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

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ABSTRACT

Objectives: To investigate the effect of cognitive support (an associative orienting instruction at encoding) on contextual memory in depressed patients.
Methods: Seventeen patients (age 20–40 years, 14 women) diagnosed with major depressive disorder (MDD) and 22 healthy controls matched for age, gender and education completed a recognition memory task for item (object) and context (location), with or without an incidental binding cue at encoding. In addition, participants completed the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS III) and the Wisconsin Card Sorting Test (WCST). Salivary samples were collected at 7 AM, 4 PM and 10 PM on the day of testing for cortisol and DHEA level measurement.
Results: Depressed patients showed a deficit in contextual memory in the absence of a binding cue but did not differ from healthy controls in item memory or when a binding cue was present. Cortisol and cortisol/DHEA ratios were lower in depressed patients compared to healthy controls and correlated with memory deficits.
Conclusions: Contextual memory deficits in MDD patients can be reduced by providing cognitive support at encoding.

1. Introduction

Patients with a diagnosis of major depressive disorder (MDD) often complain of memory difficulties. However, studies have produced conflicting results: some finding memory impairments in patients with MDD (Austin et al., 2001; Braw et al., 2010; Fossati et al., 2004; McDermott and Ebmeier, 2009), and others finding no difference between depressed patients and healthy controls (Castaneda et al., 2008; Grant et al., 2001; Rinck and Becker, 2003; Wang et al., 2006). Differences in results are most likely due to memory tasks used, disease features and subject characteristics. Tasks requiring a high degree of cognitive effort (Hertel and Milan, 1994) and with more demands on executive functions (Fossati et al., 2002) prove to be particularly more difficult for depressive patients than normal controls. In addition, the number of past depressive episodes (MacQueen et al., 2002), length of depressive episode(s), patient age, education level and profession (Gorwood et al., 2008) are all factors that play a role in memory performance.

Along with memory impairment, a dysfunction in hypothalamus–pituitary–adrenal (HPA) activity, mainly related to cortisol secretion has been associated with depression, with hypercortisolemia as the most reported finding (Kessing et al., 2011; Pariante and Lightman, 2008). However, hypocortisolemia (Bremmer et al., 2007; Oldehinkel et al., 2001) and normocortisolemia (Young et al., 2001) have also been described. Studies on dehydroepiandrosterone (DHEA) levels in depressive illness have also provided mixed results (Michael et al., 2000). An association between depression, cortisol, and cognitive impairment has been demonstrated (Egeland et al., 2005; Gomez et al., 2009; Hinkelmann et al., 2009; Rubinow et al., 1984). Circulating cortisol binds to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) that exist in high density in brain structures with an implicated role in memory function such as the hippocampus and prefrontal cortices (Lupien et al., 2009). DHEA has been demonstrated to counteract the deleterious effects of corticosteroids on long-term potentiation, a neurophysiological correlate of learning and memory (Kaminska et al., 2000). Improvements in cognition

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have been observed after administration of DHEA in middle-aged and elderly depressed patients (Wolkowitz et al., 1997).

A series of studies have demonstrated the modulatory effect of cognitive support on verbal memory function in depressive patients. Focused attention and inhibition of task irrelevant thoughts were able to eliminate depression-related memory deficits under incidental encoding conditions in adult patients (Hertel and Rude, 1991). Taconnat et al. (2010) examined free recall in young depressed patients under low (non-organized word lists) and high (pre-organized word lists according to semantic categories) cognitive support encoding conditions. Depressive patients exhibited memory deficits only in the low cognitive support condition when they were required to organize the information themselves. However, depressed patients were also less adept at applying an organizational strategy compared to controls, revealing a poor strategic capacity mediated by a deficit in self-initiated processing. These results are corroborated by a study by Behnken et al. (2010), which demonstrated that compared to controls, individuals in remission from unipolar MDD showed more deficits in non-verbal memory function due to difficulties in organizing non-verbal information during learning.

