

# Psychobiology of childhood maltreatment: effects of allostatic load?

## Psicobiologia dos maus-tratos na infância: efeitos de peso alostático?

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### Abstract

**Objective:** Facing an adverse physical or psychosocial situation, an individual is forced to adapt in order to survive. Allostasis is the term used to refer to adapting processes used to maintain the stability of an organism through active processes. When allostatic response is excessive or inefficient, the organism develops an allostatic load. The cascade of molecular and neurobiological effects associated with childhood abuse and neglect could be an example of allostatic response that could precipitate allostatic load in organism still vulnerable during its development. This article reviews the psychobiological consequences related to childhood abuse and neglect. **Method:** A selective review with a systematic procedure was performed to investigate studies showing explicit association between childhood maltreatment and psychobiological/neurobiological consequences. We searched electronic database MedLine-PubMed to identify English-language articles from 1990 to 2007. **Results:** From 115 articles we selected 55 studies from MedLine and 30 from their reference lists, in a total of 85 articles (JCR IF range: 1-31.4; median: 5.88). Only 29 studies showed direct and explicit association between them. **Conclusion:** Structural consequences of childhood maltreatment include disruptive development of corpus callosum, left neocortex, hippocampus, and amygdala; functional consequences include increased electrical irritability in limbic areas, frontal lobe dysfunctions and reduced functional activity of the cerebellar vermis; and neurohumoral consequences include the reprogramming activity of hypothalamo-pituitary-adrenal (HPA) axis and subsequently the stress response.

**Descriptors:** Child abuse; Stress, psychological; Neurobiology; Child development; Allostasis

### Resumo

**Objetivo:** Frente a uma situação psicossocial ou física adversa, o indivíduo é forçado a se adaptar de maneira que possa sobreviver. Alostase é o termo utilizado para descrever os processos adaptativos usados para manter a estabilidade de um organismo por meio de processos ativos. Quando a resposta alostática é excessiva ou ineficiente, o organismo desenvolve um peso alostático. A cascata de efeitos moleculares e neurobiológicos associados ao abuso e negligência na infância poderia ser um exemplo de respostas alostáticas e, dessa forma, poderia precipitar peso alostático em um organismo ainda vulnerável no seu desenvolvimento. Este artigo revisa as consequências psicobiológicas relacionadas com os maus-tratos na infância. **Método:** Uma revisão seletiva com base sistemática foi realizada na base de dados MedLine, procurando artigos em inglês que investigassem uma associação direta e explícita entre maus-tratos na infância e consequências psicobiológicas em humanos durante o período de 1990-2007. **Resultados:** De 115 artigos, foram selecionados 55 estudos do MedLine e 30 de suas listas de referências, num total de 85 artigos (JCR IF: 1-31,4; mediana: 5,88). Especificamente apenas 29 estudos investigaram uma associação direta e explícita entre eles. **Conclusão:** Em resumo, as consequências estruturais dos maus-tratos na infância incluem anormalidades no desenvolvimento do corpo caloso, neocórtex esquerdo, hipocampo e amígdala; as consequências funcionais incluem um aumento da irritabilidade nas áreas límbicas, disfunções do lobo frontal e redução da atividade funcional do vermis cerebelar; e as consequências neuro-humorais englobam a reprogramação do eixo HPA e subsequentemente a resposta ao estresse.

**Descritores:** Maus-tratos infantis; Estresse, psicológico; Neurobiologia; Desenvolvimento infantil; Alostase

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Financing: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

Conflict of interests: None

Submitted: September 28, 2007

Accepted: January 15, 2008

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## Introduction

Facing an adverse physical or psychosocial situation, an individual is forced to adapt in order to survive. Allostasis<sup>1</sup> is the term used to refer to adapting processes used to maintain the stability of an organism (its homeostasis) through active processes that, when active, imply a “price to be paid” by the organism. When allostatic response is excessive or inefficient, the organism develops an allostatic load.<sup>2</sup> If these adaptive mechanisms are repeatedly activated, the organism starts functioning in an allostatic state. It is then presumed that an “allostatic load state (overload)” would have a great cost to the organism.<sup>3</sup> Child abuse and neglect would be examples of adverse situations that could generate an “allostatic load state” in an organism still vulnerable during its development.

The human organism has mechanisms that are responsible for maintaining its balance. The main system is mediated by corticosteroids. Humans are programmed to respond physiologically to situations that threaten its homeostasis. Hans Selye first used the term “stress” in 1936 to designate this response. At that time, he proposed the existence of a “general adaptation syndrome” - an emergency adaptive process to a stressor (stimulus) designed to maintain the balance.<sup>4</sup> Thus, thinking that a child needs a non-hostile, protected, and favorable environment for good development, those who are exposed to contrary stimuli will invariably have to turn on this protective mechanism earlier and in a supported manner. How does this affect child’s development? Is the stress system mature enough to support the demand? Is the response effective? What can be observed from a neurobiological point of view?

