PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
FACULDADE DE PSICOLOGIA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSICOLOGIA
DOUTORADO EM PSICOLOGIA

**TRAUMATOLOGIA DESENVOLVIMENTAL: O IMPACTO DA NEGLIGÊNCIA
NA INFÂNCIA NA MEMÓRIA DE ADULTOS**

Tese apresentada ao Programa de Pós-Graduação em Psicologia da Pontifícia Universidade Católica do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Psicologia.

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Porto Alegre, dezembro de 2007.

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LISTA DE SIGLAS

ACTH   Hormônio Adrenocorticotrófico

ANOVA   Análise de Variância

BDNF   Fator Neurotrófico Derivado do Cérebro

CTQ   Questionário Sobre Traumas Precoces

CEN   Negligência Emocional na Infância

CPN   Negligência Física na Infância

CRH   Hormônio Corticotrófico

DRM   Procedimento de Palavras Associadas

DVR   Recordação Verbal Posterior

EN+   Depressão com Negligência Emocional na Infância

EN-   Depressão sem Negligência Emocional na Infância

FFT   Teoria do Traço Difuso

HPA   Eixo Hipotálamo-Hipófese-Adrenal

IVR   Recordação Verbal Imediata

MDD   Depressão Maior

PUCRS   Pontifícia Universidade Católica do Rio Grande do Sul

SUS   Sistema Único de Saúde

TEPT   Transtorno de Estresse Pós-Traumático

TSST   Teste de Estresse Social de Trier

%R   Percentual de Retenção de Memória Verbal

RESUMO

TRAUMATOLOGIA DESENVOLVIMENTAL: O IMPACTO DA NEGLIGÊNCIA NA INFÂNCIA NA MEMÓRIA DE ADULTOS

INTRODUÇÃO: A traumatologia desenvolvimental é um termo proposto por De Bellis, (2001) e consiste na investigação sistemática do impacto psiquiátrico e psicobiológico de eventos adversos ao desenvolvimento infantil. A maioria dos estudos com animais utilizam modelos de privação materna para investigar o efeito do estresse precoce na resposta comportamental e neurobiológica de adultos, mas surpreendentemente o impacto psicobiológico das formas de negligência infantil são muito poucos investigados em humanos. OBJETIVO: Estudar o efeito da história de negligência na infância em relação à performance em testes de memória de mulheres com Depressão Maior (MDD), além de investigar associações com variáveis neurobiológicas e psicossociais. MÉTODO: A presente tese é composta por três estudos. O primeiro estudo, de cunho teórico, revisa os últimos 18 anos da literatura científica no que tange a artigos sobre psicobiologia dos maus-tratos infantis, publicados em revistas com fator de impacto maior que 1. O segundo estudo propõe um modelo de regressão múltipla, onde se investigou o papel da negligência física na infância (CPN) e do nível plasmático do Fator Neurotrófico Derivado do Cérebro (BDNF) no desempenho da memória verbal de mulheres adultas com MDD. Por fim, o terceiro estudo consistiu em um experimento onde mulheres com MDD e que relatavam ter sofrido negligência emocional na infância (CEN) foram comparadas com mulheres com MDD sem CEN e controles saudáveis em relação ao desempenho em um teste de reconhecimento para palavras semanticamente associadas. RESULTADOS: No primeiro estudo "Psicobiologia dos Maus-tratos na Infância: Efeito de Peso Alostático?" foram selecionados 75 artigos (Fator de Impacto JCR: 1 - 31.4, mediana: 5.88) para essa revisão. Os resultados do segundo estudo "Negligência Física na Infância, Baixo Fator Neurotrófico Derivado do Cérebro (BDNF) no Plasma e Prejuízo da Memória Verbal em Adultos" sugerem a existência de correlações significativas entre recordação verbal imediata e severidade da depressão, sintomas do transtorno de estresse pós-traumático, negligência física na infância (CPN) e BDNF plasmático. A recordação verbal posterior mostrou-se associada às mesmas variáveis, além de estar associada com a quantidade de anos de instrução. Ainda, o grupo com depressão maior e histórico de negligência física na infância (MDD + CPN) mostrou maior prejuízo na recordação imediata e posterior quando comparado aos demais grupos, mas o mesmo padrão não é observado para o percentual de retenção da memória. Foi observado que a severidade da CPN e o baixo BDNF plasmático predizem o prejuízo na recordação verbal imediata. Além disso, a CPN foi relacionada com o grau de comprometimento da memória verbal imediata e posterior, corroborando diversos estudos que investigaram essa relação com exposição na infância ao abuso sexual. O terceiro estudo "O Comprometimento da Memória de Essência em Mulheres com Negligência Emocional na Infância Reduz o Falso Reconhecimento" indica que o grupo com negligência emocional (EN+) teve menores porcentagens de reconhecimento falso quando comparado com os grupos sem negligência emocional (EN-) e o controle. No que diz respeito ao reconhecimento correto de palavras que foram mostradas anteriormente (taxas de acerto), os grupos não mostraram diferenças significativas entre si. Métodos de detecção de sinal apontam para diferenças significativas entre grupos na sensibilidade para memória literal. Condizente com as análises iniciais, o grupo EN+ foi menos afetado pelo

efeito semântico, indicando um comprometimento da capacidade de associação semântica, refletido pelo prejuízo na memória de essência. CONCLUSÃO: A presente tese traz resultados até então não encontrados na literatura. Os estudos sugerem um efeito das formas de negligência na infância sobre a memória que poderia ser modulado pela ação de neurotrofinas. Considerando que o modelo da traumatologia desenvolvimental consiste em uma rede de complexas interações entre genética, experiências ambientais, períodos críticos de vulnerabilidade desenvolvimental e características de resiliência, na tentativa de entender como tais fatores poderiam influenciar mudanças nos sistemas biológicos de estresse e no desenvolvimento cerebral, ressalta-se a necessidade de replicação dos resultados para conclusões mais definitivas.

Palavras-chave: memória, maus-tratos na infância, negligência infantil, BDNF, depressão, estresse precoce, psicobiologia

ABSTRACT

DEVELOPMENTAL TRAUMATOLOGY: THE IMPACT OF CHILDHOOD NEGLECT ON MEMORY OF ADULTS

INTRODUCTION: Developmental traumatology is a model of De Bellis (2001), it consists of systematic investigation of psychological and psychobiological impact on adverse events to child development. The majority of animal studies use maternal deprivation as a method to investigate the effect of early stress on behavioral and neurobiological responses of adults, but interesting the psychobiological impact of neglect forms of maltreatment are very few studied in humans. OBJECTIVE: The main goal is to investigate the effects of history of childhood neglect on memory performance of females with Major Depressive Disorder (MDD), In addition, this work tries to search for associations between memory performance and neurobiological and psychosocial variables. METHOD: The current thesis includes three studies. In the first study, the last 18 years literature on neurobiology and psychobiology of child maltreatment was carefully reviewed in journals with impact factor higher than 1. The second study proposes a multiple regression model where the impact of childhood physical neglect (CPN) and the plasmatic level of Brain Derived Neurotrophic Factor (BDNF) on verbal memory performance of adult females with MDD were investigated. The third study consists in a experiment where females with MDD who reported childhood emotional neglect (EN+) were compared to females with MDD but without EN (EN-) and healthy controls on recognition test performance for semantic related words. RESULTS: The first study "Psychobiology of Childhood Maltreatment: Effects of Allostatic Load?" selected 75 articles (JCR IF range: 1 - 31.4, median: 5.88) to the review. The results of second study "Low Plasma Brain Derived Neurotrophic Factor and Childhood Physical Neglect Are Associated with Memory Impairment in Major Depression" suggest significant correlations between immediate verbal recall and severity of depression, posttraumatic stress disorder symptoms, CPN and plasma BDNF. The delayed verbal recall showed associations with the same variables plus years of education. In addition, the MDD+CPN group showed impairment on immediate and delayed recall when compared to other groups, but the same pattern was not observed to memory retention rate. It was observed that the severity of CPN and low plasma BDNF predicted immediate verbal recall impairment and CPN was related with the both immediate and delayed recall, corroborating with previous childhood sexual abuse studies. The third study "Gist Memory Impairment in Depressed Women with Childhood Emotional Neglect Reduce False Recognition" indicates that EN+ group has lower rates of false recognition when compared to EN- and control groups. In regard to true recognition of previous studied words (correct targets recognition) there aren't significant differences between groups. Signal detection methods show significant differences between groups in regard sensitivity to verbatim memory. Corroborating with the beginning analyses, EN+ group is less affected by semantic effect, indicating a semantic association deficit, reflected by gist memory impairment. CONCLUSION: This thesis coming up with brand new results until now not published in literature. All studies suggest that childhood neglect may have an important role on memory systems and this could be modulated thorough neurotrophins actions. Considering that developmental traumatology model proposed a network of complex interactions between individual genetic constitutions, unique environmental experiences, critical periods of developmental vulnerability, and resilience to the

understanding on how these factors can influence changes in stress biological systems and brain development, it is highlighted the importance of such results replication to a more definitive conclusions.

Keywords: memory, childhood abuse, childhood neglect, BDNF, depression, early life stress, psychobiology

INTRODUÇÃO

Em relação a estudos de incidência e prevalência de maus-tratos e violência doméstica na infância, nosso país carece de pesquisas na área. O Fundo das Nações Unidas para a Infância estima que diariamente 18 mil crianças e adolescentes sejam vítimas de violência no Brasil (ISPCAN, 2006). Além disso, um dos poucos levantamentos em serviços de atenção à criança vítima de violência mostrou, com base nos casos registrados desde o ano de 1996 até 2003, que 29,1% de meninos e meninas tinham sido vítimas de abuso físico, 28,9 %, de violência sexual, 25,7% tinham sofrido negligência e 16,3%, abuso psicológico (Ferreira, 2002).

Essa tese consiste na continuidade do trabalho iniciado na dissertação de mestrado do presente autor (Grassi-Oliveira, 2004). O início desse trabalho teve por objetivo adaptar um instrumento retrospectivo de investigação de abuso e negligência na infância em adultos (Grassi-Oliveira, Stein, & Pezzi, 2006) e realizar um estudo sobre a associação entre maus-tratos na infância e Transtorno de Estresse Pós-Traumático (TEPT) e sintomas psiquiátricos gerais numa população de adultos usuários do Sistema Único de Saúde (SUS). Análises adicionais desses resultados indicaram que as formas de negligência (negligência física e emocional) na infância eram capazes de predizer sintomas de TEPT e sintomas psiquiátricos gerais em adultos de maneira superior e independente às formas abusivas de maus-tratos infantis (abuso sexual, físico e emocional) (Grassi-Oliveira & Stein, 2007). Dessa maneira, o interesse pelas formas de negligência infantil em detrimento as formas de abuso como modelo de evento estressor precoce e deletério ao desenvolvimento neuropsicológico surge como um interessante foco de pesquisa.

O entendimento dos efeitos dos maus-tratos no processo de adoecimento é ainda muito limitado. Por exemplo, até o início dos anos 90, os profissionais da área de saúde mental

acreditavam que os danos provocados por maus-tratos na infância eram, basicamente, problemas de *"software"*, tratáveis com uma reprogramação via terapia, ou que podiam simplesmente ser apagados com exortações do tipo "esqueça" ou "supere" (Teicher, Samson, Polcari, & McGreenery, 2006). Todavia, verifica-se que "cicatrizes biológicas" acompanham os danos psicológicos, implicando numa necessidade de se reconhecer os efeitos desses maus-tratos no desenvolvimento neuropsicológico. Esse impacto durante o desenvolvimento cognitivo e neurobiológico vem sendo estudado, de maneira interligada, há pouco tempo sob o nome de Traumatologia Desenvolvimental (De Bellis, Baum et al., 1999; De Bellis, Keshavan et al., 1999). Essa é uma área de estudo relativamente nova que reúne outras áreas como a psicopatologia desenvolvimental, neurociência desenvolvimental e pesquisas no campo do estresse e trauma. O modelo proposto por De Bellis é uma rede de complexas interações entre constituição genética individual, experiências ambientais singulares, períodos críticos de vulnerabilidade desenvolvimental e características de resiliência, na tentativa de entender como tais fatores podem influenciar mudanças nos sistemas biológicos de estresse e no desenvolvimento cerebral. Além disso, busca entender as conseqüências disso em termos psicossociais e neuropsicológicos (Figura 1).

Um dos achados desses estudos seria que alterações na memória poderiam estar associadas a alterações neuroanatômicas e neuroendócrinas (Bremner, Shobe, & Kihlstrom, 2000; Bremner, Vermetten, Afzal, & Vythilingam, 2004; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003). Foram verificados déficits na memória verbal em relação à recordação imediata e tardia de indivíduos que reportaram história de abuso e negligência na infância com sintomatologia para TEPT. Além disso, esses déficits foram correlacionados significativamente com a severidade do abuso (Bremner et al., 1999). Outras pesquisas têm utilizado a recordação e o reconhecimento de listas de palavras para avaliar a função de memória, incluindo a capacidade de gerar falsas memórias, em mulheres que

relatam história de abuso sexual na infância (Bremner et al., 2000; Clancy, Schacter, McNally, & Pitman, 2000; Geraerts, Smeets, Jelicic, van Heerden, & Merckelbach, 2005). Ainda que com algumas limitações metodológicas, em geral tais pesquisas têm identificado um aumento significativo na produção de falsas memórias e prejuízo na capacidade de recordação. Não foram encontrados pesquisas sobre desempenho da memória em adultos com história de negligência na infância. Assim a investigação do funcionamento mnemônico em mulheres com negligência na infância será o principal foco desse trabalho.
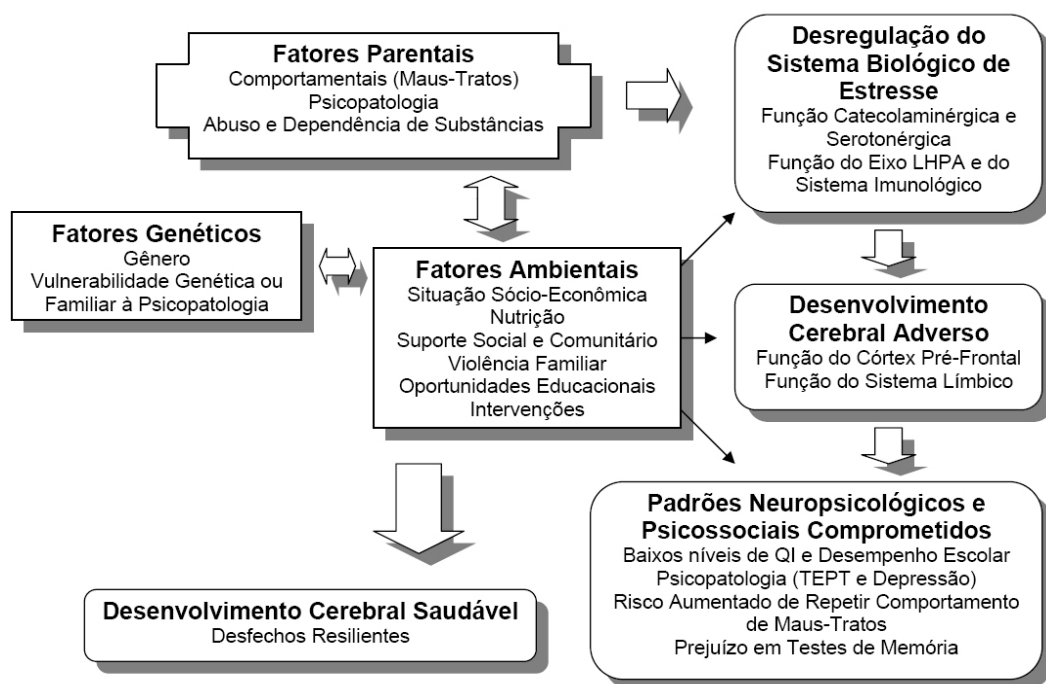
Figura 1. *Traumatologia Desenvolvimental dos Maus-Tratos na Infância* (Adaptado de De Bellis, 2005). Eixo LHPA = Eixo Límbico-Hipotalâmico-Hipófise-Adrenal.

