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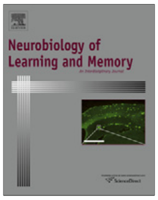

Caudate nucleus-dependent response strategies in a virtual navigation task are associated with lower basal cortisol and impaired episodic memory

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ABSTRACT

The present research examined the relationship between endogenous glucocorticoids, navigational strategies in a virtual navigation task, and performance on standard neuropsychological assessments of memory. Healthy young adult participants ($N = 66$, mean age: 21.7) were tested on the 4 on 8 virtual maze (4/8 VM) and standard neuropsychological tests such as the Rey-Osterrieth Complex Figure (RO) and the Rey Auditory Verbal Learning Task (RAVLT), which measure episodic memory. The 4/8 VM differentiates between navigational strategies, where participants either use a hippocampal-dependent spatial strategy by building relationships between landmarks, or a caudate nucleus-dependent stimulus–response strategy by automatizing a pattern of open and closed arms to learn the location of objects within the maze. Degree of stress was assessed by administering the Perceived Stress Scale (PSS) questionnaire. Cortisol samples were taken on two consecutive days upon waking, 30 min after waking, at 11 am, 4 pm, and 9 pm. There was a significant difference in basal levels of cortisol between spatial and response learners. Interestingly, response learners had significantly lower cortisol levels throughout the day. The two groups did not differ in terms of perceived stress as measured with the PSS questionnaire. Moreover, there was no significant correlation between PSS scores and salivary cortisol levels, indicating that the higher cortisol levels in the spatial group were not associated with greater perceived stress. In addition, participants who spontaneously used a spatial strategy performed significantly better on the RAVLT and RO. These data indicate that the cortisol levels in the spatial group may be optimal in terms of episodic memory performance whereas the cortisol levels in the response group may be associated with poorer memory. These results are suggestive of an inverted U-shaped curve describing the effects of basal levels of circulating cortisol on memory in young adults.

1. Introduction

Numerous studies have shown the existence of multiple memory systems in both animals and humans (Alvarez, Zola-Morgan, & Squire, 1995; McDonald & White, 1993, 1994; Milner, 2005; O'Keefe & Nadel, 1978; Packard, Hirsh, & White, 1989; Packard & McGaugh, 1996; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991; Tulving, 1972). One of these memory systems, the hippocampus, is known for its crucial role in various types of memory, including spatial memory. In contrast, the caudate nucleus is implicated in procedural learning and the formation of habits, including stimulus–response learning.

These memory systems each mediate one of the two strategies that can be used when navigating in an environment (Bohbot, Iaria, & Petrides, 2004; Hartley, Maguire, Spiers, & Burgess, 2003; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Maguire et al., 1998; McDonald & White, 1993, 1994; Mizumori, Yeshenko, Gill, & Davis, 2004; Packard et al., 1989; Packard & McGaugh, 1996; Voermans et al., 2004). The spatial strategy is used in order to form multiple associations between cues in order to construct a cognitive map of the environment and is dependent upon the hippocampus (O'Keefe & Nadel, 1978). The caudate nucleus, on the other hand, is involved in making associations linking a learned response to a perceived stimulus. The repetition of a learned sequence, such as a series of turns from an initial position (Packard & McGaugh, 1996), is known as the stimulus–response strategy, or simply the response strategy. It is reinforced through repetition and reward. Additionally, it is less demanding in terms of cognitive resources (Iaria et al., 2003; Nadel & Hardt, 2004). Brain imaging studies have shown that spatial and response learners have increased functional activity and gray matter in the hippocampus and caudate nucleus, respectively (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Iaria et al., 2003).