The present study investigated the effect of low and high cognitive support on encoding in a contextual memory task in depressed patients. We used a naturalistic experimental paradigm (e.g., objects depicted in different rooms of a house) to assess recognition memory for content (object) and context (location). The association of an object with a location plays an important role in establishing perceptual continuity within the dynamic environments of everyday experiences (Hollingworth and Rasmussen, 2010) and plays an essential role in the formation of coherent episodic memory representations. Cognitive support was manipulated during incidental encoding by presenting an object-location binding cue (high cognitive support) or an object-property cue (low cognitive support). We hypothesized that: (1) regardless of cognitive support, patients with MDD would perform poorer than control subjects on contextual memory performance and (2) the provision of high cognitive support would increase memory performance. Subject demographics, neuropsychological characteristics and hormone (cortisol, DHEA and cortisol/DHEA) levels were measured for potential confounding effects on memory task performance.

2. Methods

2.1. Participants

Participants were 17 patients (ages 20–40; 14 women) from the psychiatric outpatient clinic of Hospital de Clínicas de Porto Alegre, RS, Brazil. Patients met DSM-IV criteria for major depressive disorder (APA, 1994) as diagnosed through the Mini-International Neuropsychiatric Interview for DSM-IV (MINI, Sheehan et al., 1998) conducted by a trained psychiatrist.

All patients were on antidepressant medication for at least 6 months. The majority of patients were taking selective serotonin reuptake inhibitors either alone (fluoxetine, $n = 2$; sertraline, $n = 1$) or in combination 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 stabilizers 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 stabilizers and benzodiazepines (fluoxetine plus lithium plus diazepam, $n = 1$). Other patients were 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, $n = 1$). Patients were not required to abstain from medication prior to testing.

Severity of depression was assessed at the time of memory testing using the Beck Depression Inventory (BDI, Beck and Steer, 1993), adapted and validated in Brazil by Cunha (2001). Patients with a BDI score ≥ 12 were included in the study. Twenty-two controls (ages 20–40; 19 women) with a BDI score < 11 were recruited from the community. Exclusion criteria included the use of any psychotropic medication (except antidepressants for the depressive patients) within the previous 6 weeks, previous or current use of illegal psychoactive drugs, 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). None of the control subjects reported ongoing or previous psychiatric problems. All participants were required to abstain from alcohol use 24 h before testing. Approval of study procedures was granted by the Local Research Ethical Committee, Hospital de Clínicas de Porto Alegre and by the Pontifical Catholic University, Porto Alegre, RS, Brazil and all participants gave their informed consent.

2.2. Neuropsychological measures

Neuropsychological test, including the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS III) (Wechsler, 1997) and the Wisconsin Card Sorting Test (WCST) (Heaton, 1993) were administered for a comparison of cognitive abilities between experimental groups. The WAIS III measures general intelligence while the WCST measures executive functioning. Based on previous research and factor analysis of the WCST (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.

2.3. Memory task

The materials and procedures for the assessment of recognition memory for objects and context have been described elsewhere (Bisol Balardin et al., 2009; Dos Santos et al., 2010). Briefly, photographs of a large number of objects from different semantic categories (household appliances, tools, toys, and clothing) were 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 encoding phase, while 16 served as distracters. Participants (depressive patients and controls) were systematically assigned to 1 of 2 encoding conditions depending on the date of their recruitment into the study. The incidental binding cue absent condition included a question concerning how often each object presented in the photographs are used in daily activities while the incidental binding cue present condition included a question concerning how well each object fits into the room displayed. Thus, there were 4 experimental subgroups: (1) depressive patients without incidental binding cue, (2) depressive patients with incidental binding cue, (3) controls without incidental binding cue and (4) 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 during the encoding session and were unaware that a test session would follow. After a 5-min interval, in which participants were engaged in a distracting activity (forward and backward digit span recall), the memory test was given. The participants were shown 32 photographs during the memory test: each of the 16 objects previously presented (8 in the same room as previously presented and 8 in a different room) and 16 objects not previously presented (8 presented in the living room and 8 in the office). Participants responded verbally as to whether or not the object was presented during the encoding phase of the study. If the participant indicated that the object was previously presented, 2 consecutive photographs of the same object in each location (living room and office) were depicted on a computer screen and participants were asked to indicate in which of the 2 locations the object had appeared previously. The order of photograph presentation was randomized for each subject.