A presente tese está dividida em uma sessão teórica e duas sessões empíricas. O estudo teórico consiste de uma revisão cuidadosa da literatura que, de maneira sistematizada, objetivou reunir um corpo de conhecimento sobre possíveis mecanismos psicobiológicos relacionados com os maus-tratos na infância que poderiam explicar a presença de déficits de memória em adultos vítimas de abuso e negligência infantil. Como a literatura descreve duas metodologias distintas na investigação da memória em adultos sobreviventes de maus-tratos

na infância (descritas anteriormente), a primeira sessão empírica é constituída por um estudo que avalia o desempenho da memória verbal e a segunda sessão engloba outro estudo que visa testar a memória de reconhecimento para listas de palavras semanticamente associadas.

O estudo da primeira sessão propõe um modelo de regressão múltipla, onde se investiga o papel da negligência física na infância (CPN) e do nível plasmático do Fator Neurotrófico Derivado do Cérebro (BDNF) no desempenho da memória verbal de mulheres adultas com Depressão Maior (MDD). A segunda sessão empírica engloba o estudo "Prejuízo da Memória de Essência em Mulheres com Negligência Emocional na Infância Reduz o Falso Reconhecimento" que consiste em um experimento onde mulheres com MDD e que relatavam ter sofrido negligência emocional na infância (CEN) foram comparadas com mulheres com MDD sem CEN e controles saudáveis em relação ao desempenho em um teste de reconhecimento para palavras semanticamente associadas.

Frente ao exposto, a presente tese tenta agregar conhecimento a uma importante questão de pesquisa levantada no campo da traumatologia desenvolvimental (De Bellis, 2005), qual seja: a negligência na infância pode ser um estressor crônico capaz de alterar sistemas biológicos e levar a um desenvolvimento neuropsicológico adverso? Especificamente tenta-se testar a hipótese de que adultos com história de negligência na infância terão prejuízos em seu funcionamento mnemônico.

Frente ao exposto a presente tese tenta agregar conhecimento a uma importante questão de pesquisa levantada no campo da traumatologia desenvolvimental (De Bellis, 2005), qual seja: A negligência na infância pode ser um estressor crônico capaz de alterar sistemas biológicos e levar a um desenvolvimento neuropsicológico adverso? Ora, se já é sabido que experiências traumáticas precoces como abuso sexual ou físico na infância provocariam alterações duradouras no eixo HPA (Heim et al., 2000) que estas estariam associadas a modificações morfológicas cerebrais, principalmente alterações hipocampais

(Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003), supõe-se que situações de negligência infantil também exerçam efeitos tóxicos para o neurodesenvolvimento e cursem com padrões neuropsicológicos comprometidos. Especificamente tenta-se comprovar a hipótese de que o peso alostático das respostas adaptativas precoces frente a situações de negligência na infância provocaria seqüelas nas estruturas relacionadas com o funcionamento mnemônico levando assim a prejuízos no desempenho em testes de memória.

Em suma, a tese pressupõe que a negligência na infância exerceria efeitos deletérios para o desenvolvimento. Não só o excesso (situações abusivas), mas também a falta (negligência) seriam importantes eventos traumáticos durante períodos críticos do desenvolvimento.

SEÇÃO TEÓRICA

Psychobiology of Childhood Maltreatment: Effects of Allostatic Load?

ABSTRACT

INTRODUCTION: 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 the 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 example of allostatic response and could precipitate an allostatic load in an organism still vulnerable in its development. OBJECTIVE: This article reviews the psychobiological consequences related with 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 as PubMed to identify English-language articles from 1990 to 2007. RESULTS: From 115 articles it was selected 55 studies from the MedLine 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 them. CONCLUSION: In summary, structural consequences of childhood maltreatment include disruptive development of corpus callosum, left neocortex, hippocampus, and amygdale; 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 HPA and subsequently the stress response.

Key Words: Child Abuse; Life Stress; Neurobiology; Brain Development; Allostasis

PSYCHOBIOLOGY OF CHILDHOOD MALTREATMENT: EFFECTS OF ALLOSTATIC LOAD?

Background

Facing an adverse physical or psychosocial situation, an individual is forced to adapt in order to survive. Allostasis (McEwen, 2002a) 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 the allostatic response is excessive or inefficient, the organism develops an allostatic load (McEwen, 2002b). When these adaptive mechanisms are repeatedly activated, the organism starts functioning in an allostatic state. It is then presumed that an "allostatic load state" would have a great cost to the organism (McEwen, 2007). Child abuse and neglect would be examples of adverse situations that could generate an "allostatic load state" in an organism still vulnerable in 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" that would be an emergency adaptive process to a stressor (stimulus) designed to maintain the balance (Pacak & Palkovits, 2001),. 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 sooner and in a supported manner. How does this affect the child's development? Is the 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 would alter the neurological and psychological development (De Bellis, 2005; Teicher et al., 2003). This cascade could be example of allostatic response and could precipitate an allostatic load. This article reviews the psychobiological aspects related to childhood maltreatment.

Methods

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 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". It was also cross-referenced the selected article's references.

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

Results

From 115 articles it was selected 55 studies from the *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).

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 (Sullivan et al., 2006). These cerebral changes follow a lifelong trajectory of brain development; however, each brain region has a unique course of ontogeny (Evans, 2006). 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 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) (Andersen, 2003). Its synthesis and secretion are regulated by neuronal activity, which is directly related to environmental stimuli (Thoenen, 1995). 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 (Glaser, 2000). Even if this process is genetically determined, some synaptic connections formed cease to exist because of lack of use and others, new ones, are formed because of a necessity - that is, the environment is responsible for determining which neural connections are going to persist or emerge (Singer, 1995). 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 that has the goal of provoking a rearrangement in the cerebral architecture in a way to enhance synaptic transmission efficiency (Luo & O'Leary, 2005). 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 even later in cortical regions than in subcortical areas and that maturation of regions involved in cognitive processes is the most that take place very late in ontogeny, ending only after adolescence (Glaser, 2000).

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 in 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 (Andersen, 2003). 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 (Spear, 2000) - leading to an abnormal neurodevelopment (Whitaker-Azmitia, 1991). 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 (Sapolsky & Meaney, 1986). 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 (De Bellis, 2002).

Abuse and/or neglect during childhood can influence brain development through action factors that are extrinsic 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 and used for survival in a determined environment and disposing of what is unnecessary (Perry, Pollard, Blakely, Baker, & Vigilante, 1995). 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 (Rutter & O'Connor, 2004). 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 (Felch & Granger, 2007). 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 (Kaufman et al., 2006; Savitz et al., 2007). Particularly a large sample prospective study from birth to adulthood showed that maltreated children with a genotype conferring high levels of monoamino oxiadase A (MAOA) expression were less likely to develop antisocial problems

when adults (Caspi et al., 2002). These findings were replicated and confirmed by meta-analyses (Kim-Cohen et al., 2006)

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 (Andersen, 2003).

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 PTSD, depression and substance abuse – and to neuropsychological alterations – impairment in memory and attention tests, and the abilities of learning (Bremner et al., 2004; Teicher et al., 2004).

Childhood Maltreatment and Developmental Traumatology Model

Developmental traumatology (De Bellis, Baum et al., 1999), 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 (Charney, 2004).

Cortisol has an important regulating effect in the hippocampus, amygdale, and prefrontal cortex. It has a two-stage effect in hippocampal arousal, cognitive functions, and memory (Gold, Drevets, & Charney, 2002). Furthermore, it can increase amygdale activity and the concentration of corticotrophin release hormone (CRH) *m*RNA in the amygdale's central core, enhance the effects of CRH, and facilitate encoding processes of emotional memories (Charney, 2004). CRH is one of the most important mediators in response to stress, coordinating adaptive behavior and psychological changes that occur during stress and increasing adrenocorticotropic 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, cingular gyrus, central cores of the amygdale, *nucleus accumbens*, *locus ceruleus,* and dorsal and medial raphe (Steckler & Holsboer, 1999). Its release is controlled by plasmatic cortisol levels through negative feedback mechanisms and also by direct hippocampal action (Tsigos & Chrousos, 2002).

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 in 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 show hypercortisolemia (De Bellis, 2005; Gunnar, Morison, Chisholm, & Schuder, 2001). 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 (Putnam & Trickett, 1997). 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 (Cicchetti & Rogosch, 2001). Along the same lines, De Bellis *et al*. (De Bellis, Baum et al., 1999) 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 showed that the first group presented higher levels of salivary cortisol (De Bellis, Keshavan et al., 1999).

Many research studies have examined the neurobiological effects of early stress (Kaufman, Plotsky, Nemeroff, & Charney, 2000). 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) (Pihoker, Owens, Kuhn, Schanberg, & Nemeroff, 1993). 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 chocks in the rats' paws. Research also identified a decrease in CRH connection in the anterior pituitary (Ladd, Owens, & Nemeroff, 1996). Studies using monkeys raised in experimental stressful conditions showed higher concentrations of CRH and decreased concentrations of cortisol in the cerebrospinal fluid when they became adults (Coplan et al., 1996). 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 (De Bellis et al., 1994). This phenomenon can also be observed in adult women with PTSD who were sexually abused during childhood (Bremner, 2003). The authors suggest that childhood abuse would result in high levels of CRH, with decrease of pituitary sensitivity to CRH stimulation.

Heim *et al.* (2000) 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 group 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 (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001).

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 of 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 of its plasmatic concentration. When the physiological increase of glucocorticoids is stopped by adrenalectomy, acute stress results in even higher levels of NE (Yehuda, McFarlane, & Shalev, 1998). 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 (De Bellis et al., 1994). High levels of urinary NE in 24 hours were found in boys who were severely depressed and with parental neglect history (Queiroz et al., 1991). In addition to that is the fact that maltreated

children medicated for PTSD dispose of higher quantities of NE and dopamine (DA) than controls (De Bellis, Baum et al., 1999). 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) (Nemeroff, 2004; Penza, Heim, & Nemeroff, 2003) and present an increase of the catecholaminergic activity (De Bellis, 2005) .

Moreover, when 61 children and adolescents with PTSD and in maltreatment situation were compared to 121 healthy controls in terms of pituitary volume, it was observed that the gland was significantly higher in individuals who were maltreated, had PTSD diagnosis, and were in pubescent or post-pubescent age (Thomas & De Bellis, 2004). 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 (De Bellis, 2005).

Adverse Brain Development

A series of functional and structural neural-biological consequences associated with early stress experiences have been identified (Teicher et al., 2003). Pre-clinical studies indicate that brain regions particularly vulnerable to early stress have some of the following characteristics: (a) later postnatal development, (b) high density of glucocorticoid receptors, and (c) some degree of postnatal neurogenesis (McEwen, 2007).

Hippocampus

Early stress has been related to profound structural changes in the hippocampus (Andersen & Teicher, 2004). 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 (Sapolsky, 2000). Early exposition to stress or corticosteroids can cause a hippocampal remodeling (or atrophy) (Gould, Tanapat, Rydel, & Hastings, 2000). 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 (Sapolsky, 2000).

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 (Cameron, McEwen, & Gould, 1995), 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) (De Bellis, 2005). 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 (Cirulli, Berry, & Alleva, 2003).

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 (Sapolsky, 2000). 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 (Liu et al., 1996). It could be assumed that individuals with HPA deregulation would be more susceptible to

cortisol neurotoxic effects (Heim et al., 2001). 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 2nd to their 20th 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 (25th−100th days). The authors observed two main effects: (a) early maternal separation reduced, in a general sense, the synaptophysin levels; (b) but it was only after 60 days (which would level to the 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 (Andersen & Teicher, 2004). 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 (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005).

A structural and functional neuroimaging study was performed with three groups of women: (a) the ones who reported a history of sexual abuse as children and presented PTSD, (b) women who reported a history of sexual abuse as children but no PTSD, and (c) a control group with women with no history of childhood sexual abuse and no PTSD (Bremner et al., 2003). All participants were submitted to MRI and positron emission tomography (PET). The authors 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 TEPT 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 (Pederson et al., 2004). In addition, other authors examined the hippocampal volume of 18 young adults with child sexual abuse history and compared these with those in a healthy control group (Teicher et al., 2003). They did not find 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 (De Bellis, Keshavan et al., 1999). Other authors also failed to identify hippocampus volume reduction in maltreated children (Carrion et al., 2001).

Amygdale

The amygdala core is one of the areas of the brain that is most sensitive to the mergence of *kindling* (Buchanan & Bilkey, 1997). *Kindling* is a process in which repetitive and intermittent neuronal stimulation produces even more alterations in neuronal arousal, eventually leading to spontaneous electric discharges (Mohapel, Dufresne, Kelly, & McIntyre, 1996). It is proposed that adults with childhood abuse history would have a "limbic

irritability," that is, from an abnormal development of the amygdale or the hippocampus associated to 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 (Teicher, Glod, Surrey, & Swett, 1993). Adding to this hypothesis is the finding that children admitted to a psychiatric unit and who have abuse history presented electroencephalographic abnormalities in the front-temporal region, predominantly in the left hemisphere (Ito et al., 1993).

Image studies (Bremner et al., 1997; De Bellis, Keshavan et al., 1999; Stein, Koverola, Hanna, Torchia, & McClarty, 1997) did not reveal any volumetric difference in the amygdale of individuals with child abuse history compared with control groups. However, a study in a fear acquisition and extinction paradigm compared women with child abuse history and PTSD diagnosis to healthy control in terms of psychophysiologic measures and PET showed that clinical group presented an increase in the left amygdale activation with the acquisition of fear and a decrease in the anterior cingular cortex function during extinction (Bremner et al., 2005).