According to researchers in this area, the answers to all these questions are related to a cascade of molecular and neurobiological effects associated with childhood abuse and neglect that could alter

the neurological and psychological development.<sup>5,6</sup> This cascade could be an example of allostatic response and could precipitate an allostatic load. This article reviews the psychobiological aspects related to childhood maltreatment.

## Method

A selective review with a systematic procedure was performed to investigate studies showing explicit association between childhood maltreatment and psychobiological/neurobiological consequences. We searched electronic database MedLine such as PubMed to identify English-language articles from 1990 to 2007. The following search terms were used: “child abuse”, “human development”, and “neurobiology”. In addition, each category was cross-referenced with the others using the MeSH (Medical Subjects Headings) method and also with key words such as “brain development”, “neuroendocrinology”, “genetic”, “early stress”, “psychobiology” and “neuroimaging”. The selected article’s references were also cross-referenced.

The exclusion criteria were: 1) studies with possible brain damage due to brain trauma, 2) studies which did not include biological variables (e.g.: just included clinical consequences) and 3) articles published in scientific journals with 2006 JCR impact factor (IF) lower than 1.

## Results

From 115 articles we selected 55 studies from PubMed and 30 from their reference lists, in a total of 85 articles (JCR IF range: 1-31.4; median: 5.88). Specifically only 29 studies showed direct and explicit association between childhood maltreatment and psychobiological/neurobiological consequences in humans (Table 1).

**Table 1 - Studies showing direct and explicit association between childhood maltreatment and psychobiological/neurobiological consequences in humans from 1990 to 2007**

Design	Author	Year	Sample	Childhood Maltreatment Assessment
Case-Control	De Bellis et al.	1994	N = 26	Clinical Interview / Case Records
Case-Control	Bremner et al.	1997	N = 35	ETI
Case-Control	Stein et al.	1997	N = 42	ETI
Case-Control	De Bellis et al.	1999	N = 105	Clinical Interview / Case Records
Case-Control	Shin et al.	1999	N = 16	Clinical Interview
Case-Control	De Bellis et al.	2000	N = 22	Clinical Interview
Case-Control	Cicchetti et al.	2001	N = 384	Case Records
Case-Control	Anderson et al.	2002	N = 40	Clinical Interview
Case-Control	Bremner et al.	2004	N = 21	ETI
Case-Control	Thomas et al.	2004	N = 182	Clinical Interview
Case-Control	Bremner et al.	2005	N = 19	ETI
Controlled Comparative	De Bellis et al.	1999	N = 52	Clinical Interview / Case Records
Controlled Comparative	Heim et al.	2001	N = 66	ETI
Controlled Comparative	Bremner et al.	2003	N = 33	ETI
Controlled Comparative	Teicher et al.	2004	N = 166	Clinical Interview
Controlled Comparative	Pederson et al.	2004	N = 51	CTQ
Controlled Comparative	De Bellis et al.	2006	N = 169	Clinical Interview
Cross-Sectional	Teicher et al.	1993	N = 253	Clinical Interview
Cross-Sectional	Ito et al.	1993	N = 115	Clinical Interview
Prospective	Putnam et al.	1997	N = 149	Case Records
Prospective	Heim et al.	2000	N = 49	ETI
Selective Review	Teicher et al.	1997	-	Miscellaneous
Selective Review	Glasser	2000	-	Miscellaneous
Selective Review	De Bellis	2002	-	Miscellaneous
Selective Review	Teicher et al.	2003	-	Miscellaneous
Selective Review	Bremner	2003	-	Miscellaneous
Selective Review	Penza et al.	2003	-	Miscellaneous
Selective Review	Nemeroff	2004	-	Miscellaneous
Selective Review	De Bellis	2005	-	Miscellaneous

Note: ETI = Early Trauma Interview; CTQ = Childhood Trauma Questionnaire

### Implications in postnatal brain development

The period from birth to adulthood is marked by a progressive physical, behavioral, and emotional development. Parallel to these stages, changes in the cerebral maturation can also be identified.<sup>7</sup> These cerebral changes follow a lifelong trajectory of brain development; however, each brain region has a unique course of ontogeny.<sup>8</sup> Basically, neurons are born, become differentiated, move to different regions, then arborize and branch in an attempt to establish appropriate connections. Regarding neurogenesis, it is known that the chemical substances responsible for cell survival regulation, differentiation, and maintenance of neuron function in the brain are the neurotrophins or growth factors: brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell-line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), and insulin-like growth factor (IGF-1).<sup>9</sup> Its synthesis and secretion are regulated by neuronal activity, which is directly related to environmental stimuli.<sup>10</sup> The expression of these factors happens in an extremely high level during the prenatal period. However, in the postnatal period, these factors are produced in a specific way for each part of the brain, where a sequential growth and an extraordinary proliferation and overproduction of axons, dendrites, and synapses can be observed.<sup>11</sup> Even if this process is genetically determined, some synaptic connections formed cease to exist due lack of use, and others, new ones, are formed due a necessity – that is, the environment is responsible for determining which neural connections are going to persist or emerge.<sup>12</sup> This phenomenon is known as neuronal plasticity and it is essential for the occurrence of neuronal changes associated with learning, drug exposure, or as a consequence of tissue damage.