2.4. Cortisol and DHEA assay

Participants were asked to collect saliva samples at 7 AM, 4 PM and 10 PM on the day of the experiment. The 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 °C. Following thawing, each sample was divided for cortisol and DHEA analysis. Samples for cortisol analysis were centrifuged at 1500 rpm for 3 min (to allow precipitation of proteins and mucins) and then analyzed by radioimmunoassay (Cortisol Coat-Count -RIA, DPC Medlab, Los Angeles, CA) using a gamma counter. The sensitivity of the assay was estimated at 0.1 nmol/L. The intra- and inter-assay variation coefficients were less than 10%. Samples for DHEA analysis were centrifuged for 3 min at 2500 rpm (to enable precipitation of proteins and mucins) and then measured by radioimmunoassay with a kit for liquid phase (Diagnostic Systems Laboratories, Webster, TX). The sensitivity of the DHEA assay was estimated at 0.31 nmol/L. The intra- and inter-assay variation coefficients were less than 8%. All samples for both cortisol and DHEA were analyzed in duplicate, and results from each of the sampling times were expressed in nmol/L. Six patients and three control subjects delivered incomplete samples and were excluded from the analysis. Data were available for 11 patients and 19 control subjects.

2.5. Statistical analysis

All data are expressed as means ± standard error of the 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) were

analyzed with a mixed-design repeated measures analysis of variance (ANOVA) to examine differences between groups and encoding conditions, with object and context recognition scores as within-subject variables. Tukey's post hoc tests were performed for multiple comparisons among group means. Independent and paired sample *t*-tests were performed when appropriate. Statistical significance was set at $p < 0.05$.

Cortisol and DHEA data were analyzed by repeated measures ANOVAs, which included 1 within-subject variable (cortisol and DHEA levels at different sampling times) and 1 between-subject variable (controls versus patients). Tukey's post hoc tests were performed for multiple comparisons among group means. Independent and paired sample *t*-tests were performed when appropriate. Statistical significance was set at $p < 0.05$

3. Results

Table 1 summarizes the demographic and neuropsychological characteristics of subjects in the control and depressive groups. Groups did not differ in age [$t = 1.39$, $df = 37$, $p = 0.17$], gender [Pearson Chi-Square = 0.11, $p = 0.73$] or years of education [$t = -1.54$, $df = 37$, $p = 0.13$]. As expected, BDI scores were significantly higher in the patient group [$t = 9.53$, $df = 37$, $p < 0.001$]. Except for perseverative errors on WCST [$t = 1.09$, $df = 37$, $p = 0.28$], depressive patients scored lower than controls on the MMSE [$t = -2.66$, $df = 37$, $p = 0.007$], the vocabulary subtest [$t = -3.68$, $df = 37$, $p = 0.001$] and the number of categories completed on the WCST [$t = -3.53$, $df = 37$, $p = 0.001$].

There were significant 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 significant interactions between group and recognition test [$F_{(1,35)} = 8.23$, $p = 0.007$] and group and encoding conditions [$F_{(3,38)} = 3.00$, $p = 0.043$] (Fig. 1). While these results indicate a significant effect of depression on memory, they also suggest that this effect is dependent on the nature of the information to be recognized (object or context) and on 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 interaction between group and encoding condition in object recognition was only marginally significant [$F_{(3,38)} = 3.00$, $p = 0.043$] and thus, Tukey's post hoc tests found no significant differences between experimental subgroups [all *p*-values > 0.05]. However, significant differences were found for context recognition [$F_{(3,38)} = 47.58$, $p < 0.001$]. Tukey's post hoc tests revealed that the depressed patients performed significantly poorer than controls in the encoding condition without incidental binding cue [$p < 0.001$]. The introduction of the incidental binding cue at encoding significantly improved the context recognition scores in controls [$p < 0.001$] and depressed patients [$p = 0.029$], such that there was no longer a significant difference between groups [$p = 0.55$]. In addition, incidental binding cue presentation raised the scores of context recognition to the same level as those for object recognition, as confirmed with paired *t*-test (all *p*-values < 0.001 in the encoding condition without binding cue and all *p*-values > 0.05 in the encoding condition with incidental binding cue).

Table 1
Mean (±SEM) values of demographic and neuropsychological measures of healthy young adult controls and depressive patients.

	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 Wechsler Adult Intelligence Scale.
* $p < 0.05$ in relation to controls.