There has been an extensive amount of research regarding the effects of stress on cognitive functions (Lupien & McEwen, 1997;

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Pruessner et al., 2010), such as spatial memory (Schwabe et al., 2007). The physiological stress response is mainly accomplished by the limbic–hypothalamic–pituitary–adrenal axis (LHPA) through the eventual release of corticosteroids, which can be separated into glucocorticoids and mineralocorticoids. Glucocorticoids can act through both mineralocorticoid receptors (MR or Type-1) and glucocorticoid receptors (GR or Type-2). While MRs have a high affinity for glucocorticoids and are activated by basal levels, GRs have a 10-fold lower affinity (de Kloet, 1991) and are only activated by high levels of the hormone, which is characteristic of a physiological stress response. MRs and GRs are highly prevalent in the limbic system, especially in the hippocampus (de Kloet, Oitzl, & Joëls, 1999). At stress levels, MRs are saturated and GRs are about 70% occupied (Reul & de Kloet, 1985) resulting in a smaller ratio of MR/GR occupation and, consequently, lower cognitive performance (Lupien, Buss, Schramek, Maheu, & Pruessner, 2005).

Changes due to stress are initially adaptive, however, over time these changes increase the susceptibility for degeneration and disease (Schwabe, Dalm, Schachinger, & Oitzl, 2008). Chronic stress has been shown to cause a decrease in MR mRNA levels but not GR mRNA levels in the hippocampus, thereby reducing the MR/GR ratio (López, Chalmers, Little, & Watson, 1998). Numerous studies have shown stress to impair the hippocampus through the actions of glucocorticoids (Conrad, Galea, Kuroda, & McEwen, 1996; Kleen, Sitomer, Killeen, & Conrad, 2006; McEwen & Sapolsky, 1995; McKittrick et al., 2000; Sapolsky, 1994; Sapolsky, Uno, Rebert, & Finch, 1990). As a result of this damaging effect, chronic stress may lead to impaired performance on tasks dependent on the hippocampus and cause a shift to the use of hippocampal-independent response strategies in spatial navigation. Results from a rodent study (Kim et al., 2007) suggest that chronic stress may prevent the formation of a cognitive map which is necessary for spatial learning. Supporting this idea, stressed rats are no longer impaired on a spatial task when intramaze cues are added, allowing for the use of a response strategy (Wright & Conrad, 2005). Schwabe et al. (2008) tested chronically stressed mice and humans on memory tasks which allow for the use of either a spatial or response strategy. The chronically stressed mice, which were repeatedly exposed to a rat, were found to use response strategies on a circular hole board task significantly more than control mice. They also found that in humans, individuals with high chronic stress used response strategies more frequently than individuals with low chronic stress on a two-dimensional spatial task (Schwabe et al., 2008). Schwabe et al. (2007) also stressed participants using the Trier Social Stress Test and these exhibited a shift towards response strategies in a task that required them to locate a “win” card in a 3D model of a room compared to controls who were not stressed. Recent animal evidence suggests that this stress-induced shift in strategies is likely mediated through corticosterone action via MR (Schwabe, Schachinger, de Kloet, & Oitzl, 2010).

There is, however, very little information about the relationship between normal endogenous levels of cortisol and navigational strategies. This study explores the hypothesis that response learners should (1) show higher basal levels of cortisol compared to spatial learners and (2) exhibit lower scores on hippocampus-sensitive tasks, namely the Rey Auditory Verbal Learning Test (RAVLT) and Rey-Osterrieth Complex Figure (RO).

2. Methods

2.1. Participants

Sixty-six healthy participants (27 men and 39 women) were tested. None had a history of psychiatric or neurological disorders. Participants were divided into two groups according to their navigational strategy assessed with the 4 on 8 virtual maze (4/8 VM). Twenty-two participants (eight men, 14 women) were categorized in the spatial group and 44 participants (19 men, 25 women) were categorized in the response group. A One-Way ANOVA revealed that the two groups did not differ in terms of sex ($F_{(1,64)} = 0.275$, $p = 0.602$), age (spatial group mean age = 21.68, response group mean age = 21.66); $F_{(1,64)} = 1$, $p = 1$), or IQ (spatial group mean IQ: 110.4, response group mean IQ: 111.5; $F_{(1,64)} = 0.498$, $p = 0.483$). All participants provided written consent in accordance with procedures approved by the local ethics committee.

