PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
FACULDADE DE BIOCIÊNCIAS
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA CELULAR E MOLECULAR

MEMÓRIA CONTEXTUAL INCIDENTAL E PERFIL CIRCADIANO DOS NÍVEIS DE CORTISOL E DHEA EM ADULTOS COM DEPRESSÃO MAIOR UNIPOLAR

Dissertação apresentada ao Programa de Pós-Graduação em Biologia Celular e Molecular como requisito para a obtenção do grau de Mestre.

Autor
Márcio da Silveira Corrêa

Orientador
Elke Bromberg

Porto Alegre, RS
Janeiro, 2011

SUMÁRIO

AGRADECIMENTOS

A minha orientadora, professora Elke Bromberg, pela paciência, sabedoria, ensinamentos e por todo o empenho para o desenvolvimento deste trabalho. Obrigado pelos incentivos e principalmente pela confiança desde o início.

À Joana Bisol Balardin, doutoranda da USP, pela colaboração na realização deste estudo.

À CAPES e PUCRS, pela bolsa concedida.

A minha esposa Renata Fagundes, pelo amor incondicional e por estar ao meu lado, em todos os momentos.

A minha família, em especial a minha mãe, avós e madrinha por todo amor, orações e apoio durante estes dois anos.

RESUMO

Características: A depressão é uma das doenças mentais que mais afeta a população mundialmente. Também conhecida como um transtorno do humor é caracterizada por sentimentos de derrota, baixa autoestima e culpa, sendo duas vezes mais comum em mulheres do que em homens. Uma das suas principais conseqüências no organismo são as disfunções cognitivas.

Objetivos: Nós investigamos os efeitos do suporte cognitivo sobre a memória contextual na depressão e analisamos as características neuropsicológicas e hormonais que podem afetar a memória.

Métodos: Dezessete pacientes medicados com depressão maior unipolar (idade 20-40 anos, 14 mulheres) e 22 controles pareados por idade, gênero e educação realizaram o subteste Vocabulário do WAIS-III (VWAIS), o Wisconsin Card Sorting Test (WCST) e um teste de memória para reconhecimento de itens (objetos) e contextos (local), o qual foi aplicado com ou sem pista incidental. Amostras de salivas para análise de cortisol e DHEA foram coletadas as 07AM, 4PM e 10PM.

Resultados: Pacientes e controles apresentaram desempenho equiparado nos escores de reconhecimento de itens, mas os pacientes apresentaram um déficit de memória contextual na ausência da pista. O mau desempenho nos testes neuropsicológicos (VWAIS e WCST) e baixos níveis de cortisol e da razão cortisol/DHEA em pacientes não foram a causa relacionada a esse déficit.

Conclusão: Déficits na memória contextual em pacientes com depressão maior podem ser reduzidos fornecendo suporte cognitivo adicional na codificação.

Palavras-chavas: Depressão, Memória, Codificação, Cognitivo, Cortisol e DHEA.

ABSTRACT

Background: The depression is a mental illness that affects the population worldwide. Also known as a mood disorder is characterized by feelings of defeat, guilt and low self-esteem, being twice as common in women than in men. One of its main consequences in the body are the cognitive dysfunction

Objectives: We investigated the effect of cognitive support on contextual memory in depression and analyzed neuropsychological and hormonal characteristics that could affect memory.

Methods: Seventeen medicated patients with MDD (age 20-40 years, 14 women) and 22 controls matched for age, gender and education performed the Vocabulary subtest of WAIS-III (VWAIS), the Wisconsin Card Sorting Test (WCST) and a recognition memory task for item (object) and context (location), which was applied with or without an incidental binding cue. Salivary cortisol and DHEA were measured at 7AM, 4PM and 10PM.

Results: Patients and controls exhibited performance-matched recognition scores for items, but patients showed a deficit for contextual memory in the absence of the binding cue. Worse performance on neuropsychological tests (VWAIS and WCST) and lower cortisol and cortisol/DHEA ratios in patients were not causally related to this deficit.

Conclusions: Contextual memory deficits in MDD patients could be reduced by providing additional cognitive support at encoding.

Keywords: Depression, Memory, Encoding, Cognitive, Cortisol and DHEA

1 CAPÍTULO 1

1.1 INTRODUÇÃO

1.1.1 Depressão e déficits cognitivos em adultos

A depressão é um dos transtornos mentais mais comuns em todo o mundo (Keller, Schatzberg, Maj, 2007), caracterizada por humor deprimido, perda de interesse ou prazer em quase todas as atividades por pelo menos duas semanas, podendo ser acompanhado de planos ou tentativas suicidas (Parker & Brotchie, 2009).

A depressão maior tem uma prevalência ao longo da vida de 13 a 21% em países desenvolvidos e está associada com alterações funcionais importantes e um elevado custo para o sistema socioeconômico (Kessler et al, 2008).

Essa doença é duas a três vezes mais freqüente em mulheres do que em homens, sendo considerada um transtorno incapacitante, na qual 12% dos pacientes têm um curso crônico sem remissão de sintomas (Fleck et al., 2009).

Entre as conseqüências da depressão no organismo estão as disfunções cognitivas. Esta associação tem sido mais intensamente estudada em adultos de meia idade e idosos (Ganguli et al., 2006; Alexopoulos et al., 2005; Nebes et al., 2003; Nebes et al., 2000).

Há poucos trabalhos sobre esse assunto realizados com adultos jovens (18 a 40 anos) (Hinkelmann et al.,2009; Castaneda et al., 2008). Estudos epidemiológicos apontam para a necessidade de se estudar de forma sistemática a associação entre depressão e déficits cognitivos nesta faixa etária, a qual é caracterizada não só por um elevado risco de desenvolvimento de transtornos psiquiátricos, mas também pela

persistência de disfunções cognitivas mesmo após a remissão dos sintomas de humor (Castaneda et al, 2008).

Grant e colaboradores (2001) afirmam que o esclarecimento dos déficits cognitivos em adultos com depressão é fundamental para o desenvolvimento de modelos de fisiopatologia da doença.

Em adultos, as principais queixas neurocognitivas presentes durante o estado depressivo incluem redução das habilidades atentiva e mnêmica e lentidão do pensamento (Post, 1992), tanto na fase clínica como no período assintomático (Alexopoulos, 2005).

A análise neuropsicológica de pacientes com depressão maior indica que um componente chave do declínio cognitivo é a disfunção executiva, uma vez que a habilidade de gerar, manter e alterar estratégias adequadas para a solução de problemas encontra-se alterada (Fossati et al, 1999; Merrian et al, 1999; Hill, 2004). Outras disfunções cognitivas que parecem estar presentes em pacientes depressivos são os déficits de atenção (Hill, 2004; Smith et al, 2006), alterações da memória de curta duração e da memória de trabalho (Fossati et al, 1999), assim como disfunções em habilidades psicomotoras (Hill, 2004).

No que diz respeito à memória, grande parte das pesquisas que tem estudado as relações entre depressão e memória tem utilizado medidas de memória episódica, como a recordação de itens (Burt, Zembar, Niederehe, 1995). Apesar da grande divergência dos resultados de tais trabalhos, existem evidências de que os déficits de memória relacionados à depressão são mais pronunciáveis em tarefas de recordação livre, ao passo que a diferença de desempenho entre indivíduos depressivos e não depressivos é menor em tarefas de reconhecimento. Da mesma forma, depressivos tendem a ter piores desempenhos de memória quando existem

altas demandas cognitivas na fase de codificação/aprendizado (Brand, Jolles, Gispen-de-Wied, 1992; Hayslip, Kennelly, Maloy, 1990). Isso pode ser explicado pelo fato de pacientes com depressão não fazerem uso espontâneo de estratégias de organização, beneficiarem-se menos do uso de imagens mentais e terem dificuldades com listas de memória longas, que contenham muitos itens de teste.

Menos exploradas ainda são as relações entre a depressão e um outro aspecto da memória episódica, a chamada memória contextual, relacionada às características contextuais da informação a ser aprendida e da situação na qual tal informação foi adquirida (Johnson, Hashtroudi, Lindsay, 1993). Este tipo de memória é extremamente importante no dia-a-dia e faz parte de um tipo de memória chamada de incidental, ou seja, aquelas memórias que não nos esforçamos para obter, mas que dizem respeito a informações importantes de nossa vida. A memória contextual é utilizada, por exemplo, quando tentamos nos lembrar de onde conhecemos uma determinada pessoa (memória contextual de localização), ou de como obtemos uma informação (memória contextual de modalidade de apresentação), ou quando realizamos uma determinada atividade (memória contextual de ordenação temporal).

Este tipo de memória é dependente de duas estruturas do sistema nervoso que sofrem alterações funcionais e/ou estruturais em decorrência da depressão: o lobo frontal e hipocampo. Nesta mesma linha, várias pesquisas demonstram alterações no volume hipocampal de indivíduos com essa doença (Vythilingam et al., 2004). Portanto, como esperado, os pacientes depressivos mostram-se menos eficientes do que indivíduos saudáveis em tarefas de memória contextual (Behnken et al. 2010).

Esses prejuízos de memória contextual têm sido encontrados principalmente em idosos, associando-se aos efeitos negativos do envelhecimento. Tornam-se

necessários mais estudos com pacientes depressivos jovens adultos para fortalecer o entendimento desta relação e contribuir de forma significativa na prática médica.

Um aspecto particularmente importante a respeito das disfunções cognitivas decorrentes da depressão em adultos jovens é a sua persistência mesmo após a remissão dos sintomas de humor, particularmente no que diz respeito a funções executivas e memória (Smith et al, 2006). A persistência destes sintomas indica que eles não são simples manifestações secundárias das alterações de humor. Entretanto, é necessário ainda elucidar se este achado pode ser generalizado ou se diz respeito somente aos pacientes com depressão severa (Wang et al, 2006). Uma vez que algumas pesquisas mostram uma relação bastante significativa entre o aumento da severidade depressão e o maior comprometimento das habilidades cognitivas (McDermott & Ebmeier, 2009). Dentre os domínios cognitivos afetados nesses casos, os trabalhos são bastantes controversos, alguns mostram que quanto maior a sintomatologia depressiva, maior são os déficits na função executiva (Grant, Thase, Sweeney, 2001). Outros estudos apontam essa relação com a velocidade de processamento (Austin, Mitchell, Goodwin, 2001).

É importante destacar que a farmacologia antidepressiva não é capaz de reverter estas disfunções cognitivas, pelo menos nos quadros mais graves. Portanto, existe a necessidade de investigar técnicas de reabilitação cognitiva, que combinadas à farmacoterapia, poderiam minimizar estas alterações.

Embora já exista um conjunto considerável de evidências indicando a existência de déficits cognitivos em adultos jovens com depressão, a maioria destes trabalhos simplesmente se preocupou em caracterizar o tipo de alteração cognitiva presente na depressão (Castaneda et al., 2008). Portanto, torna-se extremamente importante relacioná-las com fatores neurobiológicos sabidamente envolvidos na

patogênese da depressão e capazes de interagir com os mecanismos subjacentes aos diferentes aspectos cognitivos.