After birth, approximately 50% of neurons are eliminated, in a process known as apoptosis leading to a rearrangement in the cerebral architecture in a way to enhance synaptic transmission efficiency.<sup>13</sup> However, as mentioned previously, it is important to point out that each cortical region has a specific time for synaptic production and elimination. For example, synapses density in the primary visual cortex has its peak at 6 months old, whereas in the prefrontal cortex, it happens at 2 years old. Besides, it is important to remember that synaptic overproduction and elimination processes occur later in cortical regions than in subcortical areas and that maturation of regions involved in cognitive processes takes place very late in ontogeny, ending only after adolescence.<sup>11</sup>

But how do adverse early events relate to these development processes? While discussing trajectories and mechanisms involved in brain development, it is important to make clear that childhood maltreatment can have an impact on this path, influenced by factors that are intrinsic and extrinsic to the individual. As for intrinsic factors, it is known that some neurotransmitters, neuroendocrine hormones and neurotrophic factors are crucial for the normal brain development.<sup>9</sup> Thus, any environmental event that could cause inappropriate stimulation would alter these intrinsic factors levels as expected for a certain period of brain development – especially during prepubescent period<sup>14</sup> – leading to an abnormal neurodevelopment.<sup>15</sup> As for mechanisms, stress effectors change drastically in the postnatal period. For example, rat fetuses have high levels of corticosterone in the blood responding to multiple stressors. Between 2 and 14 days old, these corticosterone levels drop according to a decrease in responsiveness of the hypothalamic-pituitary-adrenal axis (HPA) to some stressors, a period known as long-term stress hyperresponsiveness.<sup>16</sup> It is believed that these changes are vital to the programming of the HPA and possibly of the dopaminergic system when confronted with environmental stressor events.<sup>17</sup>

Abuse and/or neglect during childhood can influence brain development through extrinsic factors to the individual. The concept of “use-dependent” takes form and establishes that physiological

and molecular mechanisms involved in neurodevelopment obey a simple rule: developing what is necessary for survival and disposing of what is unnecessary.<sup>18</sup> There are two ways in which environment can have different effects in adult topography at the end of normal brain development: experience-expectant development and experience-dependent development.<sup>19</sup> Experience-expectant development involves the processes that will only develop in the presence of a particular experience during a critical period. A classic example is the need for visual stimuli to develop the visual cortex. In a similar way, if early stimuli such as touching, talking, and affection are absent, the synaptic connections that are responsible for these stimuli will be interpreted as useless and will be eliminated. Experience-dependent development refers not to pruning but to producing new synapses caused by an environmental demand. For example: exposing a child to a particular affective interaction can generate asymmetries in the prefrontal structures, which can lead to later behavioral and emotional consequences.<sup>20</sup> Assuming this perspective, it is easy to understand gene-environment (GXE) studies associating childhood maltreatment with gene polymorphisms (i.e. COMT Val158Met and BDNF Val66Met) in the prediction of psychiatric and neuropsychological disorders.<sup>21,22</sup> Particularly a large sample prospective study from birth to adulthood showed that maltreated children with a genotype conferring high levels of monoamine oxidase A (MAOA) expression were less likely to develop antisocial problems when adults.<sup>23</sup> These findings were replicated and confirmed by meta-analyses.<sup>24</sup>

The lasting impact of an early-life stressful event depends on the maturing stage of exposition as much as the direction the disturbances in synaptic environment can inflict in a regular developing trajectory. An immature organism tries to adapt by permanently embodying environmental information to its structure and function. On the other hand, a mature organism establishes ways of compensating to settle in to environmental changes.<sup>9</sup>

In this sense, child abuse and neglect can be perceived as agents for neurodevelopmental disruption and, depending on when it occurs, can cause serious neurological “scars” in some structures, which could make some individuals vulnerable to certain types of psychopathology – especially posttraumatic stress disorder (PTSD), depression and substance abuse – and to neuropsychological alterations – impairment in memory and attention tests, and the abilities of learning.<sup>25,26</sup>

### Childhood maltreatment and developmental traumatology model

Developmental traumatology<sup>27</sup> consists of systematic investigation of psychological and psychobiological impact on adverse events to child development. It is a relatively new field of study that gathers other research disciplines as developmental psychopathology, developmental neuroscience, and research on stress and trauma. The model proposed is a network of complex interactions between individual genetic constitutions, unique environmental experiences, critical periods of developmental vulnerability, and resilience in facing early life stress episodes. It tries to gain understanding on how these factors can influence changes in stress biological systems, brain development, and its consequences in the last instance in psychosocial and neuropsychological terms.