Cerebral Cortex

The neocortex slowly develops through cyclical reorganizing processes (Thatcher, 1992). The delay of corpus callosum myelinization allows the hemispheres to develop relatively independent from one another. Of all cortical regions, the prefrontal lobe is the one with 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 (Brake et al., 2000). The prefrontal functions are related to inhibitory doings in most monoaminergic projections for subcortical regions, action planning, decision making, work memory, and attention. However, a major stress that increases catecholamine activation

(especially NE and DA) can disable this frontal inhibition of the limbic system (De Bellis, 2005). This disablement of the frontal inhibition of the amygdale can be observed in adults with maltreatment history (Shin et al., 1999).

It has been postulated that early stress could activate the prefrontal cortex development, alternating its development and causing precocious maturation with a negative impact on its final capacity (Teicher et al., 2003). In a controlled study performed with children admitted to a psychiatric unit with documented abuse history, it was 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. The authors of this study observed that this finding was associated with an important delay in the development of the left hemisphere in the group of abused children (Teicher et al., 1997). 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 cingular cortex as a neuronal viability and density index (De Bellis, Keshavan, Spencer, & Hall, 2000). The authors 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.* (Carrion et al., 2001) 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 (Bremner, 2003; Nemeroff et al., 2005), as well as altering the cortical development and distribution of monoaminergic fibers that affect the degree of hemispheric laterality (Teicher et al., 2003).

Cerebellar Structures

The cerebellar vermis is the brain structure that presents a more accentuated postnatal growth period (Teicher et al., 2003) . 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 (Giedd et al., 1999). Among its functions are multisensory integration, control of epilepsy, and limbic activation.

When it was studied 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 abuse history and compared it with healthy controls, the findings indicated an important decrease in the relative perfusion of the vermis in the abused subjects indicating a functional damage in the cerebellar vermis activity (Anderson, Teicher, Polcari, & Renshaw, 2002).

In addition, cerebellar volumes positively correlated with age of onset of the trauma that lead to PTSD and negatively correlated with the duration of the trauma that lead to PTSD in maltreated children and adolescents with DSM-IV PTSD (De Bellis & Kuchibhatla, 2006)

Corpus callosum and hemispherical integration

Corpus callosum comprehends myelinizated 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 (Clarke & Zaidel, 1994). 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 concluded that primates that suffered physical and emotional neglect during early years present deficient prefrontal functions and normal myelinization as expected for their age (Sanchez, Hearn, Do, Rilling, & Herndon, 1998).

The first indication that childhood trauma can affect the development of the corpus callosum in humans was given by a study that found a significant reduction in the medial portions of the corpus callosum in abused children (Teicher et al., 1997). 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 (De Bellis, Keshavan et al., 1999). 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 (Teicher et al., 2004).

Reduction in size of corpus callosum has been associated with a decrease in communication between the brain hemispheres (Clarke & Zaidel, 1994). 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 (Schiffer, Teicher, & Papanicolaou, 1995).

Conclusions

Not all children victimized by abuse report further problems (Caspi et al., 2002), in the same sense that there is no "abused child syndrome" (De Bellis, 2005). If there are sequels, it is shown with considerate interpersonal differences (Glaser, 2000). However, some common points can be identified.

First, it is important to remember that usually among the elder the reduction of the hippocampus is correlated to the damage in the consolidation of long-term explicit memory

and to the increase of cortisol levels (Golomb et al., 1994; Lupien, Gillin, & Hauger, 1999). To explain how neuronal damage is done, one of the suggested hypotheses would be that the high levels of glucocorticoids (cortisol) would be released during an acute stress situation (abuse) and would result in hippocampal damage (Sapolsky, 2000). 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 (Bremner et al., 2003). 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 (Yehuda et al., 2000).

Early stress could start a chain reaction of neurohormonal and neurotransmissor 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 structure and function (psychological and neurological) 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 (Bremner, Bolus, & Mayer, 2007; Bremner, Vermetten, & Mazure, 2000). 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 (Roy & Perry, 2004). 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 (Bifulco, Bernazzani, Moran, & Jacobs, 2005). 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 (Bremner et al., 2000).

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

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

b) 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.

c) 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, neurophysiology. Understanding the psychobiology of maltreatment through allostasis framework could be helpful to future interventions based on evidences, 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 an intervention research (De Bellis, 2001).

More than that, there is a need for prospective studies that aim to search "points of vulnerability or windows of opportunity" (Andersen, 2003) during brain development of children victimized by abuse or neglect. A new model of resilience is coming up.

Acknowledgments

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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

SEÇÃO EMPÍRICA I

Low Plasma Brain Derived Neurotrophic Factor and Childhood Physical Neglect Are Associated With Memory Impairment in Major Depression

ABSTRACT

BACKGROUND: Early life stress has been suggested to mediate vulnerability to affective disorders. Animal models of repeated maternal separation have been shown reduced brain-derived neurotrophic factor (BDNF) levels in specific brain regions implicated with hypothalamic-pituitary-adrenal axis and memory formation. In addition, BDNF levels are also reduced in major depression disorder (MDD) and bipolar disorder. The aim of this study was to investigate whether childhood physical neglect (CPN) and plasma BDNF levels would impact on memory performance in adult females with recurrent major depression. METHODS: Recurrent female MDD outpatients with CPN (MDD + CPN, n=17) and without CPN (MDD, n=17), and healthy controls (n = 15) were assessed for plasma BDNF content and verbal memory performance. Memory was assessed through Logical Memory component of the Weschler Memory Scale – Revised (WMS-R) for immediate and delayed recall. BDNF was assessed with ELISAs. RESULTS: MDD patients showed low plasma BDNF concentrations than healthy controls ($p < 0.001$). MDD + CPN had even lower BDNF levels compared with controls and MDD ($p < 0.05$). BDNF levels were negatively related to psychological morbidity and positively correlated to memory performance. Regression models showed that severity of self-reported CPN and low plasma BDNF predicted impairment on immediate verbal recall. Delayed recall impairment was predicted by severity of CPN and depression, and memory retention by PTSD severity symptoms. CONCLUSIONS: Our data suggest that CPN and plasma BDNF are important factors associated with depression and verbal memory performance, particularly with encoding processes.

LOW PLASMA BRAIN DERIVED NEUROTROPHIC FACTOR AND CHILDHOOD PHYSICAL NEGLECT ARE ASSOCIATED WITH MEMORY IMPAIRMENT IN MAJOR DEPRESSION

Introduction

Early life stress has been suggested to mediate vulnerability to affective disorders including unipolar depression (Heim & Nemeroff, 2001). A variety of studies have shown the close relationship between childhood abuse (particularly sexual and physical abuse) and neurobiological consequences in adult life (Teicher et al., 2003; Teicher, Tomoda, & Andersen, 2006). On the other hand, there are few studies that examined the psychobiological consequences of neglect forms of childhood maltreatment (De Bellis, 2005; Widom, DuMont, & Czaja, 2007).

The brain derived neurotrophic factor (BDNF) has been shown as a key mediator of synaptic efficacy, neuronal connectivity and neuroplasticity (Cotman & Berchtold, 2002; Duman, 2002). BDNF regulates neuronal development and survival and controls the activity of many neurotransmitter systems, including the serotonergic and glutamatergic systems (Cotman, 2005). BDNF levels have been found to be correlated (Hashimoto, Shimizu, & Iyo, 2004) and reduced in major depression or bipolar disorder (Karege et al., 2005; Machado-Vieira et al., 2007). Moreover, several antidepressants have been able to increase serum BDNF levels (Huang, Lee, & Liu, 2007) or in postmortem hippocampus (Russo-Neustadt, Alejandre, Garcia, Ivy, & Chen, 2004). These data have provided the current framework for the neurotrophic model of mood disorders (Duman & Monteggia, 2006).

Maternal separation (an animal model for early life stress in which rat pups are deprived of maternal contact once or repeatedly during the first postnatal weeks) could program widespread and lifelong changes in various transmitter systems that regulate the hypothalamus-pituitary-adrenal (HPA) axis (Champagne & Meaney, 2001). Some authors

have suggested that repeated maternal separation could reduce BDNF levels in specific brain regions (i.e. hippocampus) implicated with HPA axis and memory formation early in development (Duman, 2002). Despite any direct investigation was found in literature between maternal deprivation, BDNF activity and memory performance, a reduction in BDNF activity in hippocampus of rats has been associated with a marked deficit in memory persistence (Bekinschtein et al., 2007) and an important impairment in memory formation in parietal cortex (Alonso et al., 2005). However, it is largely unknown to what extent BDNF levels are related to childhood physical neglect (CPN) and memory performance in major depression. Thus, the aim of this study was thus to investigate whether CPN and plasma BDNF levels would impact on memory performance in adult females with major depressive disorder (MDD).

Methods and Materials

Subjects and Clinical Assessment

Sixty MDD outpatients (all females, 20–55 yrs) of an affective disorder treatment unit (Hospital Presidente Vargas, Porto Alegre, Brazil) were interviewed by two well trained clinical psychiatrists with the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to confirm the diagnosis of recurrent MDD. A group of 17 outpatients with recurrent major depression without CPN (MDD) and 17 outpatients with recurrent major depression with CPN (MDD + CPN) were enrolled in this study. All patients had been medicated with SSRI or tryciclics at least for 3 months with a stable dosage. Severity of depressive symptoms was evaluated by Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Gorenstein & Andrade, 1996) and post-traumatic stress disorder (PTSD) symptoms by PTSD Checklist – Civilian Version (PCL-C) (Berger, Mendlowicz, & Figueira, 2004; Lang, Laffaye, Satz, Dresselhaus, & Stein, 2003). CPN was assessed through Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Grassi-Oliveira et al., 2006)

and was considered present if its score could be classified as moderate to extreme using the cut-off point postulated by Bernstein (percentile 90) to adult females (Bernstein et al., 2003). The CTQ is a self-report inventory that provides a retrospective assessment of childhood trauma and it is composed of the following clinical sub-scales: physical, sexual, and emotional abuse; and physical and emotional neglect (Bernstein et al., 2003). The therapists' ratings were used as a stringent test of validity of retrospective reports of childhood neglect demonstrating "good" criterion-related validity (r = .45, p < .001), whereas convergent and discriminant validity was demonstrated with a structured trauma interview (Bernstein et al., 2003). Participants presenting past or current Axis I disorders other than MDD, severe or unstable clinical illness, neurological disorder, psychotic symptoms or any psychoactive substance use in last 30 days (excepting nicotine, caffeine and antidepressants) were excluded.

Ninety four healthy hospital employees (all females, 20–50 yrs) were screened by the Self-Report Questionnaire (Harding et al., 1980; Mari & Williams, 1986) - a screening instrument to psychiatric disorders. Twenty seven participants with negative screening were clinically assessed with SCID-I, BDI, PCL-C and CTQ. All participants with any past or current Axis I disorder, any history of childhood maltreatment, severe or unstable clinical illness, neurological disorder, or any psychoactive substance use in last 30 days (excepting nicotine and caffeine) were excluded. The remaining participants consisted the Control group (n=15). The current research was approved by Pontifical Catholic University of Rio Grande do Sul (PUCRS) Ethics Committee. Written informed consent was obtained from all participants.

Memory assessment

Memory tests were performed from 8:30 – 9:30 AM, after 30 minutes of blood drawn. The Logical Memory Test (LM) was administered to all subjects. LM is a verbal declarative

memory subtest from The Wechsler Memory Scale-Revised (WMS-R) (Plass, 1991). The WMS-R LM immediate and 30-minute delay trials were administered by two well trained psychologists according to test manual guidelines. During the experiment, an audio CD containing a story (story A) with 25 memory elements was played to the examinee who was asked to orally provide any information recalled after the story end. After story A recall, the same procedure was repeated for a second story (story B). Participant's answers were recorded and scored later by examiner following normative established by Wechsler (1987). Each story generates a partial score and the sum of both trials gives the immediate verbal recall score (IVR). The examinee is instructed to memorize the stories because she will be asked to recall them again later. Following 30 minutes filling self-report measures and conversation, the examinee was asked to provide any information recalled from Story A and then Story B. A standard cue is provided if the examinee has no memory of a story. The recall unit scores are again recorded and scored. The sum of both trials gives the delayed verbal recall score (DVR). The percent retention (%R) scores represent the number of story units recalled on the immediate memory trial (IVR) divided by the number of units recalled after the 30-minute (DVR) (Bremner et al., 1995).

Plasma BDNF levels

All participants were instructed not to eat or take medication for at least 8 hours before the blood draw. Human blood was collected from 8 – 9 AM, before memory assessments. Plasma was separated within 30 min and the supernatant was stored at -80º C for up to 6 months. For BDNF measurement it was used a commercially available BDNF immunoassay ELISA kit (R&D Systems, Minneapolis MN). All samples were assayed on duplicate. The detection limits for these assays were 20 pg/mL. In brief, the capture antibody (concentration provided by the manufacturer) was diluted in phosphate-buffered saline (PBS), added to each well and left overnight at 4°C. The plate was washed four times in PBS with 0.05% Tween 20

(Sigma, St. Louis, MO, USA). The plate was blocked with 1% bovine plasma albumin and incubated for 1 h at room temperature before washing four times with PBS and 0.05% Tween 20. The samples and standards were added and the plate incubated overnight at 4°C. After washing the plate, detection antibody (concentration provided by the manufacturer) diluted in PBS was added. The plate was incubated for 2h at room temperature. After washing the plate, streptavidin (DuoSet R & D Systems, Minneapolis, MN, USA) was added and the plate incubated for 30 minutes. At last, color reagent o-phenylenediamine (Sigma, St. Louis, MO, USA) was added to each well and the reaction was allowed to develop in the dark for 15 min. The reaction was stopped with the addition of 1M H_2SO_4 to each well. The absorbance was read on a plate reader at 492 nm wavelength (Emax, Molecular Devices, Minneapolis, MN, USA). BDNF levels are expressed as pg/mL.

Statistical analysis

All variables were tested for normality of distribution by means of the Kolmogorov-Smirnov test. Group mean differences were assessed by means of the analysis of variance (ANOVA). Multiple comparisons among group mean differences were checked with Tukey HSD test. The relationships between demographic/psychosocial variables and memory performance were explored by Pearson's correlation. The distribution of BDNF concentrations failed in normality test and data were thus log transformed. Multiple Regression analyses were employed to control for potential confounding variables and determine the independent correlations between memory performance, childhood neglect and plasma BDNF. Factors that showed significant association with each memory dependent variable were included in the correspondent regression equation following the *Stepwise* method (Hosmer & Lemeshow, 1989). *P*-value of less than 0.20 was required for a factor to be included and retained in the analysis. Due the high variability on BDNF plasma concentrations found in literature (from 22 to 14000 pg/mL) (Karege et al., 2005; B. H. Lee,

Kim, Park, & Kim, 2007; Piccinni et al., 2007, in press), it was performed a dummy coding in which subjects with concentrations 2 SD below the mean of the controls (2347.03 pg/mL) was considered having "low plasma BDNF" (BDNF $\leq$ 2347.03 = 1; BDNF > 2347.03 = 0) following the same procedure used previously to evaluate "low platelet serotonin" in psychiatric patients (Muck-Seler, Jakovljevic, & Deanovic, 1991). The significance level was set at α = 0.05 (two-tailed). Statistics analyses were performed through the SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois). Results are expressed as mean $\pm$ SD in all figures and tables.