1.1.2 Depressão e alterações neurohormonais

Alterações no eixo Hipotálamo-Hipófise-Adrenal (HPA) parecem ter um papel central na patogênese e etiologia de diversos transtornos psiquiátricos (Pariante & Lightman, 2008). Duval et al. (2006), afirma que ao longo das últimas quatro décadas cresceram consideravelmente os resultados da investigação sobre o papel do eixo HPA na psicobiologia da depressão. Esses trabalhos concluíram que o estresse físico causado por essa doença promove a hipersecreção de cortisol e alterações no teste de supressão do cortisol em resposta a administração de dexametasona (Brown et al, 2004; Pariante & Lightman, 2008). A hipercortisolemia parece ser um marcador importante do curso temporal da depressão e predizer relapsos subseqüentes a uma aparente recuperação (Holsboer, Spengler, Heuser, 1992).

O cortisol é um glicocorticóide produzido na adrenal (Takebayashi et al., 1998). Os glicocorticóides têm efeitos bastantes amplos no organismo (Lupien et al., 2004). O cérebro é um dos principais alvos de corticosteróides, que prontamente atravessam a barreira hematoencefálica e se ligam a um sistema binário de receptores intracelulares, constituído pelos receptores glicocorticóides e receptores mineralocorticóides (Datson et al. 2008) que regulam a transcrição gênica (Figura 1).

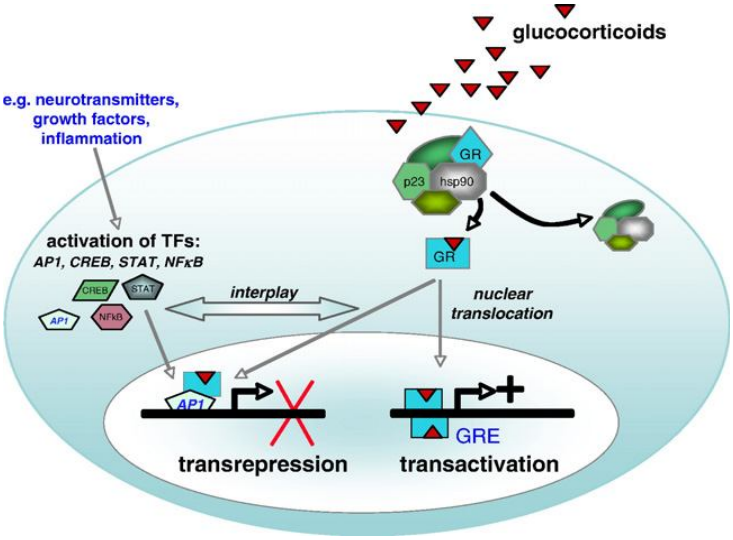


Figura 1. Mostra os glicocorticóides ligando-se aos seus receptores (glicocorticóides e mineralocorticóides) e alterando a transcrição gênica (Datson et al., 2008).

Estes receptores apresentam uma série de diferenças: na afinidade pelo cortisol, na regulação do eixo HPA e na distribuição em estruturas encefálicas. O receptor mineralocorticóide tem uma afinidade 10 vezes mais elevada para o cortisol do que receptor glicocorticóide (Reul & De Kloet, 1985). Ambos os receptores desempenham papeis diferentes na regulação da atividade do eixo hipotálamo-pituitária-adrenal (HPA): os receptores mineralocorticóides mantêm a atividade basal do eixo, enquanto os receptores glicocorticóide facilitam o feedback negativo em concentrações crescentes de glicocorticóides em resposta a um estressor (De Kloet et al., 1998).

Os receptores mineralocorticóides são encontrados exclusivamente no sistema límbico, sendo que o hipocampo é uma das estruturas que apresenta elevada densidade dos mesmos. Os receptores glicocorticóides distribuem-se em estruturas corticais (com distribuição preferencial no córtex pré-frontal) e subcorticais (incluindo o hipocampo) (Meaney & Aitken, 1985; Diorio, Viau, Meaney, 1993). Portanto, o cortisol pode atuar em regiões cerebrais (hipocampo e lobo frontal)

envolvidas com a memória e outros aspectos cognitivos (Lupien et al., 2004; Fieta & Fieta, 2007) e que mostram alterações estruturais e funcionais relacionadas a depressão (Drevets et al., 2008).

Adicionalmente, diversos trabalhos com modelos animais, assim como estudos com humanos, indicam que o cortisol pode ter um efeito neurotóxico, alterando anatômica e funcionalmente estruturas envolvidas em diferentes aspectos cognitivos (Brown et al., 2004).

Uma das principais propriedades hipocampais que é afetada pela administração aguda de glicocorticóides é a potenciação de longa duração (LTP), um dos principais mecanismos subjacentes a formação e armazenamento da memória (Datson et al.,2008). A ativação dos receptores glicocorticóides inibe a potenciação de longa duração na região CA1 do hipocampo (Kim & Diamond, 2002), provocando mudanças na expressão gênica (Datson et al., 2008).

A exposição prolongada a níveis elevados de cortisol, como em situações de estresse crônico ou transtornos psiquiátricos (Duval et al., 2006), pode levar a alterações anatômicas e funcionais dos neurônios hipocampais, a supressão da neurogênese e morte neuronal, originando ou agravando as disfunções do eixo HPA e promovendo disfunções cognitivas (McEwen, 2000). Entre as ações do cortisol que podem gerar alterações funcionais relacionadas a plasticidade sináptica e memória estão a modulação da atividade de diferentes sistemas de neurotransmissores e a regulação da disponibilidade de fatores neurotróficos (Datson et al., 2008). Especificamente no que diz respeito ao potencial neurotóxico do cortisol (Lupien et al., 2004; Haller, Mikics, Makara, 2008; Datson et al., 2008), existem evidências de sua relação com a modulação dos sistema glutamatérgico (por regular a disponibilidade de receptores NMDA e a liberação de glutamato) e gabaérgico (por

atuar especificamente na expressão RNAm para subunidades especificas dos receptores GABAa) (McEwen, 2000), além da diminuição da disponibilidade de BDNF (Duman & Monteggia, 2006; Murakami et al., 2005).

A correlação entre níveis elevados de cortisol e prejuízos de memória também já foi amplamente demonstrada (Hinkelmann et al.,2009; Li et al., 2006; Lupien et al., 2005; Wolkowitz et al., 1994).

No entanto, existem outras pesquisas que encontraram baixos níveis de cortisol em indivíduos depressivos (Bremmer et al., 2007; Oldehinkel et al., 2001). E esses estudos sugerem que a hipocortisolemia possa ser causada pela resposta dos antidepressivos que agem ajustando do eixo Hipotálamo-Hipófise-Adrenal (HPA).

Mais recentemente surgiu o interesse na relação entre depressão e outro esteróide adrenal, a dehidroepiandrosterona (DHEA) e seu componente sulfatado (DHEA-S). O DHEA e o DHEA-S têm sido classificados como neuroesteróides, pois além de serem secretados pelas adrenais, também são sintetizados pelo cérebro (Wolf et al. 1997).

O principal mecanismo de ação do DHEA são os receptores nucleares (Levin, 2005). Maurice e colaboradores (1999) sugerem receptores de superfície de membrana para o DHEA.

Esse hormônio atua como neuroesteróide que antagoniza os receptores GABAa e estimula o receptor NMDA (Wolf, et al. 1997; Wolkowitz, et al., 1999; Young, Gallagher, Porter, 2002). E que quando ativo inibe diversos sistemas neurotransmissores através de mecanismos não genômicos (Maurice et al., 1999).

DHEA e DHEA-S são ativadores endógenos do receptor neuromodulador σ1. Os receptores σ1 são uma classe de proteínas associadas à membrana que modulam sistemas de neurotransmissores excitatórios, incluindo os sistemas

glutamatérgico e colinérgico (Webb et al., 2006). Os receptores σ1 são encontrados principalmente no hipocampo e outras áreas límbicas (Maurice et al., 2006). Eles são expressos em neurônios, ependimócitos, oligodendrócitos e nas células de Schwann (Alonso et al., 2000; Palacios et al. 2003).

O DHEA também protege os neurônios hipocampais contra a morte celular causada por neurotoxinas, principalmente reduzindo os níveis nucleares de receptores glicocorticóides (Gallagher et al. 2007), desse modo o DHEA é considerado um anti-glicocorticóide.

No que diz respeito a relação entre os níveis circulantes de DHEA, DHEA-S e a depressão os resultados ainda são controversos. Existem evidências de que a concentração desses hormônios também está elevada, assim como os níveis de cortisol, e que a mesma está diretamente relacionada com a remissão da depressão, voltando a seus níveis normais após o desaparecimento dos sintomas de humor (Johnson, Hashtroudi, Lindsay, 1993). Entretanto, outros estudos demonstraram baixos níveis de DHEA-S em pacientes depressivos quando comparados a controles não-depressivos e a pacientes com remissão dos sintomas depressivos prévios (Yaffe et al., 1998 e Michael et al., 2000). Em indivíduos com depressão maior, a administração oral de DHEA diminuiu os sintomas depressivos (Herbert, 1998). Adicionalmente, pacientes que demonstraram remissão dos sintomas em resposta ao tratamento farmacológico antidepressivo apresentaram também uma correlação positiva entre a queda dos níveis de DHEA e os escores na escala de Hamilton (Hsiao, 2006).

Como existe uma ampla variabilidade inter-individual nos níveis plasmáticos de DHEA (Thomas et al, 1994) a relação cortisol/DHEA tem sido considerada como mais informativa do que os valores isolados do DHEA (Hechter, Grossman,

Chatterton, 1997). Muito mais que investigar as alterações de um ou outro hormônio na depressão, torna-se importante avaliar a relação entre cortisol/DHEA, um marcador mais fidedigno da “hipercortisolemia funcional” (Young et al., 2002).

Entretanto, além de existirem relativamente poucos trabalhos a respeito desta relação em pacientes depressivos, eles são contraditórios, pois a maioria analisa a relação entre estes hormônios em somente um horário dia. Desta forma, alguns estudos com pacientes depressivos evidenciaram uma relação cortisol/DHEA(S) aumentada em pacientes depressivos quando comparados aos controles (Osran et al., 1993; Scott et al., 1999), enquanto outros falharam ao buscar valores anormais para essa proporção junto à indivíduos com depressão (Reus et al., 1993; Dent et al., 1998). E até o momento nenhum trabalho procurou relacionar as modificações na relação cortisol/DHEA com a manifestação das disfunções cognitivas.

Desta forma, faz-se necessário considerar que os adultos jovens encontram-se numa fase da vida que parece ser crítica para evitar a cronicidade dos sintomas associados a diferentes quadros psiquiátricos (Kessler et al., 2005), tornando-se importante não só avaliar os aspectos cognitivos afetados, mas também os aspectos patofisiológicos associados com estas alterações.

O presente estudo teve por objetivo analisar em que grau a memória contextual é afetada em pacientes depressivos adultos e se esses conseguem beneficiar-se de estratégias de codificação. Adicionalmente, procuraremos estabelecer uma relação entre os níveis de cortisol/DHEA e o desempenho dos pacientes depressivos na tarefa de memória contextual incidental, procurando verificar se a relação entre estes hormônios pode ser utilizada como um indicador do risco de disfunção ou da capacidade de recuperação cognitiva dos pacientes durante a fase depressiva.

Pretendemos, através deste estudo, estabelecer parâmetros que auxiliem na identificação de pacientes com menor ou maior capacidade de recuperação de déficits cognitivos e, desta forma, contribuir para a introdução, na prática médica, de medidas de reabilitação cognitiva adequadas as necessidades do paciente. A redução dos impactos da depressão em aspectos sociais e ocupacionais dos pacientes é de extrema importância para garantir sua qualidade de vida, assim como diminuir o impacto sócio-econômico imposto por este transtorno de humor à sociedade.