### Stress biological system deregulation

Multiple neurotransmitters, neuropeptides, and hormonal systems are related to psychological stress; they present important function interactions and mediate neural mechanisms and circuits that are relevant in the regulation of reward, conditioned fear, and social behavior.<sup>28</sup>

Cortisol has an important regulating effect on the hippocampus, amygdale, and prefrontal cortex. It has a two-stage effect on hippocampal arousal, cognitive functions, and memory.<sup>29</sup> Furthermore, it can increase amygdale activity and the concentration of corticotrophin release hormone (CRH) mRNA in the amygdale's central core, enhance the effects of CRH, and facilitate encoding processes of emotional memories.<sup>28</sup> CRH is one of the most important mediators in response to stress, coordinating adaptive behavior and psychological changes that occur during stress and increasing adrenocorticotrophic hormone (ACTH) and, as a consequence, cortisol levels. In addition to that, CRH acts as a neural-transmitter and its neurons have projections to the prefrontal cortex, cingulate gyrus, central cores of the amygdale, *nucleus accumbens*, *locus ceruleus*, and dorsal and medial raphe.<sup>30</sup> Its release is controlled by plasmatic cortisol levels through negative feedback mechanisms and also by direct hippocampal action.<sup>31</sup>

Chronic elevation of glucocorticoid production that occurs under chronically stressful conditions is particularly harmful and may cause depletory effects in the body. One of the most relevant consequences to brain development occurring from this supported increase of cortisol during childhood is the harmful impact that it promotes on neurons through glutamate and calcium regulation, which facilitates cellular death, especially in areas with higher concentration of glucocorticoid receptors – hippocampus, prefrontal lobe, amygdale, and cerebellar vermis (see next section *Adverse Brain Development*).

Chronically elevated levels of cortisol seem to exist in children who are currently living in adverse situations. Studies performed with maltreated children or who are diagnosed with PTSD have shown hypercortisolemia.<sup>6,32</sup> An increase in plasmatic cortisol was observed in sexually abused girls recruited 6 months after the events, when compared with a control group, suggesting a morning hypersecretion of cortisol in these girls.<sup>33</sup> In addition, maltreated children exhibited substantial elevations in morning cortisol levels, especially for multiple-abuse subjects, but a subgroup of physically abused children showed evidence of a trend toward lower morning cortisol relative to children with no maltreatment with a significantly smaller decrease in cortisol levels from morning to afternoon, according to the expected circadian rhythm.<sup>34</sup> Along the same lines, De Bellis et al.<sup>27</sup> have verified that children who were maltreated had higher excretion of free urinary cortisol in a 24-hour period. Finally, a study comparing boys and girls who grew up in socially and economically less favored homes with another group who grew up in more resourceful environments has shown that the first group presented higher levels of salivary cortisol.<sup>35</sup>

Many research studies have examined the neurobiological effects of early stress.<sup>36</sup> In an animal model of childhood neglect, rat offspring separated from their mothers for 3 hours a day, from their second to tenth day of life, showed an increase in hypothalamic liberation of CRH in 24 hours. This effect, however, was not observed in older rats (18 days old).<sup>37</sup> When the offspring was separated from the mothers for 6 hours a day, during its first 3 weeks of life, they presented a basal increase in ACTH concentration, an effect that can also be verified after administering small electrical shocks in the rats'

paws. Research also identified a decrease in CRH connection in the anterior pituitary.<sup>38</sup> Studies using monkeys raised in experimental stressful conditions have shown higher concentrations of CRH and decreased concentrations of cortisol in the cerebrospinal fluid when they became adults.<sup>39</sup> In addition, girls who were victims of sexual abuse presented a lower response of ACTH after CRH administration, which is in conformity with a basal hypersecretion of CRH in these children.<sup>40</sup> This phenomenon can also be observed in adult women with PTSD who were sexually abused during childhood.<sup>41</sup> The authors suggest that childhood abuse would result in high levels of CRH, with decrease of pituitary sensitivity to CRH stimulation.