Results

The demographic and psychosocial characteristics of samples are shown in Table 1. It is important to note that all groups are very similar regarding to age, education or social status and that both depression groups are homogeneous in terms of severity of depression and PTSD symptoms. The MDD+CPN group showed impairment in immediate (p < 0.05) and delayed recall (p < 0.01) in comparison with other groups except for memory retention. Figure 1 shows that MDD groups presented significantly lower BDNF plasma concentration than healthy control group (p < 0.001). In addition, MDD patients with CPN had even lower BDNF levels when compared to patients without CPN (p < 0.05).

Exploratory analyses showed a significant correlation of IVR with years of education (r = .39, p = .006), severity of depression (BDI) (r = -.49, p < .001), PTSD symptoms (PCL-C) (r = -.38, p = .006), CPN (CTQ) (r = -.54, p < .001) and plasma BDNF (log) (r = .43, p = .002). Moreover, DVR was associated with the same variables: years of education (r = .34, p = .016), depression severity (r = -.52, p < .001), PTSD symptoms (r = -.43, p = .002), CPN (r = -.53, p < .001) and plasma BDNF (r = .40, p = .004). On the other hand, the %R was only correlated with severity of depression (r = -.29, p = .038) and PTSD symptoms (r = -.30, p = .035).

Multivariate analyses were employed to assess the independent roles of CPN and plasma BDNF on memory performance. Thus IVR, DVR and %R were entered as dependent variables in these regression analyses. Independent variables entered into each multivariate model were plasma BDNF, "low plasma BDNF" and CPN. Furthermore, the multivariate analyses were adjusted by entering in the equation those variables previously correlated with their dependent variables (memory performance). The model that established the factors correlated with memory measures also included the age and MDD diagnosis (MDD = 1, non-MDD = 0). Since previous study had identified age as important correlate of verbal memory performance (Price, Said, & Haaland, 2004) it was included in regression equations. In addition, having or not MDD is rarely considered as a variable in memory studies with adults and childhood abuse (Bremner et al., 1995; Bremner et al., 2004) despite it could impact Logical Memory performance (Baudic, Tzortzis, Barba, & Traykov, 2004). Thus it was also included in the regression models. During the regression models there was no evidence of high colinearity between selected variables, and all VIF values were < 2.

When plasma BDNF concentrations entered in the equation at first, the selected variables predicting IVR were CPN severity, depression severity and years of education (R = 0.66, adj R^2 = 0.40; F [3,45] = 11.65, $p < .001$) and none linear correlation was initially found between plasma BDNF and immediate recall (r = -.03, p = .83). However, when "low plasma BDNF" was included in the regression, severity of CPN and "low plasma BDNF" were found as predictors of immediate recall impairment after adjusting for potential confoundable variables (see Table 2). On the other hand, "low plasma BDNF" was not a predictor of delayed recall deficits, in contrast to CPN and depression severity. Decrease in memory retention was only predicted by PTSD symptoms.

Discussion

To our knowledge, this is the first study addressing the role of BDNF levels on cognitive performance in MDD patients with history of CPN. Patients with MDD showed low plasma BDNF concentrations in accordance to previous work (Aydemir et al., 2006; Gonul et al., 2005; Karege et al., 2002; Shimizu et al., 2003). Interestingly, patients with history of CPN had even lower BDNF levels than patients without CPN. BDNF levels were negatively related to psychological morbidity and positively correlated to memory performance. Multivariate regression models showed that severity of self-reported CPN and "low plasma BDNF" predicted impairment on immediate verbal recall. Delayed recall performance was predicted by severity of CPN and depression, and memory retention by PTSD severity symptoms.

BDNF has been speculated as a key mediator in synaptic efficacy, neuroplasticity, neuronal connectivity as a function of stage of development in both animals and humans (Duman, 2002; Post, 2007). It has been related with synaptic strengthening associated with learning and memory and also influences the development of patterned connections and the growth and complexity of dendrites in the cerebral cortex (Yamada, Mizuno, & Nabeshima, 2002). Memory acquisition is associated with an increase in BDNF mRNA and tyrosine kinase B (TrkB) activation in specific brain areas and this effect may be linked to the modulation of NMDA and non-NMDA receptor functions as well as Src-family tyrosine kinase Fyn and phosphatidylinositol 3-kinase signaling pathways (Yamada & Nabeshima, 2004).

Despite BDNF val66met polymorphism have been associated with verbal memory deficits (Harris et al., 2006; Ho et al., 2006; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007) due possible impact on intracellular trafficking and activity-dependent secretion of BDNF (Egan et al., 2003), the direct association between verbal memory and peripheral BDNF is still unknown. To our knowledge, there are just preliminary analyses indicating that

BDNF serum concentration reflects some aspects of neuronal plasticity as indicated by its association with in vivo level of cerebral N-acetylaspartate, a well established marker of neuronal integrity (U. E. Lang, Hellweg, Seifert, Schubert, & Gallinat, 2007). Our data further support the role of BDNF on memory performance. Indeed, we observed an important association between "low plasma BDNF" status and immediate verbal memory impairment, in accordance to previous polymorphism studies (Harris et al., 2006; Ho et al., 2006; Savitz et al., 2007).

Multivariate analyses revealed that exposure to CPN was related to degree of immediate and delayed verbal memory impairment, corroborating previous studies that investigated this relationship with childhood exposure to sexual abuse (Bremner et al., 1995; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Stein, Hanna, Vaerum, & Koverola, 1999). In addition, low plasma BDNF was associated with lower scores on the WMS Logical component for immediate but not delayed recall, which are consistent with a genotyping study (Ho et al., 2006). These associations are found after adjusting for age, years of education, PTSD symptoms, depression severity and severity of MDD. Despite depression severity has been negatively associated with DVR performance, low BDNF was not. Thus depression severity predicted delayed verbal memory impairment independently of BDNF activity. Furthermore, the only predictor of verbal memory retention impairment was PTSD symptoms severity in accordance with previous studies (Bremner et al., 2004; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003).

The LM component of WMS reflects short-term verbal memory (Bremner et al., 1995). It is assumed that IVR reflects encoding and retrieval of information previously studied, and DVR reflects initial encoding indirectly and storage and retrieval of the information that was initially encoded (Haaland, Price, & Larue, 2003). Considering that IVR is related with acquisition of information (Brooks, Weaver, & Scialfa, 2006), it is

hypothesized that low plasma BDNF effects on immediate recall reflect deterioration in encoding and retrieval more than storage processes. On the other hand, CPN seems to be related with general impairment in short-term verbal memory since it was negatively associated with IVR and DVR scores. Since %R is a delayed recall measure adjusted for immediate recall performance and none effect of CPN was related to memory retention, this general impairment could be associated predominantly with short-term verbal memory encoding processes.

Evidence strongly suggests that successful encoding of verbal material engages left frontal cortex, particularly ventrolateral frontal cortex and dorsolateral frontal cortex (Fletcher & Henson, 2001; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). While the present study did not examine the association between memory performance and structural and functional brain assessments, the finding of CPN and low BDNF negative effect on immediate recall suggest primarily frontal impairment as opposed to hippocampal dysfunction, for which %R and DVR are correlated positively with its volume and function (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003; Griffith, Pyzalski, Seidenberg, & Hermann, 2004; Kohler et al., 1998). This idea is supported by studies with WMS in normal aging (Haaland et al., 2003). Considering the close relationship between hippocampus, memory retention and delayed recall, and that hippocampal volume appears to be selectively decreased and hippocampal function impaired among PTSD (Nemeroff et al., 2006) and major depression patients (Sheline, Mittler, & Mintun, 2002), the findings of negative impact of depression and PTSD severity on those memory measures in the present study do not surprise.

Recent findings show that an adverse prenatal environment produces structural defects of the hippocampus and these structural changes are accompanied by a disruption in the normal expression pattern of BDNF TrkB receptor suggesting that fetal exposure to

unfavorable intrauterine conditions may compromise proper cognitive function in adult life (Gomez-Pinilla & Vaynman, 2005). On the other hand, environmental enrichment is known to induce various molecular and cellular changes in specific brain regions of wild-type animals, including altered gene expression profiles, enhanced neurogenesis and synaptic plasticity (Spires & Hannan, 2005). In that sense, an epidemiological cohort of 1,116 five-year-old twin pairs showed that maternal warmth, stimulating activities, and children's outgoing temperament appeared to promote positive adjustment in children exposed to socioeconomic deprivation (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). Interesting offspring of rat mothers with high levels of pup licking and grooming and arched-back nursing had increased hippocampal cholinergic innervation, memory and spatial learning and an increased expression of BDNF mRNA (Liu, Diorio, Day, Francis, & Meaney, 2000), as well as maternal aggression and maternal separation are associated with low neurotrophins activity in adult rats (Alleva & Santucci, 2001).

Our data suggest that an association between early adverse experience and low BDNF activity could impact negatively on verbal memory encoding through experience-dependent neural ontogeny processes. Thus an epigenetic regulation of BDNF expression could be related with the development of neural structures related with verbal memory. Such idea is supported by findings that showed histone modifications around two BDNF gene promoters (P1 and P4) after extinction of conditioned fear, as potential targets of learning-induced epigenetic regulation of gene expression, suggesting a relationship between histone H4 modification, epigenetic regulation of BDNF gene expression, and memory formation (Bredy et al., 2007).

Posttranslational modification of histones and DNA methylation plays an important role in memory, response to stress and depression through chromatin remodeling but its activity is dependent of BDNF gene regulation (Martinowich et al., 2003; Tsankova et al.,

2006). Despite none direct investigation between childhood adverse environment and histone activity was found in literature, histone acetylase activity seems to be involved with lifelong chromatin remodeling necessary for short-term memory formation and response to stress, and it is particularly related to new information acquisition (Maurice et al., 2007, in press). In addition, recent studies have shown that increased frequency maternal care during the first week of life is associated with changes in DNA methylation of promoter elements that control expression of care behavior and stress response in adult life (i.e. glucocorticoid receptor gene promoter in the hippocampus) (Weaver et al., 2004). A possible molecular scaffold by which changes in gene expression and behavioral traits induced by postnatal maternal care are lifelong maintained is the stability of DNA methylation in post mitotic cells (Kaffman & Meaney, 2007) .

There are some limitations in this study to be discussed. First, we had a relatively small sample sizes. It should be noted, however, that was very difficult to recruit healthy controls with no past or current psychopathology and any kind of childhood maltreatment from the same low socioeconomic status. The stringent inclusion/exclusion criteria have limited the sample size but yielded strictly healthy control subjects. Replication with large samples and longitudinal follow-up will be needed to overcome these limitations. Second, our interpretations are based upon findings on a single memory test and further studies should preferably include several memory tests. Third, recurrent MDD participants were using antidepressants. Despite there is some evidence that antidepressant treatment significantly increase serum BDNF in depressive women with low serum BDNF (Huang et al., 2007), we cannot discard the medication effects on memory data. It should be observed, however, that it is extremely difficult to investigate recurrent depression participants without medication. Finally, it would be interesting to provide data on other neurotrophins such as neuron growth

factor (NGF), insulin-like growth factor (IGF)-1 or neurotrophin-3 to discuss the specificity of our findings in MDD patients.

Taken into consideration these limitations, our data further support the role of childhood physical neglect and plasma BDNF levels on major depression and verbal memory performance, particularly involving encoding processes. More studies are necessary to replicate these findings in a powered design to clarify the complex relationships between childhood neglect, BDNF and verbal memory functioning. Additional studies will also be needed to determine if decreased BDNF reflects a state or trait marker and to determine the functional significance of altered peripheral BDNF.

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Figure 1. Plasma BDNF levels between patients with major depression and healthy controls.
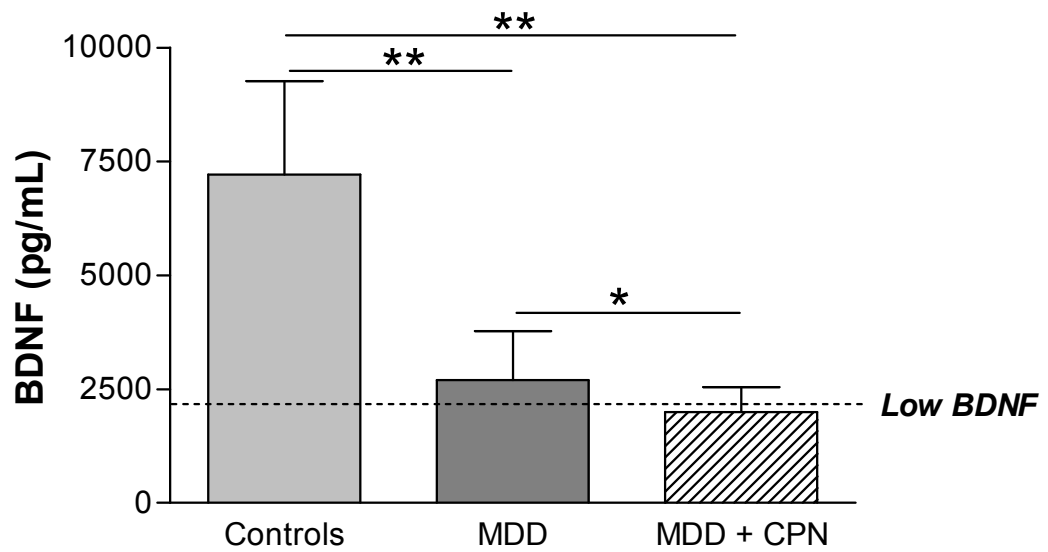
Note: Controls, healthy participants; MDD, Major depressive disorder; CPN, childhood physical neglect; Low BDNF, plasma BDNF concentrations 2 SD below the mean of the controls. Statistical significant differences are indicated: * $p < 0.05$, ** $p < .001$.

Table 1. Demographic and Psychosocial Characteristics of Samples.

	MDD + CPN (n=17)		MDD (n=17)		Control (n=15)			
	M	± SD	M	± SD	M	± SD	F	p
Age (years)	39.35	9.32	39.53	7.96	36.47	6.31	.71	.49
Education (years)	9.47	4.51	7.65	2.93	9.00	2.50	1.26	.29
Income (US$/month)	564.93	316.99	706.56	389.33	620.66	182.61	.82	.44
PTSD	58.70$_a$	11.65	52.82$_a$	15.93	22.80	5.22	40.32	< .001
DEPRESSION	30.82$_a$	10.12	26.35$_a$	11.63	4.53	3.90	35.42	< .001
IVR	15.76$_a$	6.63	21.47	7.99	22.87	6.30	4.68	.014
DVR	11.18$_a$	5.50	17.06	7.98	19.00	7.30	5.53	.007
Retention (%)	69.19	18.07	81.04	26.16	81.52	18.61	1.77	.18

Note: Statistical significance differences are indicated: a = $p < .05$ vs. control (Tukey HSD). CPN, childhood physical neglect (CTQ – Childhood Trauma Questionnaire); MDD, Major Depression Disorder, Recurrent (SCID I); PTSD, PTSD symptoms severity (PCL-C – PTSD Checklist Civilian Version); DEPRESSION (BDI – Beck Depression Inventory); IVR, immediate verbal recall (LM/WMS – Logic Memory/Wechsler Memory Scale); DVR, delayed verbal recall (LM/WMS); Memory retention was calculated by R(%) = (DVR / IVR) X 100.