1.2 OBJETIVOS

1.2.1. Geral

Analisar os efeitos da depressão maior unipolar na cognição de pacientes adultos, com enfoque especial na memória contextual incidental, verificando se esses indivíduos conseguem beneficiar-se de estratégias de codificação. Adicionalmente, iremos analisar a razão cortisol/DHEA tentando relacioná-la com esses resultados cognitivos.

1.2.2 Específicos

Evidenciar o padrão de desempenho dos voluntários dos grupos depressivo e controle em testes que medem as funções dos lobos frontal (função executiva, memória de reconhecimento do contexto) e temporal (memória de reconhecimento do objeto).

Investigar o efeito de estratégias de codificação sobre a memória contextual dos diferentes grupos experimentais.

Analisar o padrão circadiano de secreção de cortisol e DHEA nos diferentes grupos experimentais;

Verificar e comparar a relação cortisol/DHEA nos diferentes grupos experimentais.

Verificar se as características neuropsicológicas e hormonais (cortisol, DHEA, razão cortisol/DHEA) afetam o desempenho na tarefa de memória contextual.

2 CAPÍTULO 2

2.1 ARTIGO CIENTÍFICO

Contextual recognition memory deficits in major depression are suppressed by cognitive support at encoding

Márcio da Silveira Corrêa; Joana Bisol Balardin; Marcelo Pio de Almeida Fleck; Marco Antônio Knob Caldieraro; Irani Argimon; Clarice Luz and Elke Bromberg.

(Periódico escolhido: Biological Psychology)

Contextual recognition memory deficits in major depression are suppressed by cognitive support at encoding

Márcio Silveira Corrêa[a]; Joana Bisol Balardin[a]; Marco Antônio Knob Caldieraro[b]; Marcelo Pio Fleck[b]; Irani Argimon[c]; Clarice Luz[a] and Elke Bromberg [a c d] *

[a] Neurobiology and Developmental Biology Laboratory, Faculty of Biosciences, Pontifical Catholic University, Porto Alegre, RS, Brazil

[b] Departament of Psychiatric, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil

[c] Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, RS, Brazil

[d] National Institute for Translational Medicine (INCT-TM), RS, Brazil

* Corresponding author at: Neurobiology and Developmental Biology Laboratory, Faculty of Biosciences, Pontifical Catholic University, Av. Ipiranga, 6681, Prédio 12D, Sala 34, 90619-900 Porto Alegre, RS, Brazil.

E-mail address: bromberg@pucrs.br (E. Bromberg).

ABSTRACT

Objectives: We investigated the effect of cognitive support on contextual memory in depression and analyzed neuropsychological and hormonal characteristics that could affect memory.

Methods: Seventeen medicated patients with MDD (age 20-40 years, 14 women) and 22 controls matched for age, gender and education performed the Vocabulary subtest of WAIS-III (VWAIS), the Wisconsin Card Sorting Test (WCST) and a recognition memory task for item (object) and context (location), which was applied with or without an incidental binding cue. Salivary cortisol and DHEA were measured at 7AM, 4PM and 10PM.

Results: Patients and controls exhibited performance-matched recognition scores for items, but patients showed a deficit for contextual memory in the absence of the binding cue. Worse performance on neuropsychological tests (VWAIS and WCST) and lower cortisol and cortisol/DHEA ratios in patients were not causally related to this deficit.

Conclusions: Contextual memory deficits in MDD patients could be reduced by providing additional cognitive support at encoding.

Keywords: Depression, Memory, Encoding, Cognitive, Cortisol and DHEA.

INTRODUCTION

Memory complaints are common in major depressive disorder (MDD), but objective memory impairments were observed in some studies (Austin et al., 2001; Braw et al., 2010; Fossati et al., 2004; McDermott and Ebmeier, 2009), but not in others (Castaneda et al., 2008; Grant et al., 2001; Rincke and Becker, 2003; Wang et al., 2006). There is no easy way of reconciling the diverse findings, but differences in memory tasks, disease features and subject characteristics are relevant. Depressive patients have more difficulties in tasks that require more cognitive effort (Hertel and Milan, 1994) and with more demands on executive functions (Fossati et al., 2002). The number of past depressive episodes (MacQueen et al., 2003), their length and patients's age, education level and profession (Gorwood et al., 2008) can also interfere in memory performance.

Along with memory impairment, despite methodological issues and mixed results, another frequent finding in depressive patients is a dysfunction of the hypothalamus- pituitary-adrenal (HPA) activity, mainly related to cortisol secretion. The most reported finding is hipercortisolemia (Kessing et al., 2011; Pariente and Lightman, 2008), but hypocortisolemia (Bremmer et al., 2007; Morrison et al., 2000; Oldehinkel et al., 2001) and normocortisolemia (Young et al., 2001) have also been described. Fewer studies were conducted on the role of other adrenal steroids, such as dehydroepiandrosterone (DHEA), in depressive illness, and mixed results were also found (Morrison et al., 2000; Michael, et al., 2000). Evidences of the association between depression, cortisol, and cognitive impairment have also been demonstrated (Egeland et al., 2005; Gomes et al., 2009; Hinkelmann et al., 2009; Rubinow et al., 1984). It has been hypothesized that circulating cortisol binds to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) that exist in high density in the hippocampal and prefrontal cortices (Lupien et al., 2009) which are brain structures closely related to memory function. Regarding DHEA, it was demonstrated that it counteracted the deleterious effects of corticosteroids on long-term potentiation, a neurophysiological correlate of learning and memory (Kaminska et al., 2000). In middle-aged and elderly depressed patients, improvements in cognition have been observed after administration of DHEA (Wolkowitz et al., 1997).

Besides the nature and the mechanisms of memory disorder in MDD, a series of studies have demonstrated the modulatory effect of cognitive support on verbal memory function in depressive patients. Under incidental encoding, focused attention on task and inhibition of task irrelevant thoughts

were able to eliminate depression-related memory deficits in adult patients (Hertel and Rude, 1991). Taconnat et al. (2010) examined free recall of young depressed patients under low (nonorganized words lists according to semantic categories) and high (preorganized words lists) cognitive support encoding conditions. Depressive patients exhibited memory deficits only when they must organize the information themselves (ie. in the low cognitive support condition), but they were also less able to use an organizational strategy compared to controls, revealing a poor strategic capacity mediated by a deficit in self-initiated processing. These results are corroborated by the study of Behnken et al. (2010), which demonstrates that compared to controls, even remitted individuals with unipolar MDD showed more deficits in non-verbal memory function due to difficulties in organizing non-verbal information appropriately during learning.

In the present study, we investigated the effect of low and high cognitive support at enconding in contextual memory in depressed patients. We used a naturalistic experimental paradigm (eg, photos of objects displayed on house indoors) to assess recognition memory for content (object) and context (location). Binding object to locations plays an important role in establishing perceptual continuity within the dynamic environments of everyday experience (Hollingworth and Rasmussen, 2010), and has an essential contribution to form coherent episodic memory representations. Cognitive support was manipulated at incidental encoding by presenting an object-location binding cue (high cognitive support) and an object property cue (low cognitive support). We hypothesized that patients with MDD would show poorer contextual memory performance and that their impairment would be suppressed through the use of the specific encoding strategy to bind item and context. Subjects demographic, neuropsychological and hormonal (cortisol, DHEA and cortisol/DHEA) characteristics were controlled for potential effects on the interpretation of memory results.

METHODS

Participants

Participants were 17 patients (ages 20-40; 14 women) from the psychiatric outpatient clinic of Hospital de Clínicas de Porto Alegre, RS, Brazil. Subjects were selected through the Structured

Clinical Interview for DSM-IV (MINI, Sheehan et al.1998), conducted by a trained psychiatrist, and met DSM-IV criteria for major depressive disorder (APA, 1994).

All the patients were on antidepressant medication for at least 6 months. Patients were taking selective serotonin reuptake inhibitors alone (fluoxetine, n=2; sertraline, n=1) or in association with dopamine reuptake inhibitors (paroxetine plus bupropion, n=1), mood stabilizers (paroxetine plus valproic acid, n=1; paroxetine plus valproic acid plus lithium, n=1), tricyclics (sertraline plus amitriptyline, n=1), mood stabilizars and tricyclics (fluoxetine plus lithium plus amitriptyline, n=1; sertraline plus carbamazepine plus amitriptyline, n=1; sertraline plus carbamazepine plus lithium plus amitriptyline, n=1), tricyclics and benzodiazepines (fluoxetine plus amitriptyline plus clonazepam, n=1) or with mood stabilizars and benzodiazepines (fluoxetine plus lithium plus diazepam, n=1). Patients were also taking tricyclics alone (imipramine, n=1) or in association with benzodiazepines (imipramine plus clonazepam, n=1), mood stabilizers (amitriptyline plus lithium, n=1; imipramine plus valproic acid, n=1) or with benzodiazepines plus mood stabilizers (imipramine plus diazepam plus lithium, n=1).

The severity of depression was assessed at the time of memory testing using the Beck Depression Inventory (Beck and Steer, 1993), adapted and validated in Brazil by Cunha (2001). Patients were required to have a score of 12 points or over. Twenty-two controls (ages 20-40; 19 women) were recruited from the community and had to score less than 11 points on BDI for inclusion in the study. Exclusion criteria included the use of any psychotropic medication (except antidepressants for the depressives patients) within the previous 6 weeks, major unstable medical illnesses, neurological disorders, chronic diseases (diabetes mellitus, thyroid dysfunction) and cognitive impairment as evidenced by a Mini Mental Status Examination (MMSE) score ≤23 (Folstein et al., 1975). All participants gave informed consent before beginning the study. Ethical approval was granted by the Local Research Ethical Committee, Hospital de Clínicas de Porto Alegre and of the Pontifical Catholic University, Porto Alegre, RS, Brazil.

Neuropsychological Measures

Participants completed neuropsychological tests to compare cognitive ability across experimental groups, including the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS III) (Weschler, 1997), a measure of general intelligence and the Wisconsin Card Sorting Test

(WCST)(Heaton, 1993), for executive function assessment. Based on previous research on executive function in depressives patients and the results of a factor analysis of the WCST in relation to recognition memory performance (Fabiani and Friedman, 1997), the number of categories completed (ranging from 0 to 6) and the number of perseverative errors were used as WCST indexes.

Memory Task

The materials and procedures for the assessment of the recognition memory for objects and context have been described elsewhere (Balardin et al., 2009; Dos Santos et al., 2010). In brief, the task involved photographs of a large number of objects from different semantic categories (household appliances, tools, toys, and clothing) placed in 2 locations: a living room and an office. A total of 32 objects were used as critical stimuli for the memory task; 16 of these were used during the study phase, and 16 served as distracters. For the study session, participants of each group (depressive patients or control) were systematically assigned to 1 of 2 encoding conditions by the date of their recruitment in the study. These conditions relied on the judgment of each photograph with a 2-choice question: (*a*) concerning how much they use the object in daily activities (incidental binding cue absent) and (*b*) how well each object fits in the room (incidental binding cue present). Thus, there were 4 experimental subgroups: depressive patients without incidental binding cue, depressive patients with incidental binding cue, controls without incidental binding cue and controls with incidental binding cue. The incidental binding cue strategy should facilitate memory for context because participants were encouraged to integrate information about the item and context at encoding. Participants saw 16 pictures in this session and were unaware that a test session would follow. After a 5-minute interval, in which participants were engaged in a distracting activity (digit span forward and backward), the memory test was given. The participants were shown 32 photographs in this session: each of the 16 studied objects (8 in the same context and 8 in the other context in relation to the study phase) and 16 unstudied objects, equally divided between the living room and the office. Participants responded verbally as to whether or not the object was one they had seen in the study session. If they indicated the object was an previously presented one, 2 consecutive photographs of the object in each location were depicted on the computer screen and participants then made a context memory

judgment, indicating in which of the 2 locations the object had appeared in the study session. The order of photograph presentation was randomized for each subject.