2.2. Behavioral task

The 4/8 VM was created using a commercially available computer game (Unreal; Epic Games, Raleigh, NC) and was made to resemble the basic structure of the eight-arm radial maze task used for rodents (Olton & Samuelson, 1976). The task has been used in previous studies (Bohbot et al., 2004, 2007; Etchamendy & Bohbot, 2007; Iaria et al., 2003). The maze has eight arms extending out from a central platform. It is surrounded by a landscape of mountains, a sunset, two isolated trees, and a short brick wall between the trees and the mountains (Fig. 1A). At the end of each arm are stairs leading down to a small pit. In four of the arms, there is an object in the pit which can be picked up. Note that the presence or absence of the objects cannot be seen from the center of the platform and can only be seen upon entry into a given arm. The participants used the up, left and right keys on the computer’s keyboard to move in the environment but were not permitted to backup using the down key. Before testing began, participants were asked to familiarize themselves with the keys in a virtual practice room that contained a radial maze with no stairs or surrounding landscape. Once the participants were able to move effectively using the keys, the experimenter gave the instructions and started the experiment.

Participants always started from the center of the maze, on the platform, facing the same direction. There were five trials, including the probe trial, each consisting of two parts. In Part 1, four of the eight arms were accessible and four were blocked by barriers. The accessible arms each contained an object at the end of the arm. In Part 2, all eight arms were accessible and there were objects in the four arms that had been blocked in Part 1. Participants were asked to pick up all four objects from the open arms in Part 1 and to remember which arms they had visited in order to avoid them in Part 2. Entry into an arm that did not contain an object was marked as an error. There are two different configurations of open and closed arms: Sequences A and B. In Part 1 of trial sequence A, arms 1, 3, 4 and 6 were accessible and each contained an object. In Part 2 of trial sequence A, all arms were accessible but only arms 2, 5, 7 and 8 contained an object (Fig. 1B). In Part 1 of trial sequence B, arms 2, 3, 7 and 8 were accessible and each contained an object. In Part 2 of trial sequence B, arms 1, 4, 5 and 6 contained objects. In trial sequence C, the probe trial, Part 1 was identical to Part 1 of trial sequence A. Part 2, however, had no visible landmarks as the walls were raised to hide the surrounding landscape and the trees were removed. There was an object in each of the eight arms and the trial ended after the participant had retrieved four objects. The purpose of the probe trial was to see whether participants used a spatial strategy or a response strategy. If a spatial strategy was used, the participant would rely on the environmental landmarks to perform the task and would, therefore, be expected to make more errors. If a response strategy was used, on the other hand, the participant would not rely on the landmarks to remember the pattern of arms and would thus be expected to make fewer errors. Participants performed trials in the following order: A, B, A, C and A.