Table 2. Multiple linear regressions for predictors of verbal memory performances.

Dependent Variable	Predictor	Beta	t	p
Immediate Verbal Recall [a]	CPN	-.433	-3.54	.001
	low BDNF	-.329	-2.69	.010
Delayed Verbal Recall [b]	CPN	-.371	-2.87	.006
	DEPRESSION	-.359	-2.78	.008
Memory Retention [c]	PTSD	-.302	-2.17	.035

Note: Variables included in multiple regression (stepwise): Age (yrs); Education (yrs); MDD, Major Depressive Disorder, Recurrent (yes = 1, no = 0, SCID-I), DEPRESSION, depression severity (BDI); PTSD, PTSD symptoms severity (PCL-C); low BDNF, serum BDNF $\leq$ 2.343 pg/mL (yes = 1, no = 0), CPN, childhood physical neglect (CTQ). [a] Variables entered (F $\leq$ .05): CPN and Low BDNF. R = 0.62, adj R2 = 0.36; F (2,46) = 14.60, p < .001; [b] Variables entered (F $\leq$ .05): CPN and DEPRESSION. R = 0.62, adj R2 = 0.35; F (2,46) = 14.37, p = .008; [c] Variable entered (F $\leq$ .05): PTSD. R = 0.30, adj R2 = 0.07; F (2,46) = 4.71, p = .035.

SEÇÃO EMPÍRICA II

Gist Memory Impairment in Depressed Women with Childhood Emotional Neglect Reduces False Recognition

ABSTRACT

Based on neurodevelopmental findings associated with childhood neglect and the developmental aspect of recognition memory, the aim of the present study is to evaluate whether women with Major Depression Disorder (MDD) and childhood emotional neglect (CEN) are less susceptible to false recognition. During a false memory experiment with semantically related words, participants with CEN tend to decrease false recognition of critical lures. In addition, they were significantly impaired in their ability to utilize gist information available from semantically related categories of verbal presented words. The CEN group was not significantly impaired in terms of recognition of targets and novel lures, performing similarly to control and depressed patients without CEN. All these effects were found after important variables had been controlled. Taking in consideration some limitations of the study, the data provide further evidence that the reduction in false recognition in CEN is specific to gist memory impairment and could be related with semantic representations structures and functions. Particularly we suggest that the early emotional deprivation could be impact the neurocognitive development of semantic associations.

Keywords

Memory, Recognition, Gist Memory, Childhood Neglect, Depression, False Memory

GIST MEMORY IMPAIRMENT IN DEPRESSED WOMEN WITH CHILDHOOD EMOTIONAL NEGLECT REDUCES FALSE RECOGNITION

Introduction

It is suggested that childhood neglect could be related to a frontal-limbic dysfunction (De Bellis, 2005) and, particularly, emotional neglect is associated with poorer emotional and physical functioning (Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003). Prospective studies have shown that child neglect is associated with a significant delayed in cognitive development (Strathearn, Gray, O'Callaghan, & Wood, 2001), and lower IQ and academic achievement (Perez & Widom, 1994). Recently it was raised the hypothesis of an abnormal brain connectivity related with childhood neglect (Eluvathingal et al., 2006; Teicher et al., 2004), however the clinical and neuropsychological impact of these findings are still unclear. Some authors have suggested that memory deficits could be related to such neuropsychological alterations (Bremner et al., 2003). Besides that, little is known about the prolonged effects of maltreatment on basic memory processes (Howe, Cicchetti, Toth, & Cerrito, 2004), and even less about childhood neglect.

Since the majority of studies about childhood experiences are based on self-report interviews which are susceptible to memory bias, some authors started to concern if trauma victims are more susceptible to memory distortions (Zoellner, Foa, Brigidi, & Przeworski, 2000). The mistaken belief that one has previously encountered a novel item is known as false recognition. Roediger-McDermott's (DRM) (1995) procedure has been extensively used to investigate false recognition and its results have been indicating that human memories are naturally vulnerable to distortions (Schacter, Chiao, & Mitchell, 2003). The DRM paradigm has also been used to examine false recognition in adults who reported childhood sexual abuse, but

the specific impact of childhood neglect on memory recognition is still unknown. In general, theses studies found that women who reported childhood sexual abuse and have PTSD (Bremner et al., 2000) or women who had recovered memories of childhood abuse (Clancy et al., 2000) were more prone to false recognition and these is possibly related to a fantasy proneness or PTSD symptoms (Geraerts et al., 2005). In addition, this effect could be true either for neutral and trauma-related word lists (Geraerts et al., 2005).

Interesting none of the previous studies evaluated the diagnostic of Major Depression Disorder (MDD) in their samples. Bremner, Shobe, and Kihlstrom (2000) assessed PTSD but did not mention MDD in their sample, despite the fact that the abused PTSD women group showed significantly higher scores in Beck Depression Inventory (BDI) than the other comparative groups. Clancy, Schacter, McNally and Pitman (2000) found that their groups differed not only in their reports of childhood sexual abuse, but also on measures of PTSD and depression severity (BDI). Their results indicated that there was no relationship between false recognition and PTSD or depression severity, but they did not evaluate if their groups could differ in terms of current or past psychopathology. In addition, none clinical evaluation was done in Geraerts et al study (2005) to investigate depression or even PTSD. Considering: (1) the role of childhood maltreatment in PTSD and its impact on the brain regions related to memory processes (McNally, 2003); (2) the high rates of comorbidity between PTSD and MDD (>45%) (Franklin & Zimmerman, 2001); and (3) childhood abuse and neglect association with an increased risk for MDD in prospective studies (odds ratio: 1.51, $p< .05$) (Widom et al., 2007), MDD should be considered at least as a confoundable variable in the investigation of childhood maltreatment and memory performance in adults since depression has been related to memory deficits (Campbell & Macqueen, 2004).

On the other hand, developmental studies with DRM have shown that when young children study DRM lists, they do not spontaneously form the interconnected meanings that drive the memory illusion in adults (Brainerd, Forrest, Karibian, & Reyna, 2006). Thus increasing vulnerability to false memory with age is a developmental expected finding. Fuzzy Trace Theory (FTT) posits that participants in a memory experiment would have difficulty to recollect distinctive characteristics of specific studied items (verbatim memory) and instead would have a trend to respond to memory tests on the basis of general similarities between the studied and related items (gist memory) (Brainerd & Reyna, 2001).

It is argued that the DRM paradigm is ineffective in producing false memory with young children because they fail to notice the semantic relatedness between lures and studied items because they are less able in creating gist traces of the study lists (Brainerd et al., 2006). These findings suggest that gist memory processes have a protracted development in comparison with verbatim memory.

Specifically when maltreated and non-maltreated low social economic status children were compared using DRM, both true and false memories tended to increase with age in all of the samples, and regardless of whether recall or recognition measures were being used, maltreated children were just as susceptible to the false memory illusion as non-maltreated children (Howe et al., 2004). Thus, based on neurodevelopmental findings associated with childhood neglect (abnormal brain connectivity) and the developmental component of the effects in the DRM paradigm (increasing false memory with age), the present study tested the following hypothesizes: (1) If there is some relationship between susceptibility to memory distortion and childhood neglect, it may not become observable until adulthood; (2) Adults who report childhood neglect will exhibit reduced gist processing as a result of some degree of damage in

semantic association areas; (3) This functional or structural damage will result in a decrease instead of an increase of the false memory effect in the DRM paradigm.

Method

Participants

Sixty females from a low social status, between the ages of 22 and 55 years, who were outpatients of a depression disorder treatment program of a public general hospital in Porto Alegre (southern Brazil) were interviewed using the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to confirm the diagnosis of Recurrent MDD. All patients had been treated with the same dosage of antidepressants for at least for 3 months. Social status was characterized using the Hollingshead Index of Social Position to generate a social status index (SSI) (Hollingshead, 1958). Childhood maltreatment history was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Grassi-Oliveira, Stein, & Pezzi, 2006) that delivers five scores - sexual, physical, and emotional abuse, and emotional and physical neglect. Childhood emotional neglect (CEN) consists of the failure of caretakers to provide basic emotional and psychological needs, such as love, motivation, and support to the child. History of CEN was considered positive if the CEN score on the CTQ was classified as moderate to extreme (percentile 90) according to the original manual (Bernstein & Fink, 1998). Participants who presented with a past or current Axis I comorbidity other than Anxiety Disorders (due to the possible association with childhood maltreatment) or a severe or unstable clinical illness were excluded.

Thus, eighteen outpatients with recurrent unipolar depression without CEN (EN-) and 19 outpatients with recurrent unipolar depression with CEN (EN+) were enrolled in the study. The control group included 14 healthy female matched for age, education, and SES with depression

groups. The control participants did not have any past or current Axis I disorders (SCID-I), any clinical illness, or any history of childhood maltreatment (CTQ). The current research is part of a cross-sectional study approved by the Pontifical Catholic University of Rio Grande do Sul Ethics Committee. Written informed consent was obtained from all participants.

Materials

From the Portuguese version of the DRM (Stein, Feix and Rohenkohl, 2006) we selected five negative and five neutral emotional valence lists (negative: *guilt, spider, fear, black, hurt;* neutral: *cold, flag, sweet, pen, high*) that are controlled by arousal, concreteness, backward and forward associative strength (Santos, Silveira, & Stein, 2007). Each list from the Portuguese version of the DRM is composed by 15 semantically associated words, sorted from stronger to weaker semantic relatedness to a specific critical lure (e.g., DARK, DEATH, LONELINESS, ANGUISH, PANIC, SCARE, UNKNOWN, SCARY, VIOLENCE, PHOBIA, SHOUT, TERROR, TRAUMA, TREMBLE, and FRIGHTEN are all semantic associates of FEAR). We use 10 lists of 12 items by excluding the last three items from each original list. All lists were recorded consecutively but in a random sequence on an audio CD by a female professional speaker with an interval of 2 seconds between each word. Thus, the study material was composed of 120 words.

The recognition test was composed of 60 items. These items were divided into three categories: 30 studied items or targets (randomly selected from positions 2 to 8 of each study list), 10 non-presented critical lures (one for each list), and 20 novel unrelated lures (items with no semantic relatedness to the studied lists and that were not presented during the study phase). The position of words in the recognition test was randomly assigned, and the test list was audio recorded on CD by the same professional speaker.

Procedure

Participants were tested individually in an appropriate room in the hospital outpatient clinic. During the study phase, participants were instructed to pay attention and listen carefully to the audio presentation of several words for a subsequent memory test. After the presentation of the study list, a buffer activity was performed. This activity consisted of a 3-minute long spatial search game (Where's Waldo?), the purpose of which is to locate a target character (Waldo) in crowd scenes (Handford, 2007). An old/new recognition test followed the buffer activity. Participants were instructed to pay attention to the test list and told that this list would include some of the words that they studied (OLD) and some new words (NEW). They were instructed to answer OLD or NEW to each word presented to indicate whether or not they remembered hearing it during the study phase.

After the DRM memory test, participants were instructed to complete the self-report questionnaires: PTSD Checklist-Civilian Version (PCL-C) (Berger, Mendlowicz, & Figueira 2004) and Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Gorenstein & Andrade, 1996).

Results

The demographic and clinical characteristics of samples shown in Table 1 indicate the homogeneity of all groups regarding age, education, and SES. In addition, both depression groups were counterbalanced for severity of depression, PTSD symptoms, and other forms of maltreatment except for emotional neglect.

The proportions of OLD responses in the recognition test are shown in Table 2. Overall, the EN+ group recognized fewer critical lures (.54) than the EN- group (.72) and the healthy

group (.75). This pattern was observed in both negative and neutral lists. There was no reliable difference between the groups regarding target recognition (hit rates). Planned comparisons indicated that overall hit rates for negative lists were higher than for neutral lists (.70 versus .51), $F(1, 48) = 23.49$, $p < .001$, and false alarms to negative critical lures were higher than those to neutral lures (.71 versus .61), $F(1, 48) = 7.81$, $p = .007$. However, there was no interaction between the emotional valence and groups, $F(2,48) = .45$, n.s.

Signal detection analyses were used to test whether the decrease in false recognition in the EN+ group might be attributable to reduced verbatim memory or to reduced gist memory. Estimates of sensitivity (A') [1] and response bias (B'') [2] were calculated for both verbatim and gist memory. Values of A' can vary between 0 and 1, with the higher values indicating greater sensitivity to detect verbatim or gist traces. Values of B'' can vary between -1 e +1; a zero value indicates a neutral responding criterion, negative values indicate a liberal responding criterion, and positive values indicate a conservative criterion.

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[1] *A'* is a discrimination index - the nonparametric counterpart of *d'* (Snodgrass & Corwin, 1988).

Verbatim Memory: depending on the relationship between hit (H) and false alarm (FA) rates, it is computed from a pair of H/FA rates using one of two different formulae:

$$\text{For } H \geq FA: \quad A' = .5 + [(H - FA)(1 + H - FA)] / [4H(1 - FA)]$$
$$\text{For } FA > H: \quad A' = .5 + [(FA - H)(1 + FA - H)] / [4FA(1 - H)]$$

Gist Memory: It is computed from a pair of FA / novel non-related lure (NR) rates using the formula:

$$A' = .5 + [(FA - NR)(1 + FA - NR)] / [4FA(1 - NR)]$$

[2] *B''* is a nonparametric bias index (Snodgrass & Corwin, 1988).

Verbatim Memory: As for A', there are two computing formulas:

$$\text{For } H \geq FA: \quad B'' = [H(1 - H) - FA(1 - FA)] / [H(1 - H) + FA(1 - FA)]$$
$$\text{For } FA > H: \quad B'' = [FA(1 - FA) - H(1 - H)] / [FA(1 - FA) + H(1 - H)]$$

Gist Memory: it is computed using the formula:

$$B'' = [FA(1 - FA) - NR(1 - NR)] / [FA(1 - FA) + NR(1 - NR)]$$

As suggested by Simons et al. (2005), verbatim memory parameters were computed by comparing targets and critical lure items, and gist memory parameters were computed by comparing responses to critical lures and novel non-related items. Sensitivity and bias measures for verbatim and gist memory are shown in Figure 1. There was a statistically significant difference in sensitivity between groups in terms of verbatim memory, as the EN+ group showed a higher sensitivity to detect verbatim traces than the other groups (A'_v : .54, EN+; .40, EN-; .40, Control) $F(2,48) = 4.47$, $p = .017$. In addition, there was a significant difference between groups in terms of gist memory sensitivity, with the EN+ group showing lower sensitivity to detect gist traces than others (A'_g : .84, EN+; .89, EN-; .91, Control), $F(2,48) = 8.47$, p = .001. Although memory performance in all groups had been considerably affected by memory distortion in the DRM paradigm (low A' for all groups), the higher sensitivity (A'_v) values of the EN+ group might indicate a gist memory impairment, which explains the better discrimination between targets and critical lures than the comparison groups (Tukey HSD, $p < .05$). In accordance with the prediction that EN+ group would be less affected by the semantic association effect, the EN+ participants were significantly less likely than EN- and control participants to use gist memory in their recognition judgments (Tukey HSD, p < .001).