Cortisol and DHEA assay

Participants were asked to collect 3 saliva samples at 7 AM, 4 PM and 10 PM on the day of experiment. The saliva samples were stored at 4°C by the subjects and delivered to the laboratory within 3 days. On arrival in the laboratory, the samples were frozen at -20^{o}C. Following defrosting, samples were separated for cortisol and DHEA analysis. Samples for cortisol analysis were centrifuged at 1500 rpm for 3 minutes (to allow precipitation of proteins and mucins) and then analyzed by radioimmunoassay (Cortisol Coat-Count -RIA, DPC Medlab, Los Angeles, CA) using equipament Gamma Counter. The sensitivity of these assays was estimated at 0.1 nmol/L. The intra- and inter-assay coefficients of variation were less than 10%. Samples for DHEA analysis were also centrifuged for 3 minutes at 2500 rpm (to enable precipitation of proteins and mucins) and then measured by radioimmunoassay technique with a kit for liquid phase (Diagnostic Systems Laboratories, Webster, TX). The sensitivity of these assays was estimated at 0,31nmol/L. The intra- and inter-assay coefficients of variation were less than 8%. All of the samples for cortisol and DHEA were analyzed in duplicate, and the results from each of the sampling times were expressed in nanomole per liter (nmol/L). Six patients and three control subjects delivered incomplete samples and were excluded from the analysis. Data were available for eleven patients and nineteen comparison subjects.

Statistical analysis

Demographic and neuropsychological data for patients and controls are expressed as means$\pm$standard error of mean (SEM). Recognition memory scores for objects (proportion of objects correctly identified as previously presented) and context (proportion of objects attributed to the correct context considering the number of objects correctly identified as previously presented) for the 4 experimental subgroups were analyzed with a mixed-design ANOVA for repeated measures to examine differences between groups and encoding conditions, with object and context recognition

scores as within-subjects variables. Multiple comparisons among groups mean differences were checked with Tukey post hoc tests. Independent and paired samples t tests were used whenever appropriate. Results are expressed as mean $\pm$ standard error of mean (SEM) and $p<0.05$ was accepted as statistically significant.

Cortisol and DHEA data were analyzed by repeated measures analysis of variance (ANOVA), which included 1 within-participants variable (cortisol and DHEA levels at different sampling times) and 1 between-participants variable (group: healthy young adults and young adults with depressive symptoms). Multiple comparisons among groups mean differences were checked with Tukey post hoc tests. Independent and paired samples t tests were used whenever appropriate. Results are expressed as mean$\pm$standard error (SE). A level of $P < 0.05$ was accepted as statistically significant.

RESULTS

Table 1 summarizes the demographic and neuropsychological characteristics of subjects in the control and depressive groups. Both groups did not differ on age [t=1.39, df=37, p=0.17], gender [Pearson Chi-Square=0.11, p=0.73] and years of education [t= -1.54, df=37, p=0.13]. As expected, BDI scores were significantly higher in the group of patients with major depression [t=9.53, df=37, p<0.001]. Except for perseverative errors on WCST [t=1.09, df=37, p=0.28], depressive patients exhibited lower performance compared to controls on MEEM [t=-2.66, df=37, p=0.007], Vocabulary subtest [t=-3.68, df=37, p=0.001] and number of categories completed on the WCST [t=-3.53, df=37, p=0.001].

Recognition performance for objects and contexts can be found in Figure 1. The ANOVA revealed main effects of group [F(1,35)=28, p<0.001], recognition test [F(1,35)=118.35, p<0.001] and encoding condition [F(1,35)=33.01, p=0.003], as well as an significant interaction between group and recognition test [F(1,35)=8.23, p=0.007]. Although this results indicate a reliable effect of depression on memory, they also suggest that this effect is dependent on the nature of the information to be recognized (central item or its context] and on the encoding conditions (with or without incidental binding cue]. To further explore the interactions between these variables we performed planned comparisons to assess whether memory performance of subjects from different groups and recognition tests differed as a function of encoding instruction .

The ANOVA showed only a marginal significant difference between controls and depressed patients in the object recognition test performed in the different encoding conditions [F(3,38)=3.00, p=0.043], so that Tukey post hoc test could not indicate a reliable difference between the experimental subgroups [all p>0.05]. However, important significant differences were found for context recognition [F(3,38)=47.58, p=0.000]. Tukey post hoc test indicated a significantly lower performance of depressed patients in relation to controls in the encoding condition without incidental binding cue [p=0.000]. However, the introduction of the incidental binding cue at encoding was able to improve the scores of context recognition in controls [p=0.000] and depressed patients [p=0.029], match the performance of both groups (as no significant differences could be seen between them anymore [p=0.55]), and bring the scores of context recognition to the same level as those for object recognition, as confirmed with paired t test (all p=0.000 in the encoding condition without binding cue and >0.05 in the encoding condition with incidental binding cue).

Figure 2 shows the salivary cortisol, DHEA and cortisol/DHEA ratios of controls and depressed patients. The cortisol concentrations of controls showed the characteristic circadian rhythm repeatedly described in many studies for healthy subjects: significantly higher levels at morning at 7AM, decreased levels at 4 PM and the lowest levels at 10 PM [all p=0.000]. Cortisol levels of patients with major depression also differed significantly over the three sampling times [all p=0.000], decreasing from 7AM to 4 PM, and reaching the lowest concentrations at 10 PM. Besides the significant effect seen for sampling time [F(2,56)=598.69, p=0.000] we also observed a significant group effect [F(1,28)=19.63, p=0.000], indicating different cortisol levels for controls and major depression patients. As confirmed with independent samples t test, depressed patients had significantly lower cortisol levels in all sampling times [all p< 0.05].

Salivary DHEA levels also showed circadian alterations, as indicated by a significant effect of sampling time [F(2,56)=275.33, p=0.000] and confirmed with dependent samples t test, which indicated higher levels of DHEA at 7 AM, decreased levels at 4 PM and the lowest levels at 10 PM in controls and depressed patients [all p<0.000]. No significant effect for group [F(91,28)=2.18, p=0.15] or for group and sampling time interaction [F(2,56)=0.62, p=0.54] was observed, indicating the absence of differences between DHEA concentrations between controls and major depression patients at the different sampling times, as confirmed with independent t tests [all p>0.05].

As expected from the cortisol and DHEA results, cortisol/DHEA ratio was also subjected to a significant effect of sampling time [F(2,56)=208.35, p=0.000], showing the same pattern of circadian rhythm than cortisol and DHEA, with progressively decreasing ratios in controls and depressive patients from 7 AM to 4 PM [all p=0.000], and from 4 PM to 10 PM [all p=0.000]. We also found a significant group effect [F(1,28)=11.24, p=0.002] and independent samples t test indicated lower cortisol/DHEA ratios at 7AM (t= -3,68, df=28, p=0.001) and 4 PM (t= -2,15, df=28, p=0.04) for major depression patients.

The evident difference observed between controls and patients in context recognition in the incidental encoding condition without binding cue led us to examine whether this difference would remain after taking into account the between group differences in neuropsychological measures and hormonal levels. Two separate analysis of covariance (ANCOVAS) were carried out: one with MEEM, Vocabulary subtest and completed categories on the WCST as covariates and the other with cortisol levels at 7 AM, 4 PM and 10 PM, as well as cortisol/DHEA ratio at 7 AM and 4 PM, as covariates. The ANCOVA for neuropsychological measures showed that scores for Vocabulary subtest [F(1,17)=4.36, p=0.022], but not scores for MEEM [F(1,17)=0.35, p=0.56] and completed categories on the WCST [F(1,17)=4.36, p=0.056], had a significant effect as covariate, although the resulting adjustment of the means for the groups' differences in this variable could not eliminate differences between the performance of the contextual memory task between controls and depressed patients [F(1,17)=6.33, p=0.027]. The ANCOVA for hormonal levels showed that cortisol at 4 PM [F(1,16)=5.61, p=0.042] and cortisol/DHEA ratio at 7AM [F(1,16)=29.49, p=0.000] and 4 PM [F(1,16)=12.71, p=0.006] had significant effects as covariates, but they were also unable to eliminate differences in the performance of the contextual memory task between experimental groups [F(1,16)=14.43, p=0.003]. Together these results indicate that neurophsychological (Vocabulary subtest) and hormonal characteristics (cortisol at 4 PM and cortisol/DHEA ratio at 7 AM and 4 PM) are potentially capable to influence the performance in the incidental contextual memory task in the absence of a specific binding cue, but can not explain the recognition deficits of patients with major depression.

DISCUSSION

In the present study, we investigated recognition memory performance for items (ie. objects) and contexts (ie. locations), and measured basal cortisol and DHEA secretion in treatment-resistant depressed patients and healthy comparison subjects. The main findings indicate that although patients and controls exhibited performance-matched recognition scores for items, patients showed a specific deficit for incidental contextual memory in the absence of a specific binding cue at encoding (judging daily intensity use of objects). Lower basal levels of cortisol and the cortisol/DHEA ratio in patients compared to controls were not causally related to this deficit. Under incidental encoding with object-location binding (judging the degree of appropriateness of an object in relation to the location where it is portrayed) no more differences were observed between the groups.

The pattern of recognition memory deficits exhibited by depressed patients in this study indicates that they have a preserved ability to encode and retrieve central content under incidental encoding. Literature on memory deficits in depression shows that impairment in episodic memory, although common in major depressive disorders, is highly dependent on the type of task used to evaluate memory, with prominent declines observed in tasks that require greater engagement of attentional resources (Hammar and Ardal, 2009). The nature of the recognition paradigm used in our study did not require subjects to use self-iniated intentional strategies to performe it, which could contribute to their good performance. A similar pattern of recognition memory for objects can be observed in a previous study with older adults with depressive symptoms (Balardin et al., 2009), which supports the hypothesis that memory function in depression is more influenced by domain general functions than by age (Fossati et al., 2002).

Contrasting with object recognition performance, patients exhibit memory difficulties in associate object representations with their particular locations in the absence of specific binding instructions at encoding. A similar pattern of dissociation between preserved item memory and impaired contextual memory can be observed in aging (Grady and Craik, 2000) and in patients with frontal lobe damage (Butters et al., 1994). Problems in spontaneous use of organizational strategies at encoding have been previously reported in remitted major depressive patients (Behnken et al., 2010). However, as well as healthy older adults (Glisky et al., 2001; Naveh-Benjamin and Craik, 1995) and older adults with mild depressive symptoms (Balardin et al., 2009), patients in the present study could

benefit from conditions in which cognitive support at encoding was manipulated by presenting incidental associative binding instructions, suppressing their contextual memory deficits. Even in the presence of neuropsychological indicators of frontal lobe dysfunction (fewer categories completed in the WCST), patients could engaged executive mechanisms to maintain performance in front of major depressive neuropathology.