Fig. 2 shows the salivary cortisol, DHEA and cortisol/DHEA ratios of control participants and depressed patients. The cortisol concentrations of control participants showed the characteristic circadian rhythm previously described for healthy subjects: high levels in the morning (7 AM), decreased levels at 4 PM and the lowest levels at 10 PM [all time points significantly different, *p*-values < 0.001]. Cortisol levels of patients with major depression also differed significantly over the three sampling times [all *p*-values < 0.001], decreasing from 7 AM to 4 PM, and reaching the lowest concentrations at 10 PM. In addition to the significant effect of sampling time across groups [$F_{(2,56)} = 598.69$, $p < 0.001$], there was also a significant group effect [$F_{(1,28)} = 19.63$, $p < 0.001$], indicating that the cortisol levels differed significantly between control participants and patients with major depression. As confirmed with independent samples *t*-tests, cortisol levels of depressed patients were significantly lower than those of control participants at all sampling times [all *p*-values < 0.05].

Salivary DHEA levels also showed circadian alterations across groups, as indicated by a significant effect of sampling time [$F_{(2,56)} = 275.33$, $p < 0.001$]. Dependent sample *t*-tests, indicated highest 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* values < 0.001]. There was no significant effect of group [$F_{(91,28)} = 2.18$, $p = 0.15$] or group by sampling time interaction [$F_{(2,56)} = 0.62$, $p = 0.54$], indicating no difference in DHEA concentration between

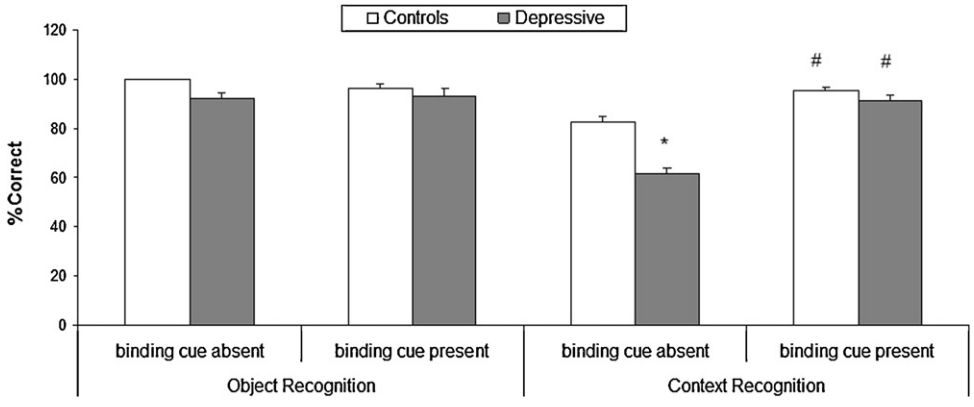

Fig. 1. Object and context recognition performance (mean ± SEM) of controls and depressive patients under two encoding conditions.*$p < 0.001$, compared to the context recognition of the other subgroups; #$p < 0.05$, compared to the context recognition of subgroups that made the task in the absence of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