Heim et al.<sup>42</sup> have performed a prospective study to evaluate neuroendocrine aspects of women with childhood abuse and depression in full factor design. As experimental manipulation, the authors exposed all groups to Trier Social Stress Test (TSST). This test elevated the plasmatic concentration of cortisol in all groups, but the group of women with childhood abuse and depression presented a significantly higher elevation of cortisol. Furthermore, regardless of depression diagnosis, women with childhood abuse history presented a much higher response of ACTH after the test. Another important finding was women with both childhood abuse and depression presented higher heart rate levels during the test. In another study the same protocol was performed in women admitted to a hospital and evaluated through venous catheter of basal concentration of ACTH and cortisol and after administration of CRH and ACTH. In the stimulation test with CRH, the group with childhood abuse history and no diagnosis for depression presented high concentration of ACTH up to 30 minutes after the test. On the other hand, both groups composed of women with major depression diagnosis presented ACTH concentrations that were lower than those in the control group. Regarding cortisol concentration rates, both groups with childhood abuse history had basal levels and after-CRH stimulation levels that were lower than those in the control group up to 120 minutes after the test. This effect was more visible in the group with major depression diagnosis, a phenomenon that was also observed after the ACTH stimulation test.<sup>43</sup>

When analyzing both works by Heim et al., one is led to conclude that early stress is related to a higher sensitivity to stress in the HPA axis in adults. Initially, early stress would lead the anterior pituitary to be more sensitive to CRH, possibly reflecting a biological vulnerability to stress effects. This vulnerability would be reflected by a high CRH secretion. First, the HPA axis would be hyperfunctioning, which could explain the hypercortisolemia observed in children under stress. These high cortisol concentrations could lead to an *upregulation* and hypersensitization of glucocorticoid receptors, as well as to an abnormal neurological development (see next section *Adverse Brain Development*). Chronic increase of CRH would cause *downregulation* of pituitary CRH regulators and, with time, this could cause a relative adrenal insufficiency ("functional adrenalectomy"), which ultimately would explain the decrease in cortisol levels circulating in women with childhood abuse history.

During stress, standard cortisol increase is followed by immediate release of norepinephrine (NE), and after that, a transitory decrease in its plasmatic concentration. When the physiological increase in glucocorticoids is stopped by adrenalectomy, acute stress results in even higher levels of NE.<sup>44</sup> Findings of high concentration of basal urinary catecholamine in 24 hours show an increase in the basal functioning of the catecholaminergic system in sexually abused girls, 58% of which had important major depression and suicidal tendencies history.<sup>40</sup> High levels of urinary NE in 24 hours were

found in boys who were severely depressed and with parental neglect history.<sup>45</sup> In addition to that is the fact that maltreated children medicated for PTSD dispose of higher quantities of NE and dopamine (DA) than controls.<sup>27</sup> The few studies that exist on this subject suggest that children with abuse or neglect history are more susceptible to depression and anxiety (particularly PTSD symptoms)<sup>46,47</sup> and present an increase in the catecholaminergic activity.<sup>6</sup>

Moreover, when 61 children and adolescents with PTSD and in maltreatment situation were compared to 121 healthy controls in terms of pituitary volume, it has been observed that the gland was significantly higher in individuals who were maltreated, had PTSD diagnosis, and were in pubescent or post-pubescent age.<sup>48</sup> Additionally, dopaminergic projections of the limbic system to the prefrontal cortex seem to be particularly sensitive to stress. The increase of prefrontal dopaminergic function in response to stress can reflect the activation of cognitive or attentive processes necessary to deal with the stressors. However, chronic stress can result in an exaggerated concentration of dopamine in the prefrontal cortex, causing inattention, hypervigilance, difficulties in learning new contents, psychotic symptoms, and inhibition difficulties.<sup>6</sup>

### Adverse brain development

A series of functional and structural neural-biological consequences associated with early stress experiences have been identified.<sup>5</sup> Pre-clinical studies indicate that brain regions particularly vulnerable to early stress have some of the following characteristics: 1) later postnatal development, 2) high density of glucocorticoid receptors, and 3) some degree of postnatal neurogenesis.<sup>3</sup>

### 1. Hippocampus

Early stress has been related to profound structural changes in the hippocampus.<sup>49</sup> This region seems to be particularly vulnerable to the effects of stress. In addition, the hippocampus presents a late development, a high concentration of glucocorticoid receptors, and high neuronal plasticity.<sup>50</sup> Early exposition to stress or corticosteroids can cause a hippocampal remodeling (or atrophy).<sup>51</sup> Considering the hypercortisolemia state that would be observed in children exposed to abuse and neglect, it is important to point out that glucocorticoids can produce depletory effects to the hippocampus, through dendritic atrophy processes, inhibition of neurogenesis in adults, and neurotoxic effects.<sup>50</sup>

The hippocampus is a neurological structure that maintains a neurogenic activity during its whole existence. However, corticoids or stress can inhibit this neuronal growth, an effect that could be related to chronic activation of N-methyl-D-aspartate (NMDA) receptors by glutamate,<sup>52</sup> since they facilitate the activation of NMDA receptors. Prolonged stress can decrease the extension of apical dendrites of the CA3 hippocampal neurons in rodents and nonhuman primates, an effect that can start after a few weeks of overexposure to glucocorticoids (findings that are correlated to losses in explicit memory).<sup>6</sup> These atrophic effects would be mediated by an excess of arousal amino acids, such as glutamate, since glucocorticoids increase these substances' concentration in hippocampal synapses. In parallel, glucocorticoids can influence the efficiency of neurotrophins, particularly BDNF.<sup>53</sup>