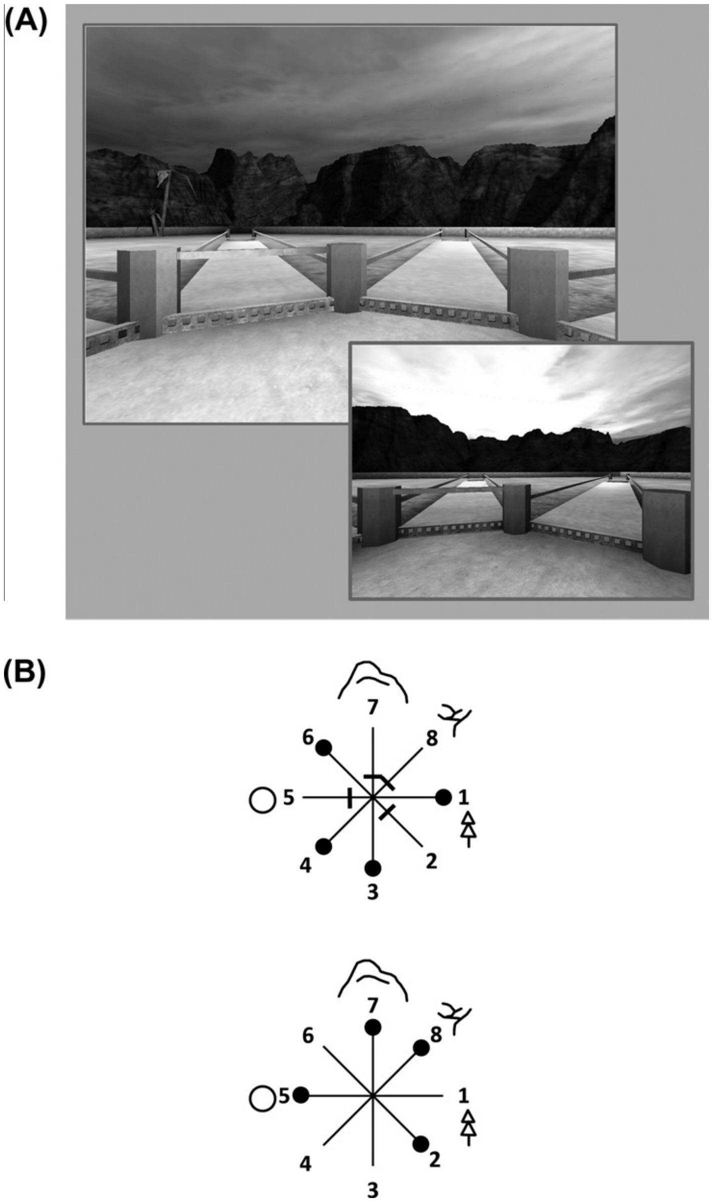

Fig. 1. (A) Participant views of the 4 on 8 virtual maze. Image courtesy of Bohbot et al. (2007). (B) Schematic representation of trial A Part 1 (above) and Part 2 (below) of the 4 on 8 virtual maze. Pathways are numbered 1–8. Landmarks around the maze are shown. Black circles represent objects and bars represent closed pathways.

The time spent on each trial and the number of errors were measured. Errors consisted in revisiting an arm during a given trial or entering an arm that contains no object. Rotational probe errors represent the number of errors based on the pattern of correct arms only. For example, if the participant entered into arms 1, 4, 6, and 7, instead of the correct arms (2, 5, 7, and 8), then they would have zero rotational probe errors as the pattern is correct if the starting position is corrected for. If the participant enters into arms 3, 6, 7, and 8, and this pattern is rotated in order to best fit with the correct arms (2,5,6,7) then it would result in one rotational probe error.

Following the behavioral task, participants were asked how they solved the task. Participants were categorized as response learners if a counting or pattern strategy was used (ex. open, open, closed, etc.). Participants who mentioned using two or more landmarks but no counting or pattern strategy were categorized as spatial learners.

2.3. Neuropsychological tasks

The Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1995) involves the experimenter reading a list of 15 words (list A) to the participant and asking them to repeat as many words as they can remember. This is repeated five times. Next, the experimenter reads a different list of 15 words (list B) and asks the participant to name as many as they can recall, as interference for the memory of list A. The experimenter then asks the participant to name as many words from list A as they can recall. After a 30-min delay, the participant is again asked to list as many words from list A as they can. The recognition portion of the task is a list of words given to participants, who are asked to put the number “1” next to any words that appeared on list A, a “2” next to any words from list B and to leave blank any other words that were not on either list. For the Rey-Osterrieth Complex Figure (RO) task (Lezak, 1995), participants are asked to copy a complicated figure in as much detail as possible. Following a 30-min delay, participants are asked to draw the figure from memory. Lastly, participants are given 20 min to complete the Shipley IQ test (Zachary, 1991), which includes both pattern completion and vocabulary sections.