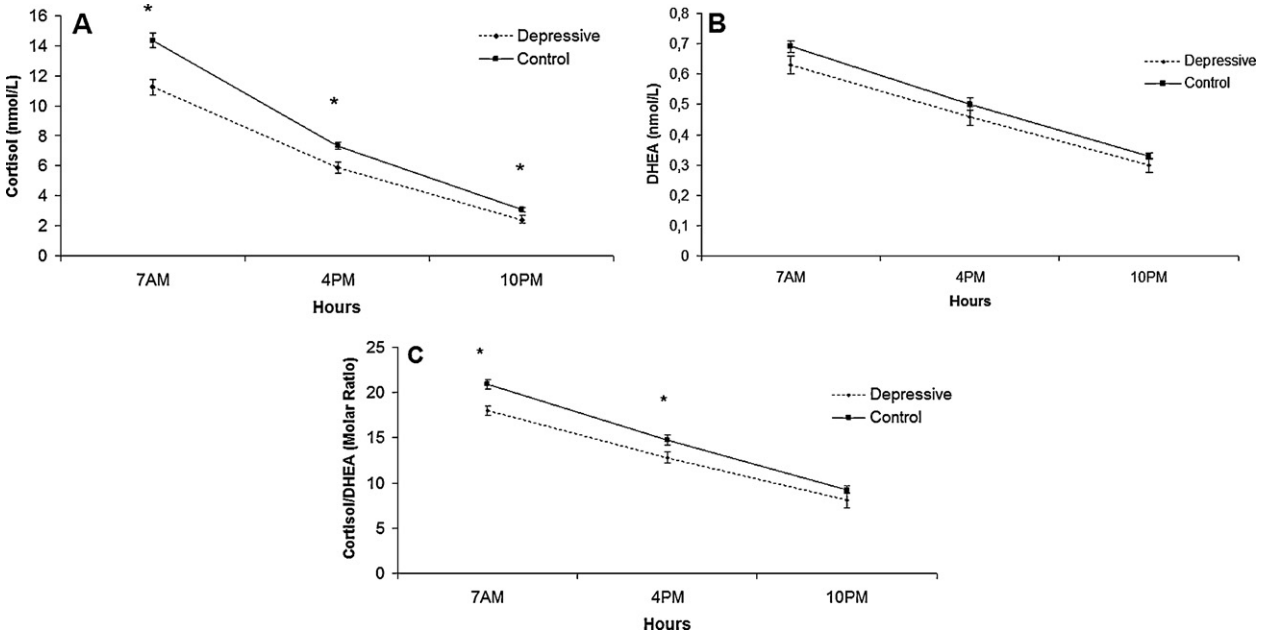

Fig. 2. Levels (mean ± SEM) of cortisol (A), DHEA (B) and Cortisol/DHEA ratios (C) in saliva samples of depressive patients and healthy controls at 7 AM, 4 PM and 10 PM. *$p < 0.05$, between-group differences at each sampling time.

control participants and patients with major depression at the different sampling times.

Cortisol/DHEA ratios were also significantly affected by sampling time [$F_{(2,56)} = 208.35$, $p < 0.001$]. As with cortisol and DHEA levels, the cortisol/DHEA ratio was highest at 7 AM, significantly decreased at 4 PM [all p values <0.001], and decreased further at 10 PM [all p values <0.001]. There was a significant group effect on cortisol/DHEA ratio [$F_{(1,28)} = 11.24$, $p = 0.005$] and independent sample t-tests indicated significantly lower cortisol/DHEA ratios in depressed patients compared to healthy controls at 7 AM [$t = -3.68$, $df = 28$, $p = 0.001$] and 4 PM [$t = -2.15$, $df = 28$, $p = 0.04$].

The evident difference between control participants and depressed patients in context recognition in the no binding cue condition 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 analyses of covariance (ANCOVAS) were carried out. The first ANCOVA explored neuropsychological measures with MEEM, vocabulary subtest and completed categories on the WCST as covariates. The ANCOVA for neuropsychological measures revealed that the vocabulary subtest score had a significant effect as a covariate [$F_{(1,17)} = 6.90$, $p = 0.022$], while MEEM score [$F_{(1,17)} = 0.35$, $p = 0.56$] and completed categories on the WCST [$F_{(1,17)} = 4.36$, $p = 0.056$] were not significant covariates. However, the resulting adjustment of the means did not eliminate differences in contextual memory task performance between control participants and depressed patients [$F_{(1,17)} = 6.33$, $p = 0.027$]. The second ANCOVA explored hormone levels with cortisol levels at 7 AM, 4 PM and 10 PM, as well as the cortisol/DHEA ratio at 7 AM and 4 PM, as covariates. The ANCOVA revealed that cortisol levels at 4 PM [$F_{(1,16)} = 5.61$, $p = 0.042$] and cortisol/DHEA ratio at 7 AM [$F_{(1,16)} = 29.49$, $p < 0.001$] and 4 PM [$F_{(1,16)} = 12.71$, $p = 0.006$] had significant effects as covariates, however, they were also unable to eliminate differences in contextual memory task performance between experimental groups [$F_{(1,16)} = 14.43$, $p = 0.003$]. Together these results indicate that neurophsychological (vocabulary subtest) and hormonal characteristics (cortisol level at 4 PM and cortisol/DHEA ratio at 7 AM and 4 PM) are potentially capable of influencing incidental contextual memory task performance in the absence of a specific binding cue. To investigate the direction of the hormonal effects on contextual memory we performed a linear regression analysis and found a significant relationship ($r = 0.73$, $p < 0.001$) between the performance in the context recognition task without binding cue and the hormonal parameters that revealed significant effects as covariates in the ANCOVA (cortisol level at 4 PM and cortisol/DHEA ratio at 7 AM and 4 PM).

