to war (Roy et al., 2010) or in cerebral blood flow during trauma script-driven imagery (Lindauer et al., 2008) after therapy. Evidence for medication (SSRI[v]) induced changes in brain measures come from two single photon emission computed tomography (SPECT) studies on PTSD (Carey et al., 2004; Seedat et al., 2004).

Is there evidence for specific time windows of vulnerability?
There has been one neuroimaging study suggesting specific vulnerability windows for certain brain structures (Andersen et al., 2008). This finding also converges with the current knowledge on the structural and functional development of the brain. Different brain regions show different maturational curves and thus may be especially vulnerable to traumatic events during specific time windows. Phylogenetically older structures and primary sensory-motor areas e.g. mature prior to more higher-level association areas in the dorsal, medial and orbitofrontal cortex. Even within structures (e.g. hippocampus) developmental differences have been reported (Gogtay et al., 2004; Gogtay et al., 2006; Sowell et al., 2003).

Is there potential for reversing the effects of juvenile violence victimization on the psychobiological or health outcome?
Animal and human studies show that early stress alters the function of the ***hypothalamic-pituitary-adrenal (HPA)*** stress response. Alterations of the HPA response along with the potential neurotoxic effects of prolonged exposure to glucocorticoids in brain regions such as e.g. the hippocampus (Carrion et al., 2007) in turn may have detrimental effects on the development of the brain and predispose subjects to psychiatric vulnerability (for a review see (McCrory et al., 2010)). Potential reversing effects could be expected when targeting arrangements that help children to effectively regulate stress. McCrory et al thus suggest that "*better-structures around children – essentially a systematic scaffolding*" (cited from (McCrory et al., 2010)) should be developed that may help the children to deal with stress.

What new data should be collected to evaluate the effects of interventions on psychobiological outcomes?
When clinical studies examine effects of specific treatment on behavioural outcomes we recommend that also brain imaging measures are collected. Such measures allow insights into changes in the brain related to treatment and may be indicative on whether the effects of treatment are due to "normalization" of brain structure/function or due to compensatory processes. Such knowledge may not be gained by pure behavioural measures.
From clinical trials with longitudinal follow-ups we moreover also gain knowledge about the potential value of brain measures to predict the success of treatment and/or whether brain imaging measures can complement behavioural/diagnostic measures to improve the selection of the most effective therapy.

[v] SSRI: selective serotonin reuptake inhibitor

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