The neurotoxic hippocampal effects caused by glucocorticoids can be observed in studies with rodents where prolonged exposure to this hormone caused the death of CA3 neurons, decreasing plasticity in the hippocampus.<sup>50</sup> A hypothesis for this neurotoxic effect would

be the influence of this particular hormone in the calcium channels. Glucocorticoids increase the activity in calcium channels, which can contribute to the production of free radicals and other processes that can damage neurons.<sup>54</sup> It could be assumed that individuals with HPA deregulation would be more susceptible to cortisol neurotoxic effects.<sup>43</sup> Thus, transitory overexposure to glucocorticoids could alter hippocampal morphology.

There is a study in which rat offspring were separated from the mother for 4 hours a day, from their 2<sup>nd</sup> to their 20<sup>th</sup> day of life. This group was compared with a control group for immunoreactivity to synaptophysin, a protein associated with synapses, quantified in CA1 and CA3 hippocampus, amygdale, and prefrontal cortex through optical densitometry during many stages of development (25<sup>th</sup>-100<sup>th</sup> days). The authors have observed two main effects: 1) early maternal separation reduced, in a general sense, the synaptophysin levels; 2) but it was only after 60 days (beginning of adult life in humans) that the early separated group presented significant differences regarding this protein until the end of the trial when compared with the control group. Thus, the authors suggest that early isolation from the mother seems to have a lasting effect on hippocampal development and this effect was time-dependent, emerging as a consequence of a prolonged synaptic overproduction stage.<sup>49</sup> Therefore, stress-induced hippocampal alterations would only be apparent in early adult life. This may explain why magnetic resonance imaging (MRI) in patients with PTSD only showed hippocampal decrease in adults but not in children.<sup>55</sup>

A structural and functional neuroimaging study was performed with three groups of women: 1) women who reported a history of sexual abuse as children and presented PTSD, 2) women who reported a history of sexual abuse as children but no PTSD, and 3) a control group with women with no history of childhood sexual abuse and no PTSD.<sup>56</sup> All participants were submitted to MRI and positron emission tomography (PET). The authors have verified that the volume in the left hippocampus in the abuse/PTSD group was 15% lower when compared with the abuse/no PTSD group and 17% lower than the control group. In the same sense, the volume of the left hippocampus in the abuse/PTSD group was 16% lower when compared with the abuse/no PTSD group and 22% lower than the control group. There were no differences between abuse/no PTSD group and the control group. Women with PTSD showed a loss in the activation of the left hippocampus, identified by PET, during a verbal memory test compared with the abuse/no PTSD group, even after correction for hippocampal atrophy. It was also noted by the authors that dissociative symptoms are positively correlated to the reduction of the left hippocampus volume, even if the PTSD symptoms are positively correlated to the reduction of the right hippocampus. However, when another study was performed with women with child sexual abuse history and diagnosed with PTSD but who were 20 years younger than the average age of women in the previous studies, hippocampal reduction was not observed.<sup>57</sup> In addition, other authors have examined the hippocampal volume of 18 young adults with child sexual abuse history and compared these with those in a healthy control group.<sup>5</sup> They have not found any differences between the two groups. This finding seems to support the idea that volumetric hippocampal reduction associated with childhood maltreatment is likely to be detected only in older adults. Corroborating these findings is a study performed with children who were maltreated and diagnosed with PTSD and healthy controls – i.e., there were no differences between the groups with respect to hippocampal measures obtained through MRI.<sup>35</sup> Other

authors also failed to identify hippocampus volume reduction in maltreated children.<sup>58</sup>

## 2. Amygdala

The amygdala core is one of the areas of the brain that is most sensitive to the emergence of *kindling*.<sup>59</sup> *Kindling* is a process in which repetitive and intermittent neuronal stimulation produces even more alterations in neuronal arousal, eventually leading to spontaneous electric discharges.<sup>60</sup> It is proposed that adults with childhood abuse history would have a "limbic irritability," that is, from an abnormal development of the amygdala or the hippocampus associated with disturbances of the benzodiazepine receptors, an electric activity similar to a convulsive pattern would begin when stress occurred, even though no clinical signs of said convulsion are shown.<sup>61</sup> Children admitted to a psychiatric unit and who have abuse history presented electroencephalographic abnormalities in the front-temporal region, predominantly in the left hemisphere.<sup>62</sup>