4. Discussion

The current study examined recognition memory performance for items (i.e. objects) and contexts (i.e. locations), along with cortisol and DHEA levels in treatment-resistant depressed patients and healthy controls. The main findings indicate that there was no difference between depressed patients and healthy controls in recognition memory performance under incidental encoding with a binding cue (judging the degree of appropriateness of an object in relation to the location where it is portrayed). However, depressed patients showed a specific deficit for incidental contextual memory in the absence of a specific binding cue during the encoding phase. An ANCOVA found that basal cortisol level (4 PM) and cortisol/DHEA ratios (7 AM and 4 PM) were positively correlated with the observed contextual memory deficit.

Depressed patients in the current study demonstrated an ability to encode and retrieve object content under incidental encoding comparable to healthy controls. Prior literature on memory deficits in depression indicates that impairment in episodic memory, although common in major depressive disorders, is highly dependent on the type of task used to evaluate memory with a prominent decline in performance in tasks that require a high degree of attentional resources (Hammar and Ardal, 2009). The nature of the recognition paradigm used in the current study did not require subjects to use self-initiated intentional strategies which could contribute to their successful performance. A similar pattern of recognition memory for objects was found in a previous study on older adults with depressive symptoms (Bisol Balardin et al., 2009), supporting the hypothesis that memory function in depression is influenced more by domain general functioning than by age (Fossati et al., 2002).

In contrast to results on object recognition performance, depressed patients exhibited memory deficits in associating a recognized object with its associated location in the absence of specific binding instructions at encoding. A similar pattern of dissociation between preserved item memory and contextual memory has been observed in aging (Grady and Craik, 2000) and in patients with frontal lobe damage (Butters et al., 1994). Deficits in spontaneous use of organizational strategies at encoding have been previously reported in remitted major depressive patients (Behnken et al., 2010). However, as previously seen in healthy older adults (Glisky et al., 2001; Naveh-Benjamin and Craik, 1995) and older adults with mild depressive symptoms (Bisol Balardin et al., 2009), patients in the present study benefited from cognitive support at encoding in the form of incidental associative binding instructions. The beneficial effects of cognitive support remained even in the presence of neuropsychological indicators of frontal lobe dysfunction (fewer categories completed in the WCST). To our knowledge, there are no prior studies on the neural correlates of encoding strategy influence on source/contextual memory in clinically depressed patients. Most neuroimaging studies in healthy young and aged subjects, have investigated differences in brain activation in item and context recognition at retrieval (Nolde et al., 1998; Slotnick et al., 2003; Dobbins et al., 2002; Kahn et al., 2004; Rugg et al., 1999; Mitchell et al., 2004). The most commonly cited brain regions associated with source memory are the dorsolateral and ventrolateral prefrontal cortex. However, the specific role of these structures must be further investigated. To further study findings that source memory deficits could be mediated by encoding strategies (Glisky et al., 2001), Kuo and Van Petten (2006) found that when subjects were encouraged to attend to object/color relationships during an encoding task, late electrical activity in the prefrontal cortex, typically associated with source retrieval attempts, was eliminated, and performance was improved. These results suggest that the reinforcement of binding processes during encoding may contribute to the formation of a well-integrated memory trace that is more easily accessible at recall (Craik and Lockhart, 1972).