Although the contextual memory deficits seen in the absence of specific binding instructions at encoding could not be explained by cortisol an DHEA levels, it is important to note that cortisol and cortisol/DHEA ratios had significant effects as covariates, suggesting their potential roles in the modulation of cognitive deficits. Findings on cortisol levels in major unipolar depression are controversial. The most reported finding is hipercortisolemia (Kessing et al., 2011; Pariente and Lightman, 2008), but hypocortisolemia (Bremmer et al., 2007; Oldehinkel et al., 2001; Morrison et al., 2000) and normocortisolemia (Young et al., 2001) have also been described. In our study we found lower cortisol levels in depressed patients compared with controls. Bremmer et al. (2007) suggested that the hypocortisolemia associated with depression could be a sign of exhaustion of the HPA axis as a result of chronic stress. Elderly patients with long-lasting and recurrent depressive episodes also showed lower cortisol levels (Oldehinkel et al., 2001). However, it should be taken in consideration that the characterization of adrenal fatigue should also consider, besides hormonal changes, other signs and symptoms (Heim et al, 2000) that were not analyzed in this study. This issue is especially important when cortisol levels are not extremely altered, as is the case of the results for our major depressive patients, and deserves more attention in future studies. Another important aspect that could be involved in the hypocortisolemia observed in this study is antidepressant drug therapy (Michelson et al., 1997; Cooney and Dinan, 2000; Deuschle et al., 2003; Piwowarska et al., 2008). Although the mechanisms of action of antidepressants on the HPA axis are not completely known, studies in human and animal models have demonstrated that these drugs can act through direct modulation of the expression and function of the glucocorticoid receptor (GR), which in turn reduces the HPA axis activity (see Juruena et al, 2004 for a discussion on this topic).

The modulatory role of corticosteroid systems on memory function have been explained by an inverted U-shaped function, with moderate glucocorticoid concentrations enhancing encoding and consolidation, but very low and very high concentrations exerting a impairing effect (Roozendaal, 2000; Abercrombie et al. 2003). The majority of studies on this topic examined the effects of elevated

cortisol levels induced by pharmacological intervention or acute stress (Maheu et al., 2004; Het et al., 2005)), and emphasized the negative impact of chronic hypercortisolemia on memory (León-Carrión et al., 2009; Grillon et al., 2004; Li et al., 2006). However, a deleterious effect of acute suppression of cortisol synthesis on free recall was demonstrated, although recognition was preserved (Rimmele et al., 2010). This finding is corroborated by the results of studies in medical conditions that present a pattern of diminished cortisol secretion, such as fibromyalgia and chronic fatigue syndrome. Lower salivary cortisol levels were associated with worse visual and verbal memory performance in the former (Sephton et al., 2003), and lower urinary free cortisol levels were associated with poor response in cognitive behavioral therapy in the latest (Roberts et al., 2010).

The depressive patients of this study also showed a diminished cortisol/DHEA ratio. Considering the ratio of both steroids is important because they have different and often antagonistic effects on each other. Besides, several groups have found that cortisol/DHEA ratio in serum and saliva, rather than concentrations of either hormone alone, more accurately discriminate depressed from non-depressed patients (review in Maniger et al., 2009). The diminished cortisol/DHEA ratio shown by our depressive patients was resultant from the lower cortisol levels of this subjects, since no significant differences in DHEA levels were found between controls and patients. As occurs for cortisol, findings on DHEA levels in major unipolar depression are also controversial. The great majority of studies show that depressed patients have increased DHEA levels (Heuser et al., 1998; Fabian et al, 2001; Hsiao., 2006), which can decrease to normal values with remission. However, some studies also report lower (Michael et al., 2000) as well as normal DHEA levels in patients with depression (Romeo et al., 1998).

There are some limitations that need to be addressed regarding the present study. First, the cross-sectional design does not permit us to investigate the associations between the persistence of an altered cortisol secretion pattern and the remission/progression of depression. Additional longitudinal studies are needed to clarify this association, and, moreover, to try to disentangle the effects of treatment-resistant depressive symptomatology, antidepressant therapy and HPA axis dysfunction on memory function in major depression. Another limitation concerns our sample, which proved to be heterogeneous in symptom severity (BDI mean=29.8 $\pm$ SEM=2.57) and consisted of first instance patients as well as subjects with recurrent depressive episodes. Number of depressive episodes has been described as a good predictor of hippocampal volume and related memory

function in MDD (Campbell et al., 2004; McKinnon et al., 2009). Although all patients in our study were on medication for at least six months, they were taking different drugs that could impact cognitive function and HPA axis activity function through different mechanisms. Some of these drugs, such as selective serotonin reuptake inhibitors (SSRIs), could have positive effects on memory and other cognitive aspects (Cassano et al., 2002; Levkovitz et al., 2002). Others, like benzodiazepines, can have negative impact on memory and cognitive performance (Stewart, 2005).

In conclusion, in this study we provide evidence that contextual memory deficits in major depressive patients could be reduced by providing additional cognitive support at encoding. The potential role of this incidental memory strategy should be investigated in future studies on the effects of cognitive interventions in MDD.

ACKNOWLEDGEMENTS

Financial support for this study was provided by a CNPq grant (474271/2007-2) to Dr Elke Bromberg. M.P. Fleck and I.I. Argimon are CNPq research fellows. M.S. Correa was a CAPES Ministry of Education and Culture fellowship and J.B. Balardin is a FAPESP fellowship.

REFERENCES

Abercrombie, H.C., Kalin, N.H., Thurow, M.E., Rosenkranz, M.A., Davidson, R.J., 2003. Cortisol variation in humans affects memory for emotionally laden and neutral information. Behav. Neurosci. 117, 505–516.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). American Psychiatric Association. Washington D.C., 886p.

Austin, M.P., Mitchell, P., Goodwin, G.M. 2001. Cognitive deficits in depression: Possible implications for functional neuropathology. British Journal of Psychiatry 178, 200-6.

Balardin, J.B., Vedana, G., Ludwing, A., Lima, D.B., Argimon, I., Schneider, R., Luz, C., Schroder., N., Bromberg., E. 2009 .Contextual memory and encoding strategies in young and older adults with and without depressive symptoms. Aging Ment Health 13, 313-18.

Beck, A.T., Steer, R.A. 1993. Beck depression inventory. Manual. San Antonio, TX: Psychology Corporation.

Behnken, A., Schöning, S., Gerss, J., Konrad, C., Jong-Meyer, R., Zwanzger, P., Arolt, V., 2010. Persistent non-verbal memory impairment in remitted major depression - caused by encoding deficits? J. Affect. Disord. 122, 144-8.

Braw, Y., Aviram, S., Bloch, Y., Levkovitz, Y. 2010. The effect of age on frontal lobe related cognitive functions of unmedicated depressed patients. Journal of Affective Disorders.

Bremmer, M.A., Deeg, D.J.H., Beekman, A.T.F., Penninx, B.W.J.H., Lips, P., Hoogendijk, W.J.G. 2007. Major Depression in Late Life Is Associated with Both Hypo- and Hypercortisolemia. Biol Psychiatry 62, 479–86.

Butters, M.A., Kaszniak, A.W., Glisky, E.L., Eslinger, P.J., Schacter, D.L. 1994. Recency discrimination deficits in frontal lobe patients. Neuropsychology 8, 343–53.

Campbell, S., Marriott, M., Nahmias, C., MacQueen, G.M., 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. The American Journal of Psychiatry 161, 598–607.

Castaneda, A.E., Tuulio-Henriksson A., Marttunen M., Suvisaari J., Lönnqvist J. 2008. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J. Affect. Disord. 106, 1-27.

Cassano, G.B., Puca, F., Scapicchio, P.L., Trabucchi, M. 2002. Paroxetine and Fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. J Clin Psychiatry 63, 396–402.

Cooney, J.M., Dinan, T.G. 2000. Hypothalamic Pituitary Adrenal Axis Early Feedback Responses are Preserved in Melancholic Depression A Study of Sertraline Treatment. Human Psychopharmacology 15, 351-6.

Cunha, J.A. 2001. Escalas Beck [Beck Scales]. São Paulo: Casa do Psicólogo.

Deuschle, M., Hamann, B., Meichel, C., Krumm, B., Lederbogen, F., Kniest, A., Colla, M., Heuser, I. 2003. Antidepressive Treatment with Amitriptyline and Paroxetine: Effects on Saliva Cortisol Concentrations. Journal of Clinical Psychopharmacology 23, 201-5.

Dos Santos, C.M., Balardin, J.B., Irigaray, T.Q., Schröder, N., Rieder, C.R.M., Bromberg., E. 2010. Incidental Encoding Strategies Did Not Improve Contextual Memory in Parkinson's Disease Patients. Neurorehabilitation and Neural Repair 24, 450– 456.

Egeland, J., Lund, A., Landro, N.I., Rund, B.R., Sundet, K., Asbjornsen, A., 2005. Cortisol level predicts executive andmemoryfunction in depression, symptom level predicts psychomotor speed. Acta Psychiatry Scand 112, 434–441.

Fabian, T.J., Dew, M.A., Pollock, B.G., Reynolds, C.F., Mulsant, B.H., Butters, M.A., Zmuda, M.D., Linares, A.M., Trottini, M., Kroboth, P.D. 2001. Endogenous concentrations of DHEA and DHEA-S decrease with remission of depression in older adults. Biol. Psychiatry 50, 67–74.

Fabiani, M., Friedman, D. 1997. Dissociations between memory for temporal order and recognition memory in aging. Neuropsychologia 35, 129–141.

Fossati, P., Coyette, F., Ergis, A.M., Allilair, J.F. 2002. Influence of age and executive functioning on verbal memory of inpatients with depression. Journal of Affective Disorders 68, 261–271.

Fossati, P., Harvey, P.O., Le Bastard, G., Ergis, A.M., Jouvent, R., Allilaire, J.F. 2004. Verbal memory performance of patients with a first depressive episode and patients with unipolar recurrent depression. Journal of Psychiatric Research 38, 137–144.

Folstein, M.F., Folstein, S.E., McHugh, P.R. 1975. 'Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12, 189–198.

Glisky, E.L., Rubin, S.R., Davidson, P.R.S. 2001. Source Memory in Older Adults: An Encoding or Retrieval Problem? Journal of Experimental Psychology 27, 1131-1146.

Gomez, R.G., Posener, J.A., Keller, J., DeBattista, C., Solvason, B., Schatzberg, A.F. 2009. Effects of major depression diagnosis and cortisol levels on indices of neurocognitive function. Psychoneuroendocrinology 34, 1012–1018.

Gorwood, P., Corruble, E., Falissard, B., Goodwin, G.M. 2008. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. Am. J. Psychiatry 165, 731-9.

Grady, C.L., Craik, F.I. 2000. Changes in memory processing with age. Current. Opinion in Neurobiology 10, 224–31.

Grant, M.M., Thase, M.E., Sweeney, J.A. 2001. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. Biol. Psychiatry 50, 35-43.

Grillon, C., Smith, K., Haynos, A., Nieman, L.K. 2004. Deficits in hippocampus-mediated Pavlovian conditioning in endogenous hypercortisolism. Biol Psychiatry. 56, 837-43.

Hammar, A., Ardal, G. 2009. Cognitive functioning in major depression--a summary. Front. Hum. Neurosci. 3, 26.

Heaton, R. 1993. Wisconsin card sorting test manual (revised, & expanded). Odessa: Psychological Assessment Resources.

Heim, C., Ehlert, U., Hellhammer, D.H., 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25, 1-35.

Hertel, P.T., Rude, S.S. 1991. Depressive deficits in memory: focusing attention improves subsequent recall. J. Exp. Psychol. Gen. 120, 301-9.