2.4. PSS stress questionnaire

After 25 participants had entered the study, 41 of the 66 participants also completed the 14-question Perceived Stress Scale (PSS) questionnaire (Cohen, Kamarck, & Mermelstein, 1983) which measures the frequency of stressful situations that occurred within the past month.

2.5. Salivary cortisol

Saliva samples were collected by all 66 participants for 2 days, five times a day, for a total of 10 samples per participant. Recommended sampling times were: upon awakening, 30 min after awakening, 11 am, 4 pm and 9 pm. Each participant filled out a form, indicating the exact time that each sample was taken. The samples were taken on days following behavioral testing, while participants were at home. The form also asked the following question: *Has any particular positive or negative event occurred today that may have affected you in a significant way? If so, can you please tell us about it?* Samples were analyzed in the laboratory of Claire-Dominique Walker at the Douglas Institute. Average salivary cortisol was calculated for each participant based on their 10 samples.

3. Results

Forty-four participants spontaneously used a response strategy and 22 participants used a spatial strategy on the 4/8 VM task based on the verbal reports. The groups were balanced in terms of age, IQ, and sex (see Table 1). A *t*-test analysis revealed a significant difference between spatial and response learners on probe errors of the 4/8 VM task ($t = -1.906$, $p = 0.03$). As expected, response learners made fewer errors (mean = 0.23) than spatial learners (mean = 0.50) (Fig. 2A).

An ANOVA was performed to examine cortisol levels across five different time points throughout the day and strategy. Overall across all time points, there was a significant difference between spatial and response learners ($F_{(1317)} = 5.52$; $p < 0.02$), with spatial learners having overall higher cortisol levels (spatial mean = 0.29 ± 0.03; response mean = 0.23 ± 0.02) (Fig. 2B). There was also a significant difference between the different time points ($F_{(4317)} = 32.35$; $p < 0.001$). No interaction was seen between time and strategy, indicating that both spatial and response learners had similar rise and falls in cortisol levels throughout the day. Each time point was examined separately to determine whether spatial learners differed from response learners more greatly during certain times of the day (Fig. 2C). A trend towards significance was observed at the beginning of the day (awakening: $t_{(62)} = -1.447$; $p = 0.076$; 30 min: $t_{(62)} = -0.745$; $p = 0.23$; 11 am: $t_{(61)} = -1.307$; $p = 0.098$; 4 pm: $t_{(62)} = -1.267$; $p = 0.11$; 9 pm: $t_{(62)} = -1.318$; $p = 0.096$). A multivariate analysis revealed that the spatial and response groups had significantly different scores on the RAVLT after interference (spatial group mean: $F_{(1,63)} = 6.29$; $p < 0.02$), RAVLT delayed recall ($F_{(1,63)} = 6.08$; $p < 0.02$) (Fig. 3A), RAVLT recognition ($F_{(1,63)} = 6.86$; $p < 0.02$), and the RO delayed recall ($F_{(1,63)} = 4.24$; $p < 0.05$) (Fig. 3B) tasks. The spatial group performed better than the response group on all four measures of memory (see Table 1 for means).

Table 1
Participant demographics and test means.

	Spatial	Response
Participant characteristics		
N	22	44
Women:men	14:8	25:19
Age (years)	21.68 [0.81]	21.66 [0.51]
IQ	111.5 [1.45]	110.36 [0.88]
Stress measures		
Cortisol level (μg/dl)	0.30 [0.05]	0.23 [0.02]
PSS	24.90 [1.57]	24.10 [0.99]
4/8 VM and neuropsychological test scores		
4/8 VM probe errors	0.50 [0.14]	0.23 [0.07]
RO delayed recall	20.02 [0.93]	17.10 [0.89]
RAVLT delayed recall	91.55 [2.75]	81.91 [2.29]
RAVLT after interference	15.36 [1.61]	9.55 [1.35]

We also sought to investigate whether the effect of strategy on memory was mediated by cortisol levels. We found no significant correlations between cortisol and the various memory measures (RAVLT after interference: $r = 0.044$, $p = 0.731$; RAVLT delayed recall: $r = 0.062$, $p = 0.621$; RAVLT recognition: $r = 0.084$, $p = 0.505$; RO delayed recall: $r = -0.059$, $p = 0.643$).