Image studies<sup>35,63,64</sup> did not reveal any volumetric difference in the amygdala of individuals with child abuse history compared with control groups. However, a study in a fear acquisition and extinction paradigm has compared women with child abuse history and PTSD diagnosis to healthy control in terms of psychophysiologic measures and PET showed that the clinical group presented an increase in the left amygdala activation with the acquisition of fear and a decrease in the anterior cingulate cortex function during extinction.<sup>65</sup>

## 3. Cerebral cortex

The neocortex slowly develops through cyclical reorganizing processes.<sup>66</sup> The delay of corpus callosum myelinization allows the hemispheres to develop relatively independent from one another. Of all cortical regions, the prefrontal lobe has the most delayed ontogeny and because of that, most projections for the prefrontal lobe are myelinated between adolescence and the third decade of life. The prefrontal lobe also has a high density of glucocorticoid receptors and dopaminergic projections that are specifically stress-activated.<sup>67</sup> Prefrontal functions are related to inhibitory processes in most monoaminergic projections for subcortical regions, action planning, decision making, working memory, and attention. However, a major stress that increases catecholamine activation (especially NE and DA) can disable this frontal inhibition of the limbic system.<sup>6</sup> This disablement of frontal inhibition of amygdala can be observed in adults with maltreatment history.<sup>68</sup>

It has been postulated that early stress could activate prefrontal cortex development, alternating its development and causing precocious maturation with a negative impact on its final capacity.<sup>5</sup> In a controlled study performed with children admitted to a psychiatric unit with documented abuse history, it has been observed that the electroencephalographic coherence indicates that the right hemisphere was significantly more developed than the left one. However, in the control group the dominant left hemisphere was more developed. This finding was associated with an important delay in the development of the left hemisphere in the group of abused children.<sup>69</sup> Another study compared children with PTSD and maltreatment history and a control group as for N-acetyl aspartate (NAA) and creatinine concentration in the anterior cingulate cortex as a neuronal viability and density index.<sup>70</sup> The authors have observed a significant reduction in the NAA/creatinine ratios in the maltreated groups, suggesting neuronal loss and a dysfunction in this region. Carrion et al.<sup>58</sup> have identified that 24 abused children diagnosed with PTSD had an asymmetry in the frontal lobe and lower total cerebral volume.

In conclusion, early stress seems to be associated with a general template of cortical failure in the suppression of exaggerated reactions to stress,<sup>41,71</sup> as well as altering the cortical development and distribution of monoaminergic fibers that affect the degree of hemispheric laterality.<sup>5</sup>

## 4. Cerebellar structures

The cerebellar vermis is the brain structure that presents a more accentuated postnatal growth period.<sup>5</sup> Thus, like the hippocampus, it has a high density of glucocorticoid receptors during development, and it could be particularly vulnerable to the effects of stress hormones.<sup>72</sup> Among its functions are multisensory integration, control of epilepsy, and limbic activation.

When the association between the activity in the cerebellar vermis measured by T2 relaxometry and symptoms of limbic irritability in young adults with repetitive childhood sexual abused history was studied and compared and compared it with healthy controls, the findings indicated an important decrease in the relative perfusion of the vermis in the abused subjects demonstrating a functional damage in the cerebellar vermis activity.<sup>73</sup>

In addition, cerebellar volumes positively correlated with age of onset of the trauma that led to PTSD and negatively correlated with the duration of the trauma that led to PTSD in maltreated children and adolescents with DSM-IV PTSD.<sup>74</sup>

## 5. Corpus callosum and hemispherical integration

Corpus callosum comprehends myelinated commissural fibers of interhemispheric association. It is the thickest band of fibers in the brain and has, as main function, anatomically and functionally connecting the two brain hemispheres, allowing them to exchange information.<sup>75</sup> Some studies have shown that the size of the corpus callosum can be affected by early stressful experiences. A group of *Rhesus* monkey's offspring was separated from their mother when they were 2 years old, while the other group was not separated. Primates that were separated showed a reduction in corpus callosum size, and this decrease occurred in parallel to a decrease in the volume of the white substance in the prefrontal and parietal cortexes, as well as cognitive losses. Thus, the authors have concluded that primates that suffered physical and emotional neglect during early years present deficient prefrontal functions and normal myelinization as expected for their age.<sup>76</sup>

The first indication that childhood trauma can affect the development of the corpus callosum in humans was given by a study that has found a significant reduction in the medial portions of the corpus callosum in abused children.<sup>69</sup> These findings were replicated by another study showing that reduction in corpus callosum was the most significant anatomic finding in children with childhood abuse history and PTSD diagnosis.<sup>35</sup> Subsequently, another study compared the volume of the corpus callosum in neglected children and healthy controls. The total corpus callosum area in neglected participants was 17% lower than that in the control group and 11% lower than psychiatric patients without maltreatment history.<sup>26</sup>

Reduction in the size of corpus callosum has been associated with a decrease in communication between the brain hemispheres.<sup>75</sup> Adults with a history of childhood maltreatment showed a dramatic difference in hemispherical activation when remembering neutral and disturbing memories, evaluated through evoked potentials. While the control group showed bi-hemispherical activation during neutral and disturbing remembering tasks, the group with abuse history showed a lateralization in the hemispherical processing, dramatically juggling this activation between the two tasks.<sup>77</sup>

## Discussion

Not all children victimized by abuse report further problems,<sup>23</sup> and there is no “abused child syndrome”.<sup>6</sup> If there are sequels, it is shown with considerable interpersonal differences.<sup>11</sup> However, some common points can be identified.