Hertel, P. T., Milan, S. 1994. Depressive deficits in recognition: Dissociation of recollection and familiarity. Journal of Abnormal Psychology, 103, 736–742.

Het, S., Ramlow, G., Wolf, O.T. 2005. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology 30, 771-84.

Heuser, I., Deuschle, M., Luppa, P., Schweiger, U., Standhardt, H., Weber, B. 1998. Increased Diurnal Plasma Concentrations of Dehydroepiandrosterone in Depressed Patients. Journal of Clinical Endocrinology and Metabolism 83, 3130-33.

Hinkelmann, K., Moritz, S., Botzenhardt, J., Riedesel, K., Wiedemann, K., Kellner, M., Otte, C. 2009. Cognitive Impairment in Major Depression: Association with Salivary Cortisol. Biol. Psychiatry 66, 9879-885.

Hollingworth, A., Rasmussen, I.P. 2010. Binding objects to locations: the relationship between object files and visual working memory. J. Exp. Psychol. Hum. Percept. Perform. 36, 543-64.

Hsiao, C.C. 2006. Difference in pre- and post-treatment plasma DHEA levels were significantly and positively correlated with difference in pre- and post-treatment Hamilton depression scores following successful therapy for major depression. Psychoneuroendocrinology 31, 839-46.

Juruena, M.F., Clearea, A.J., Pariantea, C.M. 2004. The hypothalamic pituitary adrenal axis, glucocorticoid receptor function and relevance to depression. Rev. Brás. Pisquiatr. 26, 189-201.

Kaminska, M., Harris, J., Gijsbers, K., Dubrovsky, B. 2000. Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP: implications for depression. Brain Res. Bull. 52, 229–34.

Kessing, L.V., Willer, I.S., Knorr, U. 2011. Volume of the adrenal and pituitary glands in depression. Psychoneuroendocrinology 36, 19-27.

León-Carrión, J., Atutxa, A.M., Mangas, M.A., Soto-Moreno, A., Pumar, A., Leon-Justel, A., Martín-Rodriguez, J.F., Venegas, E., Domínguez-Morales, M.R., Leal-Cerro, A. 2009. A clinical profile of memory impairment in humans due to endogenous glucocorticoid excess. Clin. Endocrinol 70, 192-200.

Levkovitz, Y., Caftori, R., Avital, A., Richter-Levin, G. 2002. The SSRIs drug Fluoxetine, but not the noradrenergic tricyclic drug Desipramine, improves memory performance during acute major depression. Brain Res Bull 58, 345–50.

Li, G., Cherrier, M.M., Tsuang, D.W., Petrie, E.C., Colasurdo, E.A., Craft, S., Schellenberg, G.D., Peskind, E.R., Raskind, M.A., Wilkinson, C.W. 2006. Salivary cortisol and memory function in human aging. Neurobiol. Aging 27, 1705-14.

Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C. 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434-45.

MacQueen, G., Galway, T., Hay, J., Young, L.T., Joffe, R.T. 2002. Recollection memory deficits in patients with major depressive disorder predicted by past depressions but not current mood state or treatment status. Psychol. Med. 32, 251–58.

Maheu, F.S., Joober, R., Beaulieu, S., Lupien, S.J. 2004. Differential Effects of Adrenergic and Corticosteroid Hormonal Systems on Human Short- and Long-Term Declarative Memory for Emotionally Arousing Material. Behav. Neurosci. 118, 420-8.

Maninger, N., Wolkowitz, O.M., Reus, V.I., Epel, E.S., Mellon, S.H. 2009. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol. 30, 65-91.

Maveh-Benjamin, M., Craik, F.I. 1995. Memory for context and its use in item memory: comparisons of younger and older persons. Psychology and Aging 10, 284–93.

McKinnon, M.C., Yucel K., Nazarov, A., MacQueen, G.M. 2009. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J. Psychiatry Neurosci. 34, 41–54.

Michael, A., Jenaway, A., Paykel, E.S., Herbert, J. 2000. Altered salivary dehydroepiandrosterone levels in major depression in adults. Biol. Psychiatry 48, 989–95.

Michelson, D., Galliven, E., Hill, L., Demitrack, M., Chrousos, G., Gold, P. 1997. Chronic imipramine is associated with diminished hypothalamic-pituitary-adrenal axis responsivity in healthy humans. Journal of Clinical Endocrinology and Metabolism 82, 2601-6.

Morrison, M.F., Redei, E., TenHave, T., Parmelee, P., Boyce, A.A., Sinha, P.S., Katz, I.R. 2000. Dehydroepiandrosterone Sulfate and Psychiatric Measures in a Frail, Elderly Residential Care Population. Biol. Psychiatry 47,144-50.

Oldehinkel, A.J., Berg, M.D., Flentge, F., Bouhuys, L.A., Horst, G.J., Ormel, J. 2001. Urinary free cortisol excretion in elderly persons with minor and major depression. Psychiatry Research 104, 39-47.

Pariante, C.M., Lightman, S.L. 2008. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 31, 464-8.

Piwowarska, J., Dryll, K., Szelenberger, W., Pachecka, J. 2008. Cortisol level in men with major depressive disorder treated with fluoxetine or imipramine. Acta Poloniae Pharmaceutica 65, 159-64.

Rimmele, U., Meier, F., Lange, T., Born, J. 2010. Suppressing the morning rise in cortisol impairs free recall. Learn. Mem. 17, 186-90.

Rinck, M., Becker, E. 2003. Selective memory and memory deficits in depressed inpatients. Depress. Anxiety 17, 197–206.

Roberts, A.D., Charler, M.L., Papadopoulos, A.., Wessely, S., Chalder, T., Cleare, A.J. 2010. Does hypocortisolism predict a poor response to cognitive behavioural therapy in chronic fatigue syndrome? Psychol. Med. 40, 515-22.

Romeo, E., Ströhle, A., Spalletta, G., di Michele, F., Hermann, B., Holsboer, F., Pasini, A., Rupprecht, R. 1998. Effects of Antidepressant Treatment on Neuroactive Steroids in Major Depression. Am. J. Psychiatry 155, 910-3.

Roozendaal, B., 2000. Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 25, 213–38.

Rubinow, D.R., Post, R.M., Savard, R., Gold, P.W. 1984. Cortisol hypersecretion and cognitive impairment in depression. Arch. Gen. Psychiatry 41, 279– 283.

Sephton, S.E., Studts, J.L., Hoover, K., Weissbecker, I., Lynch, G., Ho, I., McGuffin, S., Salmon, P. 2003. Biological and psychological factors associated with memory function in fibromyalgia syndrome. Health Psychol. 22, 592-7.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C. 1998 .The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22-33.

Stewart, S.A. 2005. The effects of benzodiazepines on cognition. J. Clin. Psychiatry 66, 9-13.

Taconnat, L., Baudouin, A., Fay, S., Raz, N., Bouazzaoui, B., El-Hage, W., Isingrin, M., Ergis, A.M. 2010. Episodic memory and organizational strategy in free recall in unipolar depression: The role of cognitive support and executive functions. J. Clin. Exp. Neuropsychol. 32, 719-27.

Young, E.A., Carlson, N.E., Brown, M.B. 2001. Twenty-four-hour ACTH and cortisol pulsatility in depressed women. Neuropsychopharmacology 25, 267-76.

Wang, C. E., Halvorsen, M., Sundet, K., Steffensen, A. L., Holte, A., Waterloo, K. 2006. Verbal memory performance of mildly to moderately depressed outpatient younger adults. J. Affect. Disord. 92, 283–286.

Wechsler, D. 1997. WAIS III: Administration and scoring manual. San Antonio, TX: Harcourt.

Wolkowitz, O.M., Reus, V.I., Roberts, E., Manfredi, F., Chan, T., Raum, W.J., Ormiston, S., Johnson, R., Canick, J., Brizendine, L., Weingartner, H. 1997. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry 41, 311–318.

LEGEND OF FIGURES AND TABLES

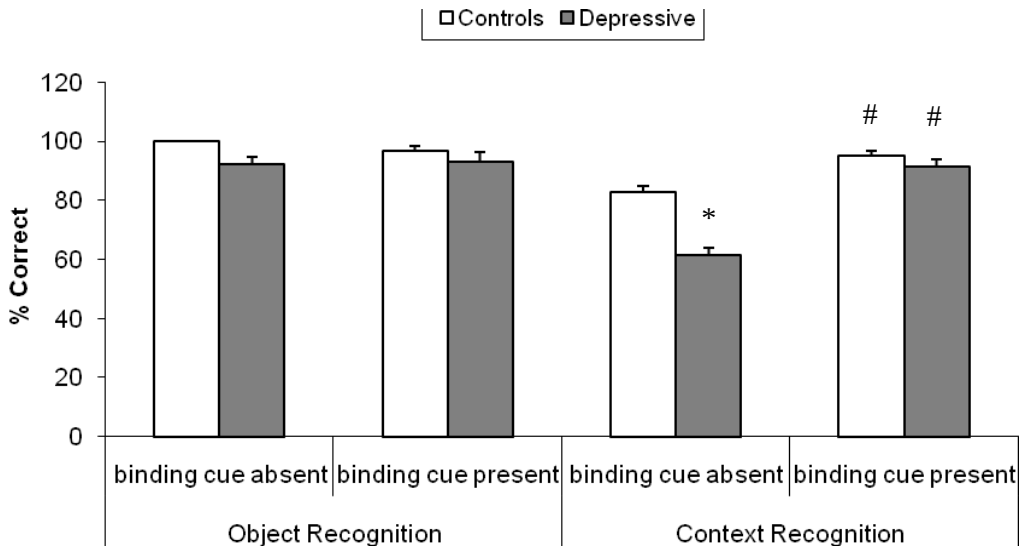
Table I. Mean (±SEM) values of demographic and neuropsychological measures for young adult controls and depressive patients.

Abbreviations: MMSE, Mini Mental Status Examination; WCST, Wisconsin Card Sorting Test; [a]Scaled scores from the Weschler Adult Intelligence Scale

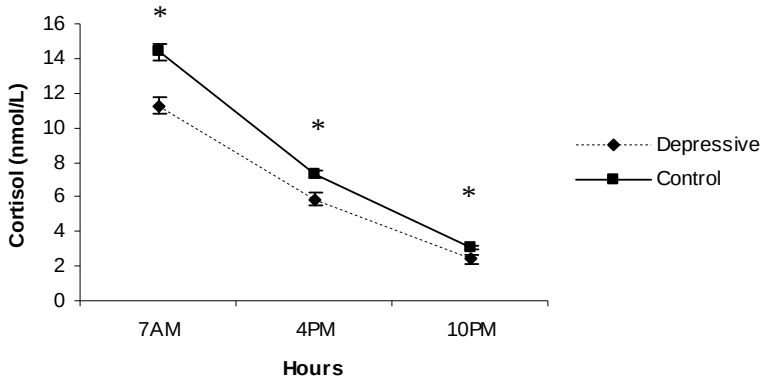
* P<0.05 in relation to controls

Figure 1. Object and context recognition performance (mean±SEM) of controls and depressive patients under two encoding conditions.*$P < 0.001$, compared to the context recognition of the other subgroups; [#]$P < 0.05$, compared to the context recognition of subgroups that made the task in the absence of a binding cue at encoding.

