Effects on the brain assessed with neuroimaging

Susanne Walitza & Silvia Brem

PART 1 of the briefing paper: The evidence base

The psychobiological outcome: Neuroimaging measures

Neuroimaging measures provide direct insight into the structural and/or functional integrity of the brain and about the timing of mental functions. Structural measures such as the size of specific brain regions and volume of grey and white matter are assessed with ***magnetic resonance imaging (MRI)*** while ***diffusion tensor imaging (DTI)*** can be specifically applied to determine integrity of white matter tracts.

While there are in principle several methods to asses brain function, we concentrate on those three methods that have been used most often. ***Functional magnetic resonance imaging (fMRI)*** relies on changes in the blood oxygenation level as a consequence of neuronal activation and thus measures neuronal activity indirectly and with a delay of several seconds but a high spatial resolution. ***Positron emission tomography (PET)*** measures changes in the blood flow to reveal active brain regions. Similar to fMRI its spatial resolution is good but its temporal resolution poor. In contrast, the ***event-related potentials (ERPs)*** derived from ***electroencephalography (EEG)*** represent neuronal mass activation directly and with high temporal but poor spatial resolution.

For the recording of functional neuroimaging data patients are typically administered 1-2 tasks that measure brain activation during specific cognitive paradigms or during resting state. When doing fMRI studies, usually a ***structural MR image (sMRI)*** of the brain is also assessed.

MRI and EEG are non-invasive measures that are well suited to be applied in patients and healthy controls from childhood to adulthood. PET uses the injection of radioactive tracers and its use is therefore somewhat more restricted for research purposes.

In neuroimaging studies, measures of intelligence and clinical scores are usually assessed in parallel. When performing cognitive tasks, behavioural measures such as reaction time and/or accuracy are recorded as well.

Alterations in neuroimaging measures mirror behavioural problems

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, Tomoda 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 et al. 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, Weems et al. 2007).

Alterations in brain structure and function basically mirror behavioural consequences of childhood abuse such as for example deficits in memory (Raine, Park et al. 2001; Teicher, Anderson et al. 2012), cognitive control (Mueller, Maheu et al. 2010), inhibition (Carrion, Garrett et al. 2008) and emotion (Maheu, Dozier et al. 2010).

There is a considerable number of neuroimaging studies examining the effect of child maltreatment (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 pediatric populations are thus very sparse.

Typically, neuroimaging studies compared CM-related PTSD patients to healthy age and gender matched control groups (De Bellis, Keshavan et al. 1999; Carrion, Weems et al. 2001; De Bellis, Keshavan et al. 2002; De Bellis and Keshavan 2003; De Bellis and Kuchibhatla 2006; Andersen, Tomada et al. 2008; Weniger, Lange et al. 2008; Hanson, Chung et al. 2010). 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, Grieve et al. 2006) and Dannlowski et al. (Dannlowski, Stuhrmann et al. 2012) included extraordinary large sample sizes and correlated the severity of CM, assessed with ***adverse childhood experience (ACE)*** and/or ***childhood trauma questionnaires (CTQ)***, with structural (Cohen, Grieve et al. 2006; Dannlowski, Stuhrmann et al. 2012) and/or functional neuroimaging measures in adults (Cohen, Grieve 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, Suzuki et al. 2009). Finally there was only one study comparing healthy children with CM-history to control children (Hanson, Chung et al. 2010).

Summary of the neuroimaging literature on child maltreatment.

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 (McCrory, De Brito et al. 2010; Hart and Rubia 2012) and especially to the summary tables in (Hart and Rubia 2012).
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.

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 cingulated 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 (Bremner, Randall et al. 1997; Andersen, Tomada et al. 2008; Weniger, Lange et al. 2008; Edmiston, Wang et al. 2011; Dannlowski, Stuhrmann et al. 2012; Teicher, Anderson et al. 2012) but not yet in maltreated children (De Bellis, Keshavan et al. 1999; Carrion, Weems et al. 2001; De Bellis, Keshavan et al. 2002; Mehta, Golembo et al. 2009; Hanson, Chung et al. 2010). 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, Stuhrmann 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, Anderson et al. 2012) through neurotoxicity (McEwen and Magarinos 1997; Carrion, Weems et al. 2007) and cause associated cognitive deficits such as impaired memory (Bremner, Scott et al. 1993; Bremner, Randall et al. 1995; Navalta, Polcari 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 in PET studies for children who experienced early deprivation during resting state condition (Chugani, Behen et al. 2001) and in abused women when exposed to traumatic scripts (Bremner, Narayan et al. 1999) or to emotionally valenced word pairs (Bremner, Vythilingam et al. 2003). Increased activation was demonstrated when neglected adolescents viewed angry or fearful faces (Maheu, Dozier et al. 2010) or when pain patients with childhood sexual abuse history performed an empathy-for-pain paradigm (Noll-Hussong, Otti et al. 2010). Finally altered activation of the hippocampus was also reported for olfactory stimulation (Croy, Schellong 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, Lange et al. 2008) or adolescents who experienced CM. This effect was especially pronounced when looking at those adolescents who suffered from emotional neglect (Edmiston, Wang et al. 2011). But prolonged time of early deprivation was also related to increased right amygdala volume in another study (Mehta, Golembo et al. 2009) or yielded no differences in size (Bremner, Randall et al. 1997; Andersen, Tomada et al. 2008). 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, De Brito et al. 2010).

The alterationsin 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, Behen et al. 2001) while increased amygdala activation was found in patients with PTSD during a fear-conditioning paradigm (Bremner, Vermetten et al. 2005) and when youth with emotional neglect processed threatening faces (Maheu, Dozier et al. 2010). Amygdala responsiveness to threat-related facial expressions was furthermore strongly related to childhood trauma scores in healthy adults (Dannlowski, Stuhrmann et al. 2012).