First, it is important to remember that usually among elder the reduction of the hippocampus is correlated with decrease in the consolidation of long-term explicit memory and to the increase of cortisol levels.<sup>78,79</sup> To explain how neuronal damage is done, one of the suggested hypotheses would be that high levels of glucocorticoids (cortisol) would be released during an acute stress situation (abuse) and resulting in hippocampal damage.<sup>50</sup> Exposure to high levels of cortisol would lead to a decrease of dendritic arborization and neuronal loss, which could explain this neuroanatomic reduction in the hippocampus.<sup>56</sup> Thus, stress would be associated with an increased activity in HPA axis. Chronic activation of this axis would reprogram it, leading the adult to present functional adrenal insufficiency.<sup>80</sup>

Early stress could start a chain reaction of neurohormonal and neurotransmitter effects that would damage brain structure and functions. High levels of cortisol could precipitate hippocampal neurotoxic lesions and excessive stress would act as a toxic agent interfering in the usual neurodevelopment process. Neuropsychiatric alterations associated with early stressful events would result from this “aggression” to the brain tissue.

Maybe neurodevelopmental alteration represents an alternative and adaptive way for the organism to go through stressors. A child born in a stressful environment will have to modify the psychological and neurological structure and function to adapt to a toxic childhood experiences. In early development stages, these rearrangements would be necessary, but, in an attempt to be used out of context, could become non adaptive, useless, and potentially damaging (or “very expensive” from allostatic load point of view) for the individual when placed in a more favorable environment.

Thus the concept of allostatic load is once again used and, currently, seems to be the most appropriate model for understanding neurobiological and neuropsychological findings associated with childhood abuse and neglect.

Summarily, the present review found an incipient literature showing direct and explicit association between childhood maltreatment and psychobiological consequences in humans. This study is a selective review based in systematic review procedures. The majority of studies are case-control designs or selective reviews connecting childhood abuse to some neuroendocrine or neural abnormalities. Despite the importance of assessing childhood maltreatments, there is considerable controversy surrounding the consistency and accuracy of reports of incidents occurring during childhood.<sup>81,82</sup> Most studies used instruments to assess sexual and physical abuse but do not include other types of maltreatment such emotional or neglect forms. A number of instruments are designed to measure a single type of trauma, usually sexual abuse, but most of these do not report psychometric properties.<sup>83</sup> In addition, childhood maltreatment assessment vary between studies, from self-reports to case records, which could impact their results. On the other hand, some authors suggest that there are no significant differences between clinical interview and self-report measures of child maltreatment.<sup>84</sup> Most currently available assessments of childhood trauma are also limited by the fact that they do not provide specific information about the event (for example age of occurrence) that may be critical in understanding the magnitude and significance of the stressor and that validity and reliability of some of these assessments have not yet been generated.<sup>82</sup>

Taken the above mentioned limitations, the present review should be considered in the light of such key findings:

1) The major structural consequences of childhood maltreatment include disruptive development of corpus callosum, left neocortex, hippocampus, and amygdala.

2) The major functional consequences of childhood maltreatment include increased electrical irritability in limbic areas, frontal lobe dysfunctions and reduced functional activity of the cerebellar vermis.

3) The major neurohumoral consequence is the reprogramming activity of HPA and subsequently the stress response.

An important goal for field research in childhood maltreatment is to reveal the complex interaction between molecular biology, neuroscience, cognitive psychology, and neurophysiology. Understanding the psychobiology of maltreatment through allostasis framework could be helpful to future interventions based on evidence, for both treatment and prevention. For example, given that maltreating parents are likely to have serious but treatable comorbid mental disorders, parent’s treatment, psychoeducation about family relations, problem-solving, maternal care, including breastfeeding are some extremely important areas for future prevention and intervention research.<sup>85</sup>

More than that, there is a need for prospective studies that aim to search “points of vulnerability or windows of opportunity”<sup>9</sup> during brain development of children victimized by abuse or neglect. A new model of resilience is coming up.

## Acknowledgments

The authors would like to thank DBRP – Developmental Biopsychiatry Research Program, McLean Hospital and Psychiatry Department of Harvard Medical School for their positive role in the international cooperation and exchange. Also, the authors would like to thank CAPES Foundation - Brazilian Ministry of Education for financial support.

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