In terms of response bias, there was a significant difference between groups in terms of verbatim memory (B''_v : -.03, EN+; -.23, EN-; -.33, Control), $F(2,48) = 5.53$, p = .007. The EN+ group used a more lenient response criterion than did the other groups (Tukey HSD, $p < .05$). On the other hand, in terms of gist memory, all groups used a similar, relatively conservative criterion (B''_g : .57, EN+; .41, EN-; .51, Control), $F(2,48) = 1.07$, n.s.

Discussion

Independent of the presence of depression, patients with CEN were less able to produce false-memory effects in the DRM paradigm, with neglected individuals falsely recognizing fewer critical lures than the comparison groups. In addition, patients with CEN were significantly impaired in their ability to use gist information available from semantically related categories of verbally presented words, supporting the main hypothesis of the present study. The EN+ group did not show any impairment in terms of recognition of targets and novel lures, performing similarly to healthy participants and the EN- group on such tests. All of these effects are consistent, even after important variables such as gender, depression severity, PTSD symptom severity, age, education, SES, and severity of other forms of maltreatment had been controlled for.

The present results are very similar to those reported in patients with semantic dementia, who have deficits in semantic memory associated mainly with temporal lobe atrophy (Schroeter, Raczka, Neumann, & von Cramon, 2007). These patients showed an impairment in false recognition of semantically related categories of visual objects, and the impairment appeared to be relatively specific to semantic aspects of gist (Simons et al., 2005). It was suggested that deficits in semantic dementia patients on verbal tasks could reflect progressive deterioration of an amodal integrative semantic memory system involving the left rostral temporal lobes (Adlam et al., 2006). Although the present study did not examine the association between memory performance and structural and functional brain assessments, considering the semantic dementia studies, the present finding of gist memory impairment in EN+ participants suggests a possible temporal lobe dysfunction. Moreover, some authors (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Schacter & Slotnick, 2004) have reported that false recognition of related lures is associated with medial temporal lobe activation that resembles that seen during true recognition.

The important role of early environmental factors in neurodevelopment is linked to a variety of brain structures (Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007), but in particular, the temporal lobe seems to be more susceptible to epigenetic influences (Eckert et al., 2002). In addition, there is some evidence for the impairment of gist memory in individuals with schizophrenia (Lee, Iao, & Lin, 2007), a well established temporal lobe dysfunction-related psychopathology (Honea, Crow, Passingham, & Mackay, 2005). Specifically, it was suggested that schizophrenics have impairment in the storage of semantic knowledge rather than in the access of this knowledge; thus, semantic deficiency would occur in the idiosyncratic organization of semantic knowledge and not in degraded semantic representations. In light of these findings, we speculate that CEN could be an important disruptive factor to the development of brain semantic memory-related structures, specifically temporal lobe development.

Both semantic dementia and schizophrenia studies have shown that target recognition is also impaired. Thus, one possible explanation for the effect of gist memory impairment is that it could be a byproduct of an impaired veridical memory. In contrast, a study using implicit and explicit memory tasks in amnesia patients reported that the use of an implicit memory task eliminated the need for strategic processes associated with intentional retrieval but did not lessen or eliminate the impairment in gist memory in the amnesic group (Verfaellie, Page, Orlando, & Schacter, 2005). It was suggested that the impairment in veridical memory is limited to tasks requiring explicit retrieval. In addition, it was demonstrated that gist memory is impaired in both implicit and explicit memory and that a deficit in the encoding of gist information is the likely cause of amnesics' impairment (Verfaellie, Page, Orlando, & Schacter, 2005).

The corpus callosum size has a close relationship with higher-order "associative" functions such as interhemispheric support of bilateral language representation, interhemispheric

inhibitory control, and interhemispheric influences that contribute to hemispheric differences in arousal, and which is are consistent with findings on the fiber composition of the human corpus callosum (Clarke & Zaidel, 1994). Considering the interesting findings of a 15 − 18% reduced size of the corpus callosum in adults with self-reported childhood neglect (Teicher et al., 2004) in comparison with control participants, our results support the idea of "associative function impairment".

Fuzzy Trace Theory proposes that people encode multiple representations in parallel and that these representations vary in terms of their level of precision (Brainerd & Reyna, 2001). Encoding of verbatim information involves processing of the specific features of study items, whereas encoding of gist information involves processing of commonalities among study items. On memory tests, retrieval of gist traces can result in correct acceptance of targets, but it can also result in false recognition of semantically related lures. The ability to notice meaningful relations among lists of items rather than merely accessing the semantic features of individual list items is called global gist (Michael Lampinen, Leding, Reed, & Odegard, 2006). Global gist processing in the DRM paradigm requires participants to be able to process the relationships between the list items.

Considering the developmental aspect of gist memory, FTT suggests that young children show reduced storage and retrieval of relevant gist trace abilities, and as a result, they are unable to produce the same false memory rates as adults. On the other hand, with the developmental improvements of these abilities, false memory effects increase with increasing age (Brainerd & Reyna, 2001). Specifically, false recognition of critical lures increased with age between early childhood and early adolescence. Taken together, our results suggest a disruptive development in gist memory in CEN. This conclusion makes sense because emotional neglect is a chronic,

continuous, pervasive, silent, and very early adverse experience (De Bellis, 2005) that could have a drastic impact during all sensitive periods of gist development – from early childhood to early adolescence.

False memory is determined by the mix of verbatim and gist retrieval (Brainerd & Reyna, 2001)(Brainerd, Stein, Silveira, Rohenkohl, & Reyna, in press). In the present experiment, the EN+ group showed a higher sensitivity to verbatim information and a reduced sensitivity to gist memory. At first, one might conclude that "memory performance" was better in EN+ participants, but considering the FTT principle of dual-opponent processes in false memory (Brainerd & Reyna, 2001) and that all groups showed similar proportions of correct recognition, this conclusion is precocious and equivocal. Verbatim and gist retrieval have opposite effects - reducing the first will increase the second - and this is an expected effect in DRM paradigm. In addition, gist memory supports false memory, but verbatim memory suppresses it. The CEN group had almost the same proportion of true memory as the comparison groups; thus, the higher sensitivity to verbatim memory in EN+ participants is due their lower proportion of false recognition and is just a reflex of the dual-opponent processes. As occurred in semantic dementia patients in the standard old/new recognition test, an impaired gist memory in fact protected EN+ participants from making illusory memory errors.

Previous studies have indicated that there is no improvement in overall accuracy between early childhood and young adulthood, because developmental trend …..blabla there is increases in true recognition are also accompanied by increases in false recognition (Brainerd et al., 2002). Our results differ, in that we found a significant difference in A' verbatim and A' gist values between groups, suggesting a specific gist memory impairment in EN+ participants.

Although EN+ participants showed a higher sensitivity to verbatim memory, B" analyses indicated that this effect could be related to the adoption of a more conservative response criterion by these participants. On the other hand, EN+ participants showed a lower sensitivity to gist memory, but B" analyses did not indicate a bias effect, which means that the reduction in false recognition seems to be related just to a gist memory impairment and not judgment and response to decision errors.

In conclusion, the present study provides further evidence that the reduction in false recognition in EN+ individuals is specific to gist memory impairment and could be related to the structures and functions of semantic representations. Specifically, we suggest that the early emotional deprivation could have an impact on the neurocognitive development of semantic associations. It is alarming that an early adverse experience could be associated with such a severe neurological disorder as semantic dementia. As far we know, this was the first study that investigated recognition memory in depressed females with a history of childhood neglect. More studies are necessary to replicate these findings in a powered design.

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Table 1
Demographic and Clinical Characteristics of Samples

Characteristic	EN+ (n=19)		EN- (n=18)		Healthy Participants (n=14)		F	p
	M	SD±	M	SD±	M	SD±		
Age (years)	39.2	9.8	41.3	7.7	35.9	6.1	1.72	n.s.
Education (years)	8.0	3.8	8.7	3.8	8.8	3.1	.29	n.s.
SES	4.5	.50	4.5	.50	4.4	.50		n.s.
CTQ								
Sexual Abuse	1.2	5.7	8.1	6.0	6.6	3.3	1.87	n.s.
Emotional Abuse	13.3_a	4.7	12.5	5.0	9.0_b	3.2	3.92	.02
Physical Abuse	9.2	4.0	8.5	4.6	7.0	2.41	1.29	n.s.
Physical Neglect	11.6_a	4.4	9.6	4.4	8.0_b	2.6	3.85	.02
Emotional Neglect	18.5_a	3.3	1.1_b	3.0	1.5_b	3.7	36.27	<.001
PCL-C	56.2_a	12.2	54.1_a	14.5	22.9_b	5.3	38.25	<.001
BDI	29.6_a	9.8	25.3_a	1.5	4.5_b	4.0	34.49	<.001

Note: EN+ = Depression with Childhood Emotional Neglect; EN- = Depression without Childhood Emotional Neglect; SES = Socioeconomic Status; CTQ = Childhood Trauma Questionnaire; PCL-C = PTSD Checklist-Civilian Version; BDI = Beck Depression Inventory. Different subscripts across rows differ at $p < .05$ by Tukey HSD test. All $df = 2, 48$.

Table 2

Proportion of True and False Recognition Data for Each group by List Valence

List Valence	EN + (n=19)		EN - (n=18)		Healthy Participants (n=14)		F	*p*
	M	SD±	M	SD±	M	SD±		
Total								
Critical lure	$.54_a$	.19	$.72_b$	.17	$.75_b$	.16	6.78	.00
Target	.60	.13	.64	.14	.67	.19	.86	n.s.
Novel lure	.06	.05	.11	.09	.05	.07	2.74	n.s.
Neutral								
Critical lure	$.49_a$	.22	$.68_b$	.20	$.70_b$	.24	4.67	.01
Target	.52	.19	.58	.18	.62	.25	1.00	n.s.
Negative								
Critical lure	$.60_a$	.21	$.76_b$	.19	$.80_b$	.20	4.75	.01
Target	.69	.13	.70	.15	.72	.17	.24	n.s.

Note: EN+ = Depression with Childhood Emotional Neglect; EN- = Depression without Childhood Emotional Neglect. M = Mean. SD = Standard deviation. Different subscripts across rows differ at *p* < .01 by Tukey HSD test. All *df* = 2, 48.

Figure Legends

Figure 1: *Measures of Verbatim Memory and Gist Memory.* EN+ = Depression with Childhood Emotional Neglect. EN- = Depression without Childhood Emotional Neglect. Control = Healthy Participants. * *p* < .05 (Tukey HSD). ** *p* < .01 (Tukey HSD). All *df* = 2, 48.

Figure 1

Verbatim Memory

Gist Memory

Sensitivity (*A'*)   Bias (*B''*)
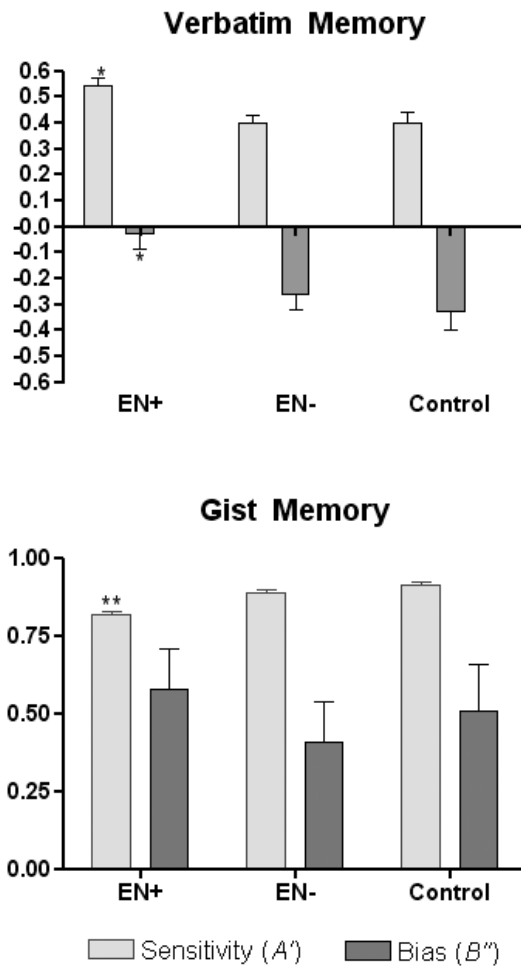
CONCLUSÕES E CONSIDERAÇÕES FINAIS

A exposição precoce ao estresse na infância induziria modificações neurodesenvolvimentais ativadas pela natureza da experiência durante estágios críticos e sensíveis do desenvolvimento. Essas mudanças seriam na realidade respostas adaptativas frente a tais estressores na tentativa de habituar os indivíduos a elevados níveis de estresse (privação) durante esses períodos (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006). De fato, indivíduos adultos saudáveis expostos à punição corporal na infância, de caráter disciplinar e não abusivo, mostram uma resposta frente a um estresse social bem mais discreta que indivíduos saudáveis que não relatam tal prática disciplinar durante a infância (Grassi-Oliveira et al., 2007). Aqueles que sofreram punições corporais na infância parecem já estar mais acostumados a elevações na resposta frente a um aumento do nível de estresse, dificultando a resposta adaptativa ao estresse o que cronicamente inviabilizaria a resposta normal de luta e fuga.

O interesse na relação entre exposição a eventos traumáticos e déficits no funcionamento da memória não é novo (Buckley, Blanchard, & Neill, 2000; Thygesen, Hermann, & Willanger, 1970). Diversos estudos têm demonstrado prejuízos na memória declarativa em pacientes com TEPT (Bremner & Narayan, 1998; Bremner et al., 2004; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib et al., 2003; Brewin, 2001; Elzinga & Bremner, 2002; Golier, Yehuda, Lupien, & Harvey, 2003).

Avaliações de memória através do *Weschsler Memory Scale*, componentes visuais e verbais do *Selective Reminding Test*, *Auditory Verbal Learning Test*,

California Verbal New Learning Test, *Rivermead Behavioral Memory Test*, bem como resultados do paradigma de *Deese* modificado por *Roediger e McDermott* (DRM) (Roediger & McDermott, 1995) – têm indicado que o prejuízo mnemônico estaria principalmente associado a conteúdos verbais, principalmente em relação à memória verbal (Bremner et al., 2004). Todavia a maior parte desses estudos tem sido realizada com pacientes com TEPT, onde o déficit na memória declarativa verbal está especificamente associado com tal transtorno, não consistindo em um efeito específico secundário à exposição traumática (Jenkins, Langlais, Delis, & Cohen, 1998).