There was no difference found between spatial and response learners on perceived levels of stress ($t = -0.409$, $p = 0.685$). In addition, no significant correlation was found between stress, as measured by the PSS questionnaire, and salivary cortisol levels ($r = 0.065$; $p = 0.685$). Moreover, few stressful events were reported in the two groups: three in the response group and four in the spatial group. These results suggest that the higher baseline endogenous cortisol found in spatial learners was not associated with perceived stress.

4. Discussion

The purpose of this study was to examine the relationship between navigational strategies, basal cortisol levels, and performance on standard neuropsychological tests. Based on the literature on the effects of stress and associated elevated cortisol on hippocampal function, we had expected that elevated basal cortisol would be associated with caudate nucleus-dependent response strategies. Instead, we found that response learners had significantly lower basal levels of cortisol than spatial learners in our sample. Higher basal cortisol levels in the spatial group were not associated with greater perceived stress and no correlation was found between cortisol levels and scores on the PSS questionnaire. Moreover, the two groups did not differ on their PSS scores, showing that their perceived stress levels were comparable. In addition, the PSS scores in our participants were similar to those previously reported. Cohen et al. (1983) did investigate PSS scores in a sample of healthy college students, and found that their average score was 23.18 in men and 23.67 in women. Our groups' averages were 24.90 for the spatial group and 24.10 for the response group. Thus, it seems that our groups have perceived stress similar to that reported in Cohen et al. (1983). In addition, we found that our participants' cortisol levels were in the normal range relative to other studies in the literature. We converted our participant's average cortisol levels, originally in μg/dl, into nmol/l (1 μg/dl = 27.6 nmol/l) and square root of nmol/l, as used in other articles to allow for a comparison (Table 2). As an example, our participants' average cortisol levels in square root nmol/l ranged from 1.34 to 3.43 throughout the day which are comparable to those reported by Edwards, Evans, Hucklebridge, and Clow (2001) which ranged from 1.6 to 2.5. In summary, our participants' cortisol levels were in the normal range, they had no significant perceived stress, yet response learners had significantly lower basal levels of cortisol than spatial learners.