Although the difference between controls and depressed patients in the context recognition task in the absence of a binding cue was not eliminated after taking into account between group differences in hormonal 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. Studies on cortisol levels in patients with unipolar major depression have produced conflicting results, with the majority finding hypercortisolemia (Kessing et al., 2011; Pariente and Lightman, 2008). However, some studies have reported hypocortisolemia (Bremmer et al., 2007; Oldehinkel et al., 2001) and yet others have described normocortisolemia (Young et al., 2001). The present results found lower cortisol levels in depressed patients compared with controls. Bremmer et al. (2007) suggested that hypocortisolemia associated with depression may be a sign of HPA axis exhaustion as a result of chronic stress. Another study found lower cortisol levels in elderly patients with long-lasting and recurrent depressive episodes compared to healthy controls (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 the current study. This issue is especially important when cortisol levels are only slightly altered, as is the case with the depressed patients in the current study. Future studies should address this matter. Antidepressant drug therapy may also be involved in the hypocortisolemia observed in the current study (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 understood, studies in human and animal models have demonstrated that these drugs can act directly to modulate expression and function of the glucocorticoid receptor (GR), which in turn can reduce HPA axis activity (see Juruena et al., 2004 for a discussion on this topic).

The Cortisol/DHEA ratio of depressed patients was low compared to healthy controls in the current study. The ratio of these two steroids is important due to their different and often antagonistic effects. Moreover, several previous studies have found that the cortisol/DHEA ratio in serum and saliva, rather than concentrations of either hormone alone, more accurately discriminates depressed from non-depressed patients (review in Maniger et al., 2009). The diminished cortisol/DHEA ratio seen in the depressive patients in the present study was the result of lower cortisol levels, since there was no significant differences in DHEA levels found between controls and patients. As with cortisol, findings on DHEA levels in major unipolar depression have also been conflicting. The great majority of studies suggest 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 have reported lower (Michael et al., 2000) as well as normal DHEA levels in patients with depression (Romeo et al., 1998).

As could be seen from the above discussion, the most important hormonal alterations seen in the depressive patients in the present study were related to cortisol levels, not DHEA.

The modulatory role of the corticosteroid system on memory function has been described by an inverted U-shaped function, with moderate glucocorticoid concentrations enhancing encoding and consolidation, and very low and very high concentrations correlated with memory impairment (Roozendaal, 2000; Abercrombie et al., 2003). The majority of studies have examined the effects of elevated cortisol levels induced by pharmacological intervention or acute stress (Maheu et al., 2004; Het et al., 2005), and have 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 cortisol synthesis suppression on free recall has also been demonstrated, although recognition was preserved (Rimmele et al., 2010). This finding is corroborated by the results of studies showing that patients with medical conditions that present a pattern of diminished cortisol secretion, such as fibromyalgia (Sephton et al., 2003) and chronic fatigue syndrome (Roberts et al., 2010) show deficits in visual and verbal memory performance and cognitive behavioral therapy, respectively. The current results found a positive correlation between hormone level (cortisol and cortisol/DHEA ratios) and contextual memory performance when no binding cue was presented. Considering the inverted U-shaped function that describes the modulatory role of corticosteroid systems on memory (Roozendaal, 2000; Abercrombie et al., 2003), these results suggest that the lower cortisol levels of depressed patients (and the resultant lower cortisol/DHEA ratios) could be partially responsible for observed memory deficits.

While the current study produced exciting findings, there are some limitations that must be considered. First, the cross-sectional design did not permit the investigation of associations between the persistence of altered cortisol levels and the remission/progression of depression. Additional longitudinal studies are needed to explore this association. In addition, studies focusing on the effects of treatment-resistant depressive symptomatology, antidepressant therapy and HPA axis dysfunction on memory function in major depression are needed to clarify current results. Another limitation of the present study concerns the characteristics of participants. The sample of depressed patients was small, had fairly high symptom severity variability (BDI mean = 29.8 + SEM = 2.57) and consisted of both patients experiencing their first depressive episode as well as those with recurrent depressive episodes. Number of depressive episodes has been described as a good predictor of hippocampal volume and has been related to memory function

in MDD (Campbell et al., 2004; McKinnon et al., 2009). While all patients in our study had been taking antidepressants for at least six months, there was a high degree of variability in medication which may impact cognitive function and HPA axis activity function through different mechanisms of action. Some of these medications, such as selective serotonin reuptake inhibitors (SSRIs), may have positive effects on memory and other cognitive aspects (Cassano et al., 2002; Levkovitz et al., 2002) while others, such as benzodiazepines, can have a negative impact on memory and cognitive performance (Stewart, 2005).

In conclusion, the present study provides evidence that contextual memory deficits in patients with major depression can 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.

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