Um trabalho (Bremner et al., 2004) realizado com 43 mulheres, cujas participantes foram alocadas em três grupos experimentais: (1) mulheres com TEPT e com história de abuso sexual na infância, (2) mulheres com TEPT e sem história de abuso sexual na infância e (3) mulheres sem TEPT e sem abuso sexual na infância, teve por objetivo comparar esses grupos de acordo com aspectos neuropsicológicos. Essas avaliações consistiram nos testes aritmético, vocabulário, arranjos de figuras e blocos do *Weschler Adult Intelligence Scale – Revised* (WAIS-R), no componente de memória lógica verbal (recordação livre de duas narrativas) e de memória visual (reprodução de um desenho após 6 segundos) do *Weschsler Memory Scale– Revised* (WMS), realizados imediatamente e após 30 minutos. Da mesma maneira foram avaliados os sintomas de TEPT (*Clinician Administered PTSD Scale* – CAPS e *Mississipi Scale*), depressão (Escala de Depressão de Hamilton), sintomas dissociativos (*Clinician Administered Dissociative States Scale* – CADSS) e maus-tratos na infância (*Early Trauma Inventory* – ETI). Os autores identificaram que as mulheres com TEPT e abuso apresentaram baixo percentual de retenção no subteste verbal do WMS em relação aos outros grupos. Não identificaram diferenças em relação ao QI e performance no teste de memória

visual. Esse déficit foi correlacionado positivamente com o aumento de sintomas de TEPT (CAPS) e com a severidade do abuso na infância (ETI). Por fim, os autores sugeriram que a memória verbal declarativa acessada envolve um circuito neural que conecta o hipocampo ao lobo pré-frontal, assim, hipoteticamente uma disfunção pré-frontal poderia estar envolvida aliada a um déficit hipocampal. O primeiro estudo da sessão empírica não observou alteração na retenção de material verbal, porém identificou prejuízos na recordação tardia e imediata em pacientes deprimidas que reportavam negligência física na infância. Todavia, chama-se a atenção para a cuidadosa seleção das amostras e controle das variáveis potencialmente confundidoras no presente estudo. Enquanto no estudo de Bremner et al. os sintomas de TEPT foram os principais responsáveis pelo prejuízo na retenção da memória verbal, no presente experimento a severidade da negligência física na infância foi relacionada negativamente com o desempenho na recordação imediata e posterior. Além disso, os dados indicam que especificamente o prejuízo na recordação imediata estaria relacionado com uma baixa concentração de BDNF plasmático. Assim pela primeira vez, estabelece-se uma associação entre estresse precoce e neurotrofinas com desempenho neuropsicológico em humanos, tal qual foi sugerido no modelo da Traumatologia Desenvolvimental explicado em detalhes na sessão teórica.

Considerando o possível impacto negativo nas regiões pré-frontais e mediais associadas com estresse precoce e o fato dessas regiões assumirem um papel crucial na gênese das distorções de memória (Schacter & Slotnick, 2004), é interessante reportar dois estudos que utilizam o DRM para investigar a presença de falsas memórias em adultos com maus-tratos na infância. Um desses estudos (Bremner et al., 2000) teve o objetivo de avaliar a capacidade de recordação e reconhecimento e também a produção

de falsas memórias, em mulheres com história de abuso sexual na infância e TEPT. Tal pesquisa identificou um aumento significativo na produção de falsos reconhecimentos e prejuízo na capacidade de recordação. Além disso, a capacidade de reconhecimento das palavras estudadas foi significativamente menor nas mulheres com sintomas de TEPT, e mais prejudicada conforme a severidade da sintomatologia. Da mesma forma, outro estudo utilizando o DRM comparou quatro grupos: (1) *recovered* (mulheres que lembraram quando adultas que foram abusadas na infância); (2) *repressed* (mulheres que achavam que tinham sido abusadas na infância, mas que não se lembravam de nada); (3) *continuous* (mulheres que sempre tiveram memória de terem sido abusadas quando criança) e (4) controles (mulheres sem nenhuma lembrança de abuso e nem achavam que isso ocorreu) (Clancy et al., 2000). Tal estudo observou que o grupo *recovered* foi mais suscetível que os outros grupos a exibirem falsos reconhecimentos de associados semânticos. Todavia, antes de qualquer conclusão é importante salientar que o grupo *recovered* diferia estatisticamente dos outros grupos em relação aos sintomas de TEPT e depressão o que deve ser encarado como um viés de confusão importante. Por outro lado, os três grupos com história de abuso mostraram índices de falsos reconhecimentos superiores aos do grupo controle.

Essas diferenças no DRM parecem ser específicas para a vida adulta, já que em crianças maltratadas a produção de falsas memórias não é diferente que a observada em controles saudáveis (Howe, Cicchetti, Toth, & Cerrito, 2004). Esse achado é consistente com as hipóteses desenvolvimentais nas quais os efeitos do trauma precoce seriam percebidos somente em etapas evolutivas posteriores (Andersen, 2003; De Bellis, 2001; De Bellis, Baum et al., 1999; De Bellis, Keshavan et al., 1999; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Uma das explicações possíveis seria a de que

indivíduos vítimas de eventos traumáticos desenvolveriam déficits gerais nos processos de monitoramento da fonte (lembrança de como, quando e onde a memória foi adquirida) fazendo com que a memória de eventos percebidos pudesse ser confundida com a memória de eventos imaginados, o que levaria a uma suscetibilidade à produção de falsas memórias (Clancy et al., 2000; Zoellner, Foa, Brigidi, & Przeworski, 2000). O monitoramento da fonte envolve os processos de julgamento e tomada de decisão, processos relacionados ao lobo pré-frontal (Schacter & Slotnick, 2004). Assim, qualquer alteração no neurodesenvolvimento dessa estrutura poderia estar relacionada com um aumento de falsas memórias.

Por outro lado os resultados do segundo experimento não replicaram tais observações e não sustentam a hipótese de problemas com o monitoramento da fonte uma vez que não se observou aumento nos índices de falsas memórias além de ter sido utilizada a mesma fonte (voz da locutora profissional) no teste de reconhecimento. As participantes que sofreram negligência emocional na infância mostraram uma redução na taxa de falsas memórias, especificamente em virtude de um prejuízo na utilização da informação de essência (*gist memory*) o que corrobora com outro modelo teórico de falsas memórias – Teoria do Traço Difuso (Brainerd & Reyna, 2001). Nesse sentido, danos em estruturas têmporo-mediais e associativas poderiam estar associados com a negligência infantil o que condiz com a literatura de neuroimagem nessa população (Teicher et al., 2004).

Em termos práticos, os déficits na memória poderiam contribuir de forma significativa para déficits mais globais em termos cognitivos, implicando em funções importantes como inteligência e capacidade de *coping* (Lysaker, Bryson, Marks, Greig, & Bell, 2004).

Em relação ao prejuízo da inteligência, até bem pouco tempo atrás a maioria das pesquisas existentes não conseguia determinar qual seria a parcela genética e qual a ambiental no desenvolvimento intelectual, o que poderia confundir possíveis associações entre vitimização infantil e prejuízo intelectual (Koenen, Moffitt, Caspi, Taylor, & Purcell, 2003). Todavia, com o surgimento de um modelo de interação gene-ambiente como proposta explicativa para uma variedade de transtornos psiquiátricos e desfechos psicológicos adversos, a busca por endofenótipos que isoladamente contribuiriam para a manifestação de tais características perde força e razão (Caspi & Moffitt, 2006). Nesse sentido cabe ressaltar um importante estudo realizado com gêmeos que testou se a violência doméstica, independente de predisposição genética, teria um impacto na capacidade intelectual da criança. O QI de 1.116 pares de gêmeos monozigóticos e dizigóticos, de aproximadamente cinco anos de idade, foram avaliados na Inglaterra através do *Wechsler Preschool and Primary Scale of Intelligence - Revised*. Paralelamente as mães eram questionadas sobre a existência de violência familiar nos últimos cinco anos. Através de modelos de regressão, os autores verificaram que a violência doméstica foi isoladamente associada com a redução do QI, numa relação dose-resposta. As crianças expostas a altos níveis de violência doméstica evidenciaram uma diminuição de oito pontos nos escores de QI, em comparação àquelas não expostas. Da mesma forma, modelos de equações estruturais mostraram que a violência doméstica foi responsável por 4% de variação no QI da criança, independente de influências genéticas latentes (Koenen et al., 2003).

O *coping* nada mais é do que a capacidade de julgamento no qual a pessoa analisa se as demandas ambientais ou internas (medo, ansiedade) são maiores do que os esforços pessoais para modular a experiência de estresse. Ele está relacionado com o

eixo fronto-límbico uma vez que é baseado na resolução de problemas e na regulação emocional (Skinner & Zimmer-Gembeck, 2007). Assim, o c*oping* centrado no problema diz respeito a todas as tentativas do indivíduo em administrar ou modificar o problema, e o *coping* centrado na emoção descreve a tentativa de substituir ou regular o impacto emocional do estresse no indivíduo, derivando principalmente de processos defensivos, fazendo com que a pessoa evite confrontar, de forma realista, a ameaça. Imagina-se que uma criança privada de ajuda afetiva e de cuidados básicos desde muito cedo, e que só irá maturar seu neurodesenvolvimento das estruturas frontais ao final da adolescência, terá de lançar mão de muitas de suas habilidades de *coping* muito precocemente. Com o acúmulo do nível de estresse esse sistema iria ficando cada vez mais sobrecarregado até que não responderia mais e a partir desse ponto poderia entrar em colapso. As estratégias de *coping* que inicialmente dariam conta da demanda de estresse com o tempo passam custar muito caro para o organismo em desenvolvimento (Figura 2). Dessa maneira, é proposto um modelo de peso alostático no esforço cognitivo para lançar mão das estratégias de *coping* necessárias durante seu desenvolvimento.

Estruturas importantes como as áreas associativas e o lobo temporal teriam um papel importante nas estratégias rudimentares de *coping* (p. ex. distração e fuga) (Compas, 2006), provavelmente as "mais econômicas" para criança (Greenberg, 2006; Skinner & Zimmer-Gembeck, 2007), mas "pagariam o preço" por seu uso excessivo.

Apesar de bastante especulativas as questões levantadas nessa seção consistem em importantes tópicos de futuras pesquisas. O que estaria em jogo seriam as questões desenvolvimentais da memória e sua relação com o desenvolvimento de características de resiliência. O modelo da Traumatologia Desenvolvimental ajudaria a entender essas

relações. A partir de alterações na resposta ao estresse, efeitos deletérios neurodesenvolvimentais emergiriam e seriam traduzidos por déficits neuropsicológicos no adulto.
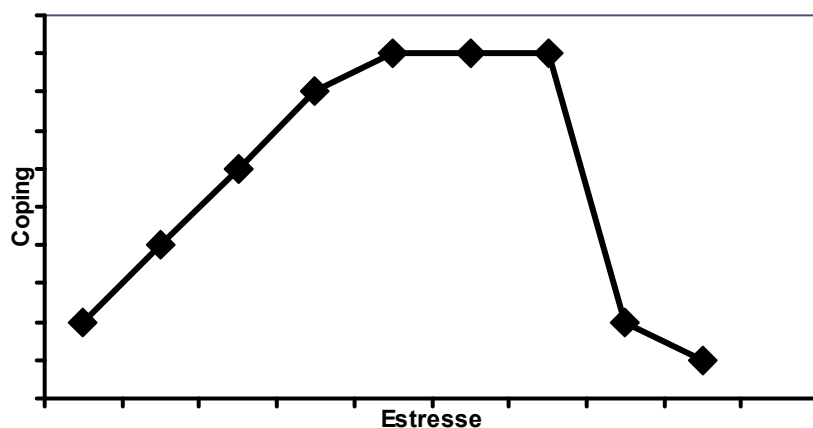

Figura 1. *Modelo de Peso Alostático no Coping*

No âmbito individual, assumindo uma perspectiva desenvolvimental, os maus-tratos precoces assumiriam um papel "tóxico" no desenvolvimento normal da criança, alteraria o estado neuroendócrino, interferiria na aquisição de habilidades (principalmente *coping*), provocaria uma distorção dos esquemas cognitivos pela repetida re-experienciação cognitivo-emocional das memórias traumáticas, e assim, modificaria algumas estruturas cerebrais definitivamente (Bremner et al., 1999). Se considerarmos que o processo desse desenvolvimento está constantemente sendo modificado por influências ambientais, a privação afetiva e física consistiria um exemplo importante dessas influências que estaria presente durante a maturação do cérebro da criança.

Essa maturação neurológica compreende uma etapa de desenvolvimento neuronal, conhecida como neurogênese. Para que esse processo ocorra existem

substâncias químicas responsáveis pela regulação da sobrevivência, diferenciação e manutenção da função dos neurônios no cérebro, denominadas neurotrofinas, particularmente o BDNF. Sua síntese e secreção são reguladas pela atividade neuronal, que é diretamente relacionada aos estímulos ambientais. Essa atividade neurogênica é especialmente aumentada nos dois primeiros anos de vida, onde se observa um crescimento seqüencial, uma extraordinária proliferação e uma superprodução de axônios, dendritos e sinapses nas diferentes regiões do cérebro (Glaser, 2000). Esse processo é geneticamente determinado, contudo algumas das conexões sinápticas formadas, deixam de existir devido à falta de uso e outras passam a ser formadas em decorrência de uma necessidade de sua existência. Esse fenômeno é conhecido como plasticidade e onde o BDNF entra como importante agente plástico. Nesse período o neurodesenvolvimento é particularmente dependente das influências ambientais, pois é o período de maior plasticidade neuronal: as conexões não utilizadas são "podadas" (Andersen, 2003). Por exemplo, se estiverem ausentes estimulações precoces como o toque, conversa e afeto, as conexões sinápticas responsáveis por esses estímulos serão interpretadas como inúteis e eliminadas. No sentido da "poda neuronal" a negligência emocional e física podem ser entendidas como importantes agentes de uma disrupção neurodesenvolvimental e não apenas as formas abusivas de maus-tratos. Os dados do estudo empírico I de BDNF diminuído corroboram em parte com a idéia de que eventos precoces teriam impacto no neurodesenvolvimento através da ação de neurotrofinas.

Em suma, a negligência tem sido negligenciada no estudo de seu potencial "traumático". Pelo menos a presente tese comprovou sua capacidade de afetar o funcionamento mnemônico e sua associação com baixa atividade de BDNF após o controle rigoroso de inúmeras variáveis. A hipótese de que o peso alostático das

respostas adaptativas precoces frente a situações de negligência na infância provocaria seqüelas nas estruturas relacionadas com o funcionamento mnemônico levando assim a prejuízos no desempenho em testes de memória só poderia ser confirmada através de estudos de neuroimagem e de interação gene-ambiente, para que aí sim conclusões mais definitivas fossem realizadas.