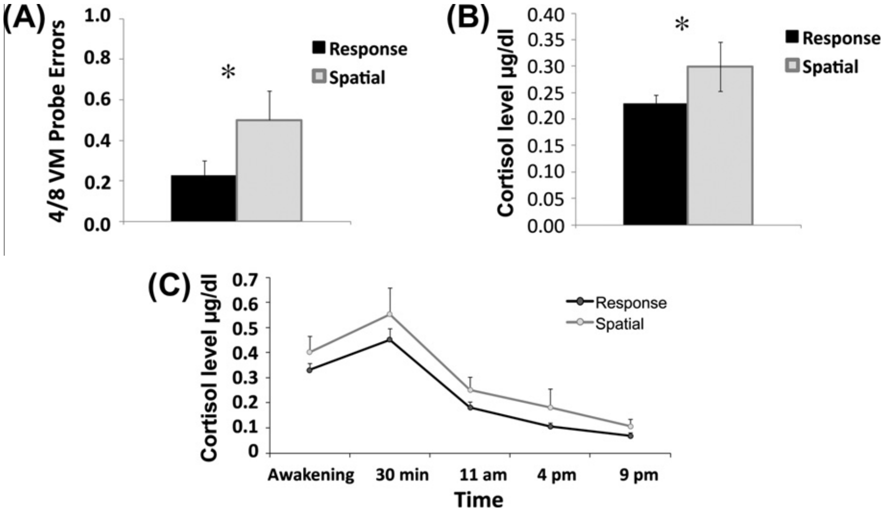

Fig. 2. (A) Spatial learners make more errors on the probe trial than response learners, showing that they were using a landmark-based spatial strategy to solve the task. (B) Spatial learners have higher basal levels of cortisol than response learners. (C) Cortisol levels of spatial and response learners at five different time points: at awakening, 30 min after awakening, 11 am, 4 pm, and 9 pm. Cortisol levels were compared for the two groups at each of these time points. A trend towards significance was observed at awakening, $p = 0.076$. Error bars represent standard errors of the mean. $^{*}p < 0.05$.

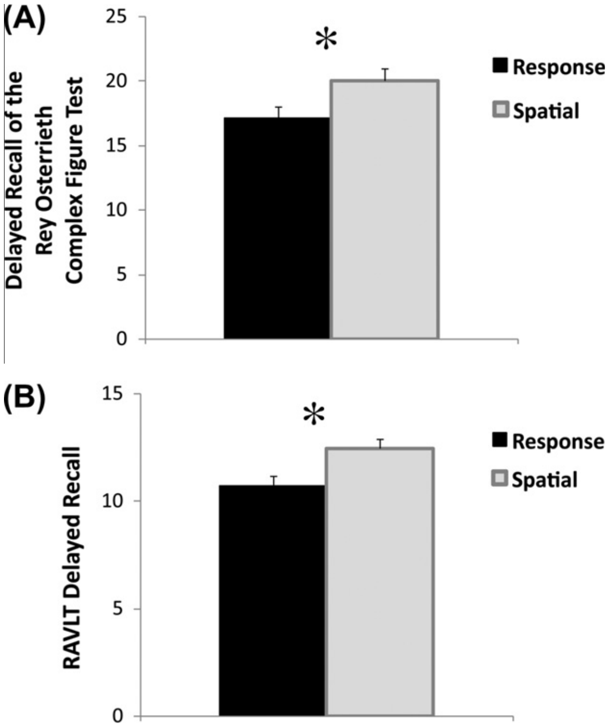

Fig. 3. Spatial learners displayed greater scores on the delayed recall of the Rey-Osterrieth Complex Figure Test (A) and the delayed recall of the Rey Auditory Verbal Learning Test (RAVLT) than response learners (B). Error bars represent standard errors of the mean. $^{*}p < 0.05$.

Spatial learners performed better than response learners on all measures of episodic memory, i.e., on the RAVLT after interference, RAVLT delayed recall, RAVLT recognition, and the RO delayed recall. Altogether, these results suggest that the higher cortisol levels seen in spatial learners are optimal with respect to their hippocampal-dependent episodic memory performance. In other words, people showing a predominant use of their hippocampus through spatial strategies are also better at other forms of hippocampal-dependent memory such as verbal and visuo-spatial memory (Bohbot et al., 1998). Further, we found no direct relationship between basal cortisol level and verbal or visuo-spatial memory, suggesting that the 4/8 VM test of navigational strategies is a more sensitive measure of the effect of neurobiological markers such as cortisol, relative to other measures of hippocampal-dependent episodic memory measured by standard neuropsychological tests.