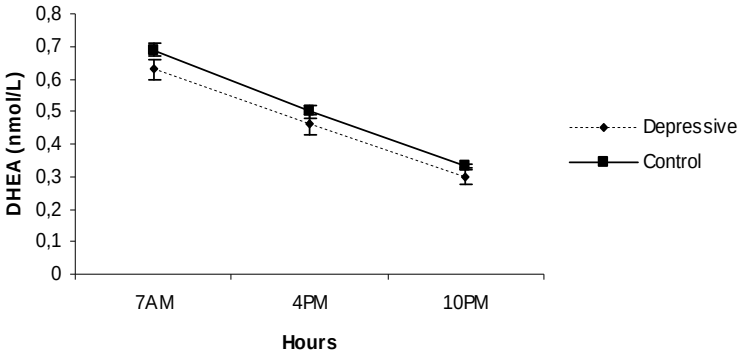
Figure 2: Levels (mean ± SEM) of cortisol (A)**,** DHEA (B) and Cortisol/DHEA ratios (C) in saliva samples of depressive patients and controls at 7AM, 4PM and 10PM. *$P < 0.05$ in relation to the between-groups differences at each sampling time.


Controls
Depressive
% Correct
120
100
80
60
40
20
0
#
#
*
binding cue absent
binding cue present
binding cue absent
binding cue present
Object Recognition
Context Recognition

A


Cortisol (nmol/L)
16
14
12
10
8
6
4
2
0
*
*
*
7AM
4PM
10PM
Hours
Depressive
Control

B


DHEA (nmol/L)
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
7AM
4PM
10PM
Hours
Depressive
Control

C

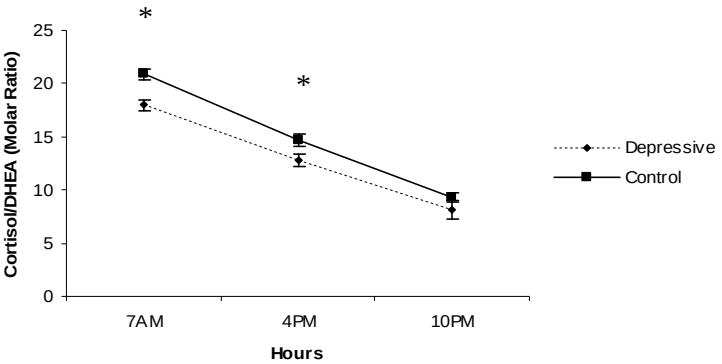

Cortisol/DHEA (Molar Ratio)
25
20
15
10
5
0
*
*
7AM
4PM
10PM
Hours
Depressive
Control

Table I. Mean (±SEM) values of demographic and neuropsychological measures for young adult controls and depressive.

	Controls	Depressive
Age (years)	29.77 ± 1.00	32.52 ± 1.83
Sex (female/male)	19 / 3	14 / 3
Education (years)	10.63 ± 0.50	9.29 ± 0.74
MMSE	29.09 ± 0.23	27.52 ± 0.53 *****
BDI	4.45 ± 0.67	29.88 ± 2.57 *****
Vocabulary [a]	11.38 ± 0.38	9.26 ± 0.41 *****
WCST (Categories Completed)	3.68 ± 0.24	2.07 ± 0.43 *****
WCST (Perseverative errors)	5.95 ± 1.03	8.00 ± 1.67

Abbreviations: MMSE, Mini Mental Status Examination; WCST, Wisconsin Card Sorting Test; [a] Scaled scores from the Weschler Adult Intelligence Scale.
***** P<0.05 in relation to controls

3 CAPÍTULO 3

3.1 CONSIDERAÇÕES FINAIS

Como já demonstrado em estudos anteriores, uma das grandes conseqüências da depressão são as alterações cognitivas (McDermott & Ebmeier, 2009; Hill, 2004; Austin, Mitchell, Goodwin, 2001). A maioria desses estudos mostra essas alterações em idosos (Butters et al., 2004; Ganguli et al., 2006; Nebes et al., 2000, 2006). Poucos trabalhos relatam disfunções cognitivas em pacientes depressivos adultos (Castaneda et al., 2008). Dentre as principais queixas desses pacientes estão na atenção, função executiva e memória (McDermott & Ebmeier, 2009; Porter et al.,2003).

Neste estudo, nós encontramos déficits cognitivos em depressivos jovens adultos. A performance nos testes de vocabulário e classificação de cartas de wisconsin (função executiva) dos pacientes depressivos foi mais baixo, se comparados aos controles. Esses resultados reforçam estudos anteriores (Braw et al., 2010; McDermott & Ebmeier, 2009; Austin, Mitchell, Goodwin, 2001) que mostram que indivíduos com essa doença têm baixo desempenho em testes neuropsicológicos.

Sobre os resultados de memória, os pacientes não diferenciaram dos controles quanto ao reconhecimento do objeto. Todavia, apresentaram escores significativamente mais baixos para memória de reconhecimento do contexto. O grupo depressivo sem estratégia de codificação foi o que teve a performance mais baixa.

Esses resultados sugerem que apesar da depressão afetar a memória contextual desses indivíduos, eles ainda têm uma reserva cognitiva que os permitem melhorar os resultados quando há estratégias de codificação, corroborando os

achados de outros trabalhos que indicam que o uso dessas estratégias pode eliminar os déficits de memória contextual (Balardim et al., 2009; Glisky, Rubin, Davidson, 2001).

Há também trabalhos que mostram que mesmo com a introdução de estratégias de codificação, pacientes depressivos idosos não conseguem melhorar o desempenho nos testes de memória contextual (resultados ainda não publicados). Isso sugere que os indivíduos do nosso estudo podem ter sido beneficiados de tais estratégias devido à idade.

Outro ponto importante de destacar é que nosso teste de memória contextual é incidental, ou seja, os indivíduos não sabiam que seriam questionados posteriormente. A maioria dos trabalhos que mostra déficits de memória utiliza testes intencionais, quando o indivíduo sabe que deve memorizar. Desta forma, acreditamos que nossos resultados sejam bastante contundentes.

Em nossa pesquisa, encontramos também alterações neurohormonais nos pacientes. Diferente da maioria dos estudos que mostram a hipercortisolemia em indivíduos com depressão (Kessing, Willer, Knorr, 2011; Pariente & Lightman, 2008), nossos pacientes apresentaram baixos níveis circadianos de cortisol. Esses resultados fortalecem achados anteriores que demonstram a hipocortisolemia durante a doença (Bremmer et al., 2007; Oldehinkel et al., 2001; Morrison et al., 2000).

Os grupos não apresentaram diferença significativa nos níveis circadianos de DHEA. Já a razão cortisol/DHEA foi mais baixa nos pacientes depressivos, devido os resultados do cortisol desses indivíduos.

Há trabalhos que sugerem que a hipocortisolemia na depressão possa ser um efeito dos antidepressivos (Piwowarska et al., 2008; Deuschle et al., 2003; Cooney &

Dinan, 2000) que ajustam o eixo HPA. Bremmer et al. (2007), sugere que baixos níveis de cortisol ocorrem quando há uma exaustão do eixo HPA devido a cronicidade do estresse.

Outros estudos sugerem que esse efeito ocorre em pacientes resistentes ao tratamento farmacológico (Oldehinkel et al., 2001), como nós verificamos nos sujeitos do nosso estudo.

Em resumo, encontramos déficits na memória contextual e baixos níveis circadianos de cortisol e razão cortisol/DHEA, em indivíduos com sintomatologia depressiva. A memória contextual foi recuperada quando foi introduzida uma estratégia de codificação. Desta forma, concluímos que esses achados são importantes, pois mostram que pacientes depressivos adultos, apesar dos déficits cognitivos, têm uma importante reserva cognitiva. Além disso, sugerem que a introdução de medidas de reabilitação cognitiva são importantes, do ponto de vista médico, para pacientes depressivos adultos, pois talvez essa idade seja crucial para reverter os danos cognitivos causados pela doença.

REFERÊNCIAS BIBLIOGRÁFICAS

ALEXOPOULOS, G.S. Depression in the elderly. **The Lancet**. v.365, p.1961-70, 2005.

ALONSO, G. et al. Immunocytochemical localization of the σ1 receptor in the adult rat central nervous system. **Neuroscience**. v.97, p.155–170, 2000.

AUSTIN, M.P., MITCHELL, P., GOODWIN, G.M. Cognitive deficits in depression: Possible implications for functional neuropathology. **British Journal of Psychiatry**. v.178, p.200-6, 2001.

BALARDIN, J.B. et al. Contextual memory and encoding strategies in young and older adults with and without depressive symptoms. **Aging Ment Health**. v.13, p.313-318, 2009.

BEHNKEN, A. et al. Persistent non-verbal memory impairment in remitted major depression - caused by encoding deficits? J. Affect. Disord. 122, 144-8, 2010.

BRAND, A.N., JOLLES, J., GISPEN-DE-WIED, C. Recall and recognition memory deficits in depression. **J Affect Disord**. v.25, n. 1, p.77-86, 1992.

BRAW et al. The effect of age on frontal lobe related cognitive functions of unmedicated depressed patients. **Journal of Affective Disorders**. 2010.

BREMMER, M.A., et al. Major Depression in Late Life Is Associated with Both Hypo- and Hypercortisolemia. **Biol Psychiatry**. v.62, p.479–486, 2007.

BROWN, E.S., VARGHESE, F.P., MCEWEN, B.S. Association of depression with medical illness: does cortisol play a role? **Biol Psychiatry**. v.55, p.1-9. 2004.

BURT, D.B., ZEMBAR, M.J., NIEDEREHE, G. Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. **Psychol. Bull**. v.117, p.285–305, 1995.

BUTTERS, M.A. et al. The Nature and Determinants of Neuropsychological Functioning in Late-Life Depression. **Arch Gen Psychiatry.** v.61, p.587-95, 2004.

CASTANEDA, A.E., et al. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. **J Affect Disord**. v.106, p.1-27, 2008.

COONEY, J.M.& DINAN, T.G. Hypothalamic_Pituitary_Adrenal Axis Early Feedback Responses are Preserved in Melancholic Depression] A Study of Sertraline Treatment. **Human Psychopharmacology**. v.15, p.351-6, 2000.

DATSON N.A. et al. Central corticosteroid actions: Search for gene targets. **European Journal of Pharmacology** v. 583 272–289, 2008.

DE KLOET, E. R. Brain corticosteroid receptor balance in health and disease. **Endocr. Rev**. v.19, p. 269–301, 1998.

DENT, O.F. et al. Association between depression and cognitive impairment in aged male war veterans. **Aging & Mental Health**. v.2, n.4, p.306-12, 1998.

DEUSCHLE, M. et al. Antidepressive Treatment with Amitriptyline and Paroxetine: Effects on Saliva Cortisol Concentrations. **Journal of Clinical Psychopharmacology**. v.23, n.2, p.201-5, 2003.

DIORIO, D., VIAU, V., MEANEY, M.J. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. **Journal of Neuroscience**. v.13(9), p.3839-47, 1993.

DREVETS, W.C., PRINCE, J.L., FUREY, M.L. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. **Brain Struct Funct**. v.213, p.93-118, 2008.

DUMAN, R.S., MONTEGGIA, L.M. A neurotrophic model for stress-related mood disorders. **Biol. Psychiatry**. v.59, p.1116–1127, 2006.

DUVAL, F. et al., Cortisol hypersecretion in unipolar major depression with melancholic and psychotic features: Dopaminergic, noradrenergic and thyroid correlates. **Psychoneuroendocrinology**. v.31, p.876–88, 2006.