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ANEXO I – Termo de Consentimento Livre e Esclarecido

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
DEPARTAMENTO DE PSICOLOGIA

TERMO DE CONCONSENTIMENTO LIVRE E ESCLARECIDO PARA A
PARTICIPAÇÃO EM PESQUISA

Está sendo realizada uma pesquisa na Faculdade de Psicologia da Pontifícia Universidade Católica de Porto Alegre (PUC-RS) sobre traumas ocorridos na infância e sua relação com problemas de memória, imunológicos e hormônios relacionados ao estresse na vida adulta.

A sua participação nesta pesquisa envolverá o fornecimento de informações sobre fatos da história da sua vida e fatos da sua situação atual. Estamos cientes que a natureza de algumas das informações que lhe solicitaremos poderá ser penosa e delicada, e não desejamos provocar maiores sofrimentos ao relembrá-las. Se você, mesmo assim, aceitar participar desta pesquisa, estaremos disponíveis para conversar sobre quaisquer sofrimentos despertados, e encaminhá-la, se necessário, para o atendimento psicológico ou médico adicional que se fizer necessário.

Além disso, será necessário realizar um exame de sangue, onde serão colhidos cerca de 20 ml (uma colher de sopa) de sangue, e cuja picada da agulha não doerá mais do que uma coleta de sangue usual. Suas entrevistas, e as coletas de sangue para os exames, serão realizadas por profissionais da área da saúde, treinados para estes procedimentos. Os objetivos das entrevistas serão os de colher dados da sua história de vida atual e passada, e para que você também preencha alguns questionários sobre seu sono e sintomas de estresse.

Será fornecido um termômetro (aparelho para medir a febre) para você medir sua temperatura oral (na boca) duas vezes por dia e anotar num papel, durante uma semana. O exame de hormônio também é feito pela saliva (cuspe). Para isso, você será ensinada a coletar um pouco de saliva em um algodão e depois guardar no seu congelador, dentro de um tubinho. Essa coleta será feita em um único dia às 8h, 12h e 21 h. Se você tiver telefone residencial ligaremos nesses horários para instruí-la. Caso não possua telefone residencial, emprestaremos a você um telefone celular durante esse

dia para que possamos falar com você nesses horários. Os pesquisadores irão visitar-lhe em casa para recolher o material da saliva, o celular (caso tenha sido emprestado) e o termômetro. Será feito um teste de memória que você terá que escutar uma lista de 120 palavras duas histórias e depois falar num gravador, o que se lembrar.

O objetivo da pesquisa é o de conhecer e compreender melhor como se encontram a memória, o sistema imunológico e os hormônios relacionados ao estresse nas mulheres que foram mal-tratadas na infância.

Seus registros médicos, e as informações que você fornecer serão tratados sempre confidencialmente (mantidos em segredo). Por outro lado, evitando que você seja identificada, os resultados desse estudo poderão vir a serem publicados em revistas científicas, ou serem levados para discussão com outros profissionais da área da saúde.

Como participante desta pesquisa, você poderá desligar-se do estudo em qualquer momento, se assim o desejar, sem nenhum prejuízo de qualquer atendimento que esteja tendo, ou que possa vir a necessitar, do seu posto de saúde. Para seu conhecimento, os responsáveis pela pesquisa são o psiquiatra Rodrigo Grassi de Oliveira (telefone 3061-3506/9129-5992) e a psicóloga Profª. Dra. Lílian Milnitsky Stein (telefone 3320-3633), com os quais você poderá entrar em contato, sempre que desejar maiores esclarecimentos sobre o estudo que estará em andamento.

Declaro que estou ciente das informações acima e que concordo em participar desta pesquisa.

Número do estudo: _____ RG: _____

Nome do participante: _____

Assinatura do Pesquisador Responsável: _____

Assinatura da participante: _____

Porto Alegre, _____ de _____ de 200__.

ANEXO II – Ficha de Identificação

Nome: _____

Telefone: _____

Endereço: _____

Data de Nascimento: _____/_____/_____

Idade: _____ **Sexo:** **(1) Masculino** **(2) Feminino**

Escolaridade: _____

     Anos de Estudo: _____

Renda Familiar (em salários mínimos): _____

Fumante: *(1) Sim*   *(2) Não*

Abuso de Álcool:

    Você alguma vez já pensou que deveria diminuir o uso de bebida?

        (1) Sim   (2) Não

    Você já se incomodou por que alguém criticou seu uso de bebida?

        (1) Sim   (2) Não

    Você alguma vez já se sentiu mal ou culpado com seu uso de bebida?

        (1) Sim   (2) Não

    Você alguma vez já teve que beber logo que acordou para se acalmar ou para se recuperar de uma ressaca?

        (1) Sim   (2) Não

    Já usou ou usa alguma das seguintes **drogas** (VER LISTA)?   (1) Sim (2) Não

        A ultima vez foi: _____

Diagnóstico:

    Eixo I: _____

    Eixo II: _____

    Eixo III: _____

Ano (época) da primeira crise: _____

Sintomas psicóticos no primeiro surto?   *(1)Sim*   *(2)Não*

Já internou em Unidade Psiquiátrica?   *(1)Sim*   *(2)Não*

    Se sim, quantas vezes? _____

    Realizou ECT?   *(1)Sim*   *(2)Não*

Que medicações está usando? _____

ANEXO III – Procedimento de Palavras Associadas

1. **Caneta:** escrever, tinta, azul, papel, útil, caderno, comunicação, esferográfica, estojo, prova

2. **Cadeira:** sentar, mesa, madeira, assento, objeto, comodidade, sala, balanço, móvel, encosto.

3. **Frio:** gelo, inverno, casaco, neve, cobertor, agasalho, blusa, aconchego, temperatura, calor.

4. **Fruta:** saudável, maçã, vitamina, banana, morango, suco, laranja, madura, pêra, nutritiva.

5. **Alto:** baixo, prédio, grande, comprido, edifício, céu, imponente, longe, distante, estatura, difícil, elevado, tamanho.

6. **Culpa:** arrependimento, consciência, remorso, perdão, mal-estar, julgamento, peso, traição, pecado, agonia, crime, responsabilidade, mentira.

7. **Dor:** sofrimento, machucado, perda, choro, incômodo, ferida, remédio, dente, cabeça, saudade, sangue, acidente, analgésico.

8. **Mágoa:** tristeza, sentimento, lágrima, rancor, decepção, desilusão, frustração, esquecida, chata, desgosto, amargura, marca, atitude.

9. **Medo:** escuro, morte, solidão, angústia, pânico, susto, desconhecido, pavor, violência, fobia, grito, terror, trauma.

10. **Raiva:** ódio, ira, briga, fúria, descontrole, maldade, vermelho, cachorro, agressão, momento, nervosismo, irritação, injustiça.

1	Balão	Sim	Não		29	Adição	Sim	Não
2	Violência	Sim	Não		30	Frio	Sim	Não
3	Bico	Sim	Não		31	Doce	Sim	Não
4	Longe	Sim	Não		32	Pernas	Sim	Não
5	Picada	Sim	Não		33	Alto	Sim	Não
6	Mula	Sim	Não		34	Lagrima	Sim	Não
7	Céu	Sim	Não		35	Comunicação	Sim	Não
8	Crime	Sim	Não		36	Rancor	Sim	Não
9	Hotel	Sim	Não		37	Pano	Sim	Não
10	Mês	Sim	Não		38	Bandeira	Sim	Não
11	Mastro	Sim	Não		39	Magoa	Sim	Não
12	Úmido	Sim	Não		40	Lavoura	Sim	Não
13	Aranha	Sim	Não		41	Gato	Sim	Não
14	Remorso	Sim	Não		42	Angustia	Sim	Não
15	Guloseima	Sim	Não		43	Noite	Sim	Não
16	Espaço	Sim	Não		44	Folheto	Sim	Não
17	Fobia	Sim	Não		45	Feitiço	Sim	Não
18	Plástico	Sim	Não		46	Arquivo	Sim	Não
19	Caneta	Sim	Não		47	Chapéu	Sim	Não
20	Bronze	Sim	Não		48	Preto	Sim	Não
21	Chata	Sim	Não		49	Perigo	Sim	Não
22	Radical	Sim	Não		50	Curva	Sim	Não
23	Culpa	Sim	Não		51	Delicia	Sim	Não
24	Papel	Sim	Não		52	Sorvete	Sim	Não
25	Neve	Sim	Não		53	Peso	Sim	Não
26	Índio	Sim	Não		54	Blusa	Sim	Não
27	Telefone	Sim	Não		55	Medo	Sim	Não
28	Temperatura	Sim	Não		56	Tela	Sim	Não

57	**Honra**	Sim	Não
58	**Grande**	Sim	Não
59	**Prova**	Sim	Não
60	**Luto**	Sim	Não

ANEXO IV – Memória Lógica

MEMÓRIA LÓGICA I	Pontos
HISTÓRIA A Ana/ Xavier/ do Sul/ de São Paulo/ empregada/	__/___
como cozinheira/ no restaurante/ da universidade/ deu queixa/ na delegacia/	__/___
da cidade/ que foi assaltada/ na noite anterior/na rua principal/ e roubada/	__/___
em 600 reais/. Ela tinha quatro/ crianças pequenas/o aluguel estava vencido/ e eles não haviam comido/	__/___
por dois dias/. Os policiais/ emocionados pela história da mulher/ juntaram algum dinheiro/ para ela/.	__/___
Máximo = 25 *Total da História A*	__/___
HISTÓRIA B Roberto/ dos Santos/ estava dirigindo/ um caminhão/ de dez toneladas/	__/___
descendo a estrada/ à noite/ perto de Foz/ de Iguaçu/ carregando ovos/	__/___
para Curitiba/ quando o seu eixo/quebrou/. O caminhão derrapou/ saindo da estrada/	__/___
caindo em uma vala/. Ele foi atirado/ contra o painel/ fortemente sacudido. Não havia tráfego/	__/___
e ele duvidou que ajuda aparecesse/. Logo a seguir seu rádio de comunicação/ chamou/. Ele rapidamente respondeu/ "Aqui é gafanhoto".	__/___
Máximo = 25 *Total da História B*	__/___
Máximo 50 **TOTAL GERAL**	__/___

Rapport da Apresentação

Bom dia! Meu nome é _____, sou psicólogo/psiquiatra, e faço parte de um grupo de pesquisa da Faculdade de Psicologia da PUCRS.

Você foi convidada para participar de uma pesquisa relacionada à memória e contamos com sua colaboração.

Vou ler um documento agora que explicar melhor do que se trata essa pesquisa.

LER TERMO

Alguma dúvida? Por favor, desligue o celular.
Bem então nós vamos coletar a primeira amostra da sua saliva agora.

COLETAR CORTISOL

Bom podemos então começar.

Rapport para escutar o CD 1 – Lista de Palavras

COLOCAR O CD 1

(Procurar fazer modelagem do comportamento)

Agora você vai escutar o primeiro CD que contém uma lista de várias palavras. Preste bem atenção! Enquanto estiver escutando, nós não podemos conversar. Vamos prestar bem atenção em todas as palavras.

Rapport para Tarefa Distratora (3 a 5 minutos)

Bem, agora você deverá procurar onde está o personagem *Wally* nas seguintes paisagens.

MOSTRAR QUEM É WALLY E FAZER UM EXEMPLO

Rapport para escutar o CD 2 – Teste de Reconhecimento

Agora você vai escutar outro CD que contém outra lista de palavras. Algumas dessas palavras você já escutou no primeiro CD, mas outras palavras são novas.

Como no primeiro CD a moça vai falar palavra por palavra.

Bem, agora preste bem atenção. Após ouvir cada palavra, você deve responder à pergunta: "Você já escutou essa palavra no primeiro CD?" A resposta vai ser SIM ou NÃO.

Vou explicar melhor: se você escutar uma palavra que já foi dita no primeiro CD, diga SIM. Se a palavra for nova para você, ou seja, você não escutou no primeiro cd responda NÃO.

Por exemplo: Se a moça falou FOTO no primeiro CD e agora ela fala de novo a palavra FOTO. O que você vai responder?
SIM. Muito bem!

Outro exemplo: Se agora a moça falar AREIA, mas a palavra AREIA não foi dita no primeiro CD. Qual será tua resposta?
NÃO. Isso mesmo!

Eu vou marcar as tuas respostas nessa folha (MOSTRAR FOLHA RAPIDAMENTE).
Agora o CD vai tocar uma palavra de cada vez, e tu deve responder SIM ou NÃO.

Tem dúvidas? Está pronta?

Vamos lá.

COLOCAR CD 2

RESPONDER AO GABARITO

Rapport para escutar o CD 3 – Memória Lógica
História A
Você vai escutar uma pequena história. Preste bem atenção e tente lembrar exatamente o que ouviu, mas tente lembrar-se das mesmas palavras. Quando a história terminar eu quero que você me diga tudo que ouviu. Você deve me dizer tudo o que conseguir lembrar, mesmo que você não tenha certeza. Você está pronta?
Agora, qual foi a história que você escutou? Conte-me tudo, começando do início.

História B
Agora você vai escutar outra pequena história e ver o quanto dessa história você consegue lembrar. Assim como na primeira história, tente lembrar exatamente como foi dito. Pronta?
Agora, qual foi a história que você escutou? Conte-me tudo, começando do início.

Mais tarde eu vou te pedir pra me contar essas histórias de novo, assim tente não esquecê-las.

Questionários (QUESI, BDI, PCL-C)

Você lembra-se das historinhas que escutou alguns minutos atrás? Agora eu quero que você me conte as histórias novamente. Conte-me tudo, comece pelo início.

Caso o examinando não recorde de uma ou ambas das histórias, é permitido oferecer os seguintes indicativos:

HISTÓRIA A – Uma história era sobre uma mulher que foi assaltada.

HISTÓRIA B - A outra história era sobre um homem que teve problemas na estrada.

Final

Bem, essa parte da pesquisa nós acabamos. Tu gostarias de conversar sobre alguma coisa que tenha te incomodado?
Agradecimentos.
Agora eu vou chamar um profissional que vai coletar o exame de sangue e explicar como será as outras amostras da saliva.

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
COMITÊ DE ÉTICA EM PESQUISA - CEP - PUCRS

Ofício 564/06-CEP   Porto Alegre, 29 de maio de 2006.

Senhor(a) Pesquisador(a)

O Comitê de Ética em Pesquisa da PUCRS apreciou e aprovou seu protocolo de pesquisa registro CEP 06/03110, intitulado: **"Um estudo interdisciplinar sobre o impacto da violência infantil na vida adulta".**

Sua investigação está autorizada a partir da presente data.

Relatórios parciais e final da pesquisa devem ser encaminhados a este CEP.

Atenciosamente,

Prof. Dr. José Roberto Goldim
COORDENADOR DO CEP-PUCRS

Ilmo(a) Sr(a)
Profa Lílian Milnitsky Stein
N/Universidade