Prefrontal and orbitofrontal cortex: Another brain structure potentially affected by CM and important for planning, control and monitoring of behavioural outcome, cognition and emotion regulation is the prefrontal cortex (PFC) and especially the orbitofrontal part of the PFC (OFC). The PFC matures particularly late (Sowell, Thompson et al. 2001; Toga, Thompson 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, Chung 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, Chung et al. 2010). Grey matter volume negatively correlated with the severity of self-reported CM in adolescents (Edmiston, Wang et al. 2011) and adults (Dannlowski, Stuhrmann 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, Rando et al. 2012). Also adolescents (Andersen, Tomada et al. 2008) or children with history of CM exhibited reduced PFC volumes (De Bellis, Keshavan 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, Chung et al. 2010) and mediate the development of stress-related disorders (Ansell, Rando 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, Park et al. 2001) and during tasks testing inhibition/cognitive control (Carrion, Garrett et al. 2008; Mueller, Maheu et al. 2010) in dorsolateral and inferior PFC. When testing memory of childhood abuse and effects of emotion on attention (Bremner, Narayan et al. 1999; Bremner, Vythilingam et al. 2003; Schmahl, Elzinga et al. 2003; Schmahl, Vermetten 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 in the PFC, inferior and middle

frontal regions (Croy, Schellong 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, Otti et al. 2010).

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

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, Teicher 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 (De Bellis, Keshavan et al. 1999; De Bellis, Keshavan et al. 2002; De Bellis and Keshavan 2003; Teicher, Dumont et al. 2004; Kitayama, Brummer et al. 2007; Andersen, Tomada et al. 2008; Jackowski, Douglas-Palumberi et al. 2008). But also the uncinate fasciculus connecting the OFC and the anterior temporal lobe (Eluvathingal, Chugani 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, Jeong 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, Muzik et al. 2009).

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

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

Event-related potential studies associated with CM: There are only few studies that have studied subjects with history of CM with event-related potentials (ERPs). Three of these studied examined alterations in ERPs evoked by processing of emotional faces (Pollak, Klorman et al. 2001; Cicchetti and Curtis 2005; Parker and Nelson 2005) one study used visual and auditory emotional cues *(Shackman, 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, Klorman et al. 2001; Shackman, 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 (Shackman, Shackman et al. 2007; Pollak 2008).

Establishing causality between abnormal brain measures and juvenile victimization is very 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, ODD, BPD, GAD 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 (Tomoda, Suzuki et al. 2009; Hart and Rubia 2012). Moreover, confounding factors that commonly are present in maltreating families such as low SES, low educational level, poor parenting skills, substance abuse or others (De Bellis, Keshavan 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 including only a low percentage of un-medicated cases without comorbidities (Cohen, Grieve et al. 2006; Tomoda, Suzuki et al. 2009; Hanson, Chung et al. 2010).
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, Keshavan et al. 2002) or volume of specific structures such as amygdala, hippocampus, striatum or anterior cingulate gyrus (Cohen, Grieve et al. 2006; Mehta, Golembo et al. 2009) and also between severity of experienced maltreatment with grey matter volume of PFC, amygdala, striatum, cerebellum and sensory association cortices (Edmiston, Wang et al. 2011). Furthermore there is some evidence for sensitive periods in which specific brain structures are especially vulnerable to maltreatment (Andersen, Tomada et al. 2008).

Effect moderation and mediation: Why do some children who are victimized develop the psychobiological outcome whilst others do not? What accounts for the influence of victimization on the psychobiological outcome?

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, Blumenthal 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, Baum et al. 1999; De Bellis and Keshavan 2003; Edmiston, Wang et al. 2011).
In the meta-analyses of Woon et al. the authors report that the higher prevalence of PTSD in women does not correspond to more pronounced hippocampal volume reductions in females. They 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, Tomada 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, Wang et al. 2011)).

PART 2 of the briefing paper: 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, Dorrepaal 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 functional 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, Dorrepaal 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 after therapy in subjects with PTSD related to war (Roy, Francis et al. 2010) or in cerebral blood flow during trauma script-driven imagery after therapy (Lindauer, Booij et al. 2008). Evidence for medication (SSRI) induced changes in brain measures come from two single photon emission computed tomography (SPECT) studies on PTSD (Carey, Warwick et al. 2004; Seedat, Warwick et al. 2004).

Is there potential for reversing the effects of juvenile violence victimization on the psychobiological or health outcome? What does the research about the effects of juvenile violence victimization on the psychobiological outcome suggest with regard to shaping the content of therapy?
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, Weems et al. 2007) in turn may have detrimental effects on the development of the brain and predispose subjects to psychiatric vulnerability (for a review please see (McCrory, De Brito 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, De Brito et al. 2010)) should be developed that may help the children to deal with stress.

What new data should be collected in the context of randomized clinical trials 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 purely behavioural measures.
From clinical trials with longitudinal follow-ups we may moreover also gain knowledge about the value of brain measures to predict the success of treatment and/or whether brain imaging measures may complement behavioural/diagnostic measures to improve the selection of the most effective therapy.

What does the research about the effects of juvenile violence victimization on the psychobiological outcome suggest with regard to the timing of interventions?
There has been one neuroimaging study suggesting specific vulnerability windows for certain brain structures (Andersen, Tomada et al. 2008). This hypothesis 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 (Sowell, Peterson et al. 2003; Gogtay, Giedd et al. 2004; Gogtay, Nugent et al. 2006).

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