FABIAN, T.J. Endogenous concentrations of DHEA and DHEA-S decrease with remission of depression in older adults. **Biol Psychiatry**. v.50, p.67–74, 2001.

FIETTA, P., FIETTA P. Glucocorticoids and brain functions. **Riv Biol.** v.100 p.403-18, 2007.

FLECK, M.P. et al. Revision of the guidelines of the Brazilian Medical Association for the treatment of depression. **Rev. Bras. Psiquiatr**. v.31, p.7-17, 2009.

FOSSATI, P. et al. Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. **Psychiatry Res**. v.89, p.171–87, 1999.

GALLAGHER, P. et al. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. **Schizophrenia Research**. v.90 p. 258–265, 2007.

GANGULI, M. Et al. Depressive Symptoms and Cognitive Decline in Late Life: *A Prospective Epidemiological Study.* **Arch Gen Psychiatry**. v.63, p.153-160, 2006.

GLISKY, E.L., RUBIN, S.R., DAVIDSON, P.S.R. Source Memory in Older Adults: An Encoding or Retrieval Problem? **Journal of Experimental Psychology**. v.27, n.5, p.1131-1146, 2001.

GRANT, M.M., THASE, M.E., SWEENEY, J.A. Cognitive Disturbance in Outpatient Depressed Younger Adults: Evidence of Modest Impairment. **Biol Psychiatry**. v.50, p.35-43, 2001.

HALLER, J., MIKICS, E., MAKARA, G. The effects of non-genomic glucocorticoid mechanisms on bodily functions and the central neural system. A critical evaluation of findings. **Frontiers in Neuroendocrinology**. v.29 p. 273–291, 2008.

HAYSLIP, B. JR., KENNELLY, K.J., MALOY R.M. Fatigue, depression, and cognitive performance among aged persons**. Exp Aging Res.** v.16, n.3, p.111-5, 1990.

HECHTER, O., GROSSMAN, A., CHATTERTON, R.T.J. Relationship of dehydroepiandrosterone and cortisol in disease. **Med Hypoth.** v.49, p.85–91, 1997.

HERBERT, J. Neurosteroids, brain damage, and mental illness. **Exp Gerontol**. v.33, p.713–27, 1998.

Hill, S.K. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. **Am. J. Psychiatry**. v.161, p.996–1003, 2004.

HINKELMANN, K. et al. Cognitive Impairment in Major Depression: Association with Salivary Cortisol. **Biol Psychiatry**. v.66, p.879–85, 2009.

HOLSBOER, F., SPENGLER, D., HEUSER, I. The role of corticotropin-releasing hormone in the pathogenesis of Cushing's disease, anorexia nervosa, alcoholism, affective disorders and dementia. **Prog Brain Res**. v.93, p.385-417, 1992.

HSIAO C.C. Difference in pre- and post-treatment plasma DHEA levels were significantly and positively correlated with difference in pre- and post-treatment Hamilton depression scores following successful therapy for major depression. **Psychoneuroendocrinology.** v.31, p.839-46, 2006.

JOHNSON, M.K., HASHTROUDI, S., LINDSAY, S.D. Source monitoring. **Psychol. Bull**. v.114, p.3-28, 1993.

KELLER, J., SCHATZBERG, A.F., MAJ, M. Current Issues in the Classification of Psychotic Major Depression. **Schizophrenia Bulletin** v.33, p.877–85, 2007.

KESSING, L.V., WILLER, I.S., KNORR, U. Volume of the adrenal and pituitary glands in depression. **Psychoneuroendocrinology**. v.36, p.19—27, 2011.

KESSLER, R.C. et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disordes in the National Comorbidity Survery Replication. **Arch. Gen. Psychiatry**. v.62, pp.593-602, 2005.

KESSLER, R.C. et al. The Prevalence and Correlates of Workplace Depression in the National Comorbidity Survey Replication. **J Occup Environ Med**. v.50(4), p.381–390, 2008.

KIM, J.J., DIAMOND, D.M. The stressed hippocampus, synaptic plasticity and lost memories. **Nat. Rev. Neurosci.** v.3, p.453–462, 2002.

LEVIN, E.R. Integration of the extranuclear and nuclear actions of estrogen. **Mol. Endocrinol**. v.19 p.1951–1959, 2005.

LI, G. et al. Salivary cortisol and memory function in human aging Neurobiology of Aging v.27, p.1705–1714, 2006.

LUPIEN, S.J. Stress hormones and human memory function across the lifespan. **Psychoneuroendocrinology**. v.30, p.225–42, 2004.

LUPIEN S.J., et al. Stress hormones and human memory function across the lifespan. **Psychoneuroendocrinology Apr**; 30(3): 225-42, 2005.

MAURICE et al. Neuroactive Neurosteroids as Endogenous Effectors for the sigma1: Recpetors Pharmacological Evidence and Therapeutic Opportunities. **Jpn J. Pharmacol**. v.81, 125-155, 1999.

MAURICE et al. Neuro(active)steroids actions at the neuromodulatory sigma1 (σ1) receptor: Biochemical and physiological evidences, consequences in neuroprotection. **Pharmacology**. **Biochemistry and Behavior**. v.84 581–597, 2006.

MCDERMOTT, L.M., EBMEIER, K.P. A meta-analysis of depression severity and cognitive function. **Journal of Affective Disorders**. v.19, p.1–8, 2009.

McEWEN, B.S. The neurobiology of stress: from serendipity to clinical relevance. **Brain Research**. V. 886 p.172–189, 2000.

MEANEY, M.J., AITKEN, D.H. The effects of early postnatal handling on hippocampal glucocorticoid receptor concentrations: temporal parameters. **Brain Research**. v. 354(2), p.301-4, 1985.

MERRIAM, E.P. Prefrontal cortical dysfunction in depression determined by Wisconsin Card Sorting Test performance. **Am. J. Psychiatry**. v.156, p.780–82, 1999.

MICHAEL A. et al. Altered salivary dehydroepiandrosterone levels in major depression in adults. **Biol Psychiatry**. v.48, p.989–95, 2000.

MORRISON, M.F., et al. Dehydroepiandrosterone Sulfate and Psychiatric Measures in a Frail, Elderly Residential Care Population. **Biol Psychiatry**. v.47, p.144-150, 2000.

MURAKAMI, S. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. **Neurosci. Res**. v.53, p.129–139, 2005.

NAFZIGER, A.N. et al. Longitudinal changes in dehydroepiandrosterone concentrations in men and women. **J. Lab. Clin. Med**. v.131, p. 316–23, 1998.

NEBES, R.D. et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. **Psychological Medicine**. v.30, p.679-91, 2000.

NEBES, R.D. et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. **Journal of Psychiatric Research**. v.37, p.99–108, 2003.

OLDEHINKEL, A.J., et al. Urinary free cortisol excretion in elderly persons with minor and major depression. **Psychiatry Research**. v.104, p.39-47, 2001.

OSRAN, H. et al. Adrenal androgens and cortisol in major depression**. Am J Psychiatry**. v.150, p.806–9, 1993.

PALACIOS, G. et al. Immunohistochemical localization of the sigma l-receptor in oligodendrocytes in the rat central nervous system. **Brain Res**. v.961 p.92–99, 2003.

PARIANTE, C.M., LIGHTMAN, S.L. The HPA axis in major depression: classical theories and new developments. **Trends Neurosci**. v.31, p.464-8, 2008.

PARKER, G., BROTCHIE, H. Major depression invites major concerns. **Rev. Bras. Psiquiatr**. v.31, p.3-6, 2009.

PIWOWARSKA, J., et al. Cortisol level in men with major depressive disorder treated with fluoxetine or imipramine. **Acta Poloniae Pharmaceutica**. v.65, n.1, p.159-164, 2008.

REUL, J.M.H.M., De KLOET, E.R. Two receptor systems for corticosterone in rat brain: micordistribution and differential occupation. **Endocrinology**. v117, p. 2505–2512, 1985.

REUS, V.I. et al. Dehydroepiandrosterone (DHEA) and memory in depressed patients (abstract). **Neuropsychopharmacology**. v.9, p.66S–66S, 1993.

PORTER, R.J. Neurocognitive impairment in drug-free patients with major depressive disorder. **British Journal Of P Sychiatry**. v.182, p.114-220, 2003.

POST, R.M. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. **Am J Psych**. v.149, n.8, p.999-1010, 1992.

SCOTT, L.V. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. **J Affect Disord**. v.54, p.129–37, 1999.

SMITH, D.J., MUIR, W.J., BLACKWOOD, D.H.R. Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. **Bipolar Disord**. v.8, p.40–46, 2006.

TAKEBAYASHI, M. et al. Plasma dehydroepiandrosterone sulfate in unipolar major depression. **Jornal of Neural Transmission**. v.105, p.537-542, 1998.

THOMAS, G. et al. Serum dehydroepiandrosterone sulfate levels as an individual marker. **J Clin Endocrinol Metab**. v.79, p.1273–1276, 1994.

VYTHILINGAM, M. et al. Hippocampal Volume, Memory, and Cortisol Status in Major Depressive Disorder: Effects of Treatment. **Biol Psychiatry**. v.56, p.101-12, 2004.

WANG, C.E. Verbal memory performance of mildly to moderately depressed outpatient younger adults. **J. Affect. Disord**. v.92, p.283–286, 2006.

WEBB et al. The Biological Actions of Dehydroepiandrosterone Involves Multiple Receptores. **Drug Metab Rev**. v.38 p.89–116, 2006.

Wilson, L.W. **Adrenal Fatigue**. Editora Smart Publication: Petaluma (CA), 16 ed., 361pp, 2010.

WOLF, O.T. A single administration of Dehydroepiandrosterone does not enhance memory performance in young healthy adults, but immediately reduces cortisol levels. **Biol Psychiatry**. v.42, p.845-848, 1997.

WOLKOWITZ, O.M. Double-blind treatment of major depression with dehydroepiandrosterone. **Am J Psychiatry.** v.156, p.646–9, 1999.

WOLKOWITZ, O.M. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. **Psychoneuroendocrinology**. v.3, p.233–55, 1994.

YAFFE K. et al. Neuropsychiatry function and dehydroepiandrosterone sulfate in elderly women: a prospective study. **Biol Psychiatry**. v.43, p.694-700, 1998.

YOUNG, A. H., GALLAGHER, P., PORTER, R. J. Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. **Am J Psychiatry**. v.159, p.1237–9, 2002.

ANEXO A - Comprovante de Submissão do Artigo

De: ees.biopsy.0.100a61.5e3fd740@eesmail.elsevier.com em nome de Biological Psychology
Enviada: sex 25/3/2011 11:18
Para: Elke Bromberg
Assunto: Submission Confirmation

Dear Mrs Elke Bromberg,

Your submission entitled "Contextual recognition memory deficits in major depression are supressed by cognitive support at encoding." has been received by Biological Psychology

You may check on the progress of your paper by logging on to the Elsevier Editorial System as an author. The URL is http://ees.elsevier.com/biopsy/.
Your username is: Elke

If you need to retrieve password details, please go to: http://ees.elsevier.com/biopsy/automail_query.asp

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to this journal.

For further assistance, please visit our customer support site at http://support.elsevier.com Here you can search for solutions on a range of topics, find answers to frequently asked questions and learn more about EES via interactive tutorials. You will also find our 24/7 support contact details should you need any further assistance from one of our customer support representatives.

Kind regards,
Elsevier Editorial System
Biological Psychology