As previously mentioned, based on the literature showing elevated cortisol in response to an acute stressor in response learners relative to spatial learners (Schwabe et al., 2007), we had expected to observe elevated basal cortisol in response learners in our task. Instead, the basal cortisol in response learners was lower relative to spatial learners. Interestingly, a similar pattern of cortisol has been observed in patients with Post-Traumatic Stress Disorder (PTSD). One study measured the basal cortisol levels of combat veterans with PTSD every half-hour during 24 h of bed rest. They were found to have significantly lower cortisol levels than healthy control participants (Yehuda, Teicher, Trestman, Levengood, & Siever, 1996). While patients with PTSD have a significant increase in cortisol during stress, they also have lower basal cortisol under low stress day-to-day conditions (Bremner et al., 2003; Marshall et al., 2002; Oquendo et al., 2003; Yehuda et al., 1996). The difference here is that our participants, who showed a similar cortisol pattern to that in PTSD, were free of psychiatric or neurological disorders. This is interesting in light of the fact that a twin study in patients with PTSD suggested significant atrophy of the hippocampus, prior to the onset of PTSD (Gilbertson et al., 2002). Coincidentally, response learners similar to the ones who showed lower basal cortisol in this study, were found to have a significant decrease in gray matter of the hippocampus (Bohbot et al., 2007). These results suggest that there may be a link between having lower basal cortisol levels and the decreased hippocampal gray matter that has been measured in people with a spontaneous use of caudate nucleus-dependent response strategies on the 4/8 VM.

There are several mechanisms through which spatial strategies may exert beneficial effects on the hippocampus. Maguire et al. (2000) showed that London taxi drivers, who have extensive navigation experience, have a larger posterior hippocampus compared to control participants. London taxi drivers, who undergo extensive training in order to obtain their taxi driving license, are thought to use spatial cognitive mapping strategies to a great extent, as they must quickly reach a target location in a straight path from any given location inside the city. This requires a well-developed cognitive map of the whole city. Bohbot et al. (2007) tested young participants on the 4/8 VM and found greater hippocampal gray

Table 2
Average cortisol levels of the spatial and response groups.

	Awakening	30 min	11 am	4 pm	9 pm
Cortisol levels					
μg/dl					
Spatial	0.40 [0.06]	0.55 [0.10]	0.25 [0.05]	0.18 [0.07]	0.11 [0.03]
Response	0.33 [0.03]	0.45 [0.04]	0.18 [0.02]	0.11 [0.01]	0.07 [0.01]
Average	0.35 [0.03]	0.49 [0.04]	0.20 [0.02]	0.13 [0.03]	0.08 [0.01]
nmol/l					
Spatial	11.07 [1.77]	15.27 [2.89]	6.92 [1.44]	5.03 [2.03]	2.98 [0.76]
Response	9.14 [0.72]	12.47 [1.21]	5.03 [0.61]	2.96 [0.37]	1.92 [0.33]
Average	9.76 [0.75]	13.37 [1.24]	5.65 [0.63]	3.62 [0.70]	2.26 [0.33]
$\sqrt{\text{nmol/l}}$					
Spatial	3.17 [0.23]	3.63 [0.33]	2.47 [0.21]	1.85 [0.29]	1.54 [0.18]
Response	2.91 [0.13]	3.34 [0.18]	2.11 [0.12]	1.62 [0.09]	1.25 [0.09]
Average	2.99 [0.11]	3.43 [0.16]	2.23 [0.11]	1.70 [0.11]	1.34 [0.09]

matter in people who spontaneously used spatial strategies compared to individuals who used response strategies in this task. Head and Isom (2010) found in healthy older adults a correlation between hippocampal volume and spatial learning ability, which was measured in terms of distance travelled to find a target in a virtual environment. Moreover, they showed a correlation between route learning and caudate nucleus volume. The use of a spatial strategy has been shown to directly stimulate the hippocampus. Iaria et al. (2003) showed that spatial learners had more activity in the hippocampus than response learners on the 4/8 VM. Finally, a mouse imaging study confirmed that training on a spatial or response strategy leads to gray matter increases in the hippocampus and caudate nucleus, respectively (Lerch et al., 2011). Altogether, there is strong evidence to suggest that the participants who used spatial strategies in the 4/8 VM in the present study may also exhibit more gray matter and functional activation in the hippocampus.

Differences in basal cortisol levels can help explain memory performance differences between spatial and response learners. It has previously been reported that the effects of cortisol on the hippocampus depend on the basal levels present. Moderate levels increase hippocampal plasticity (Joels, 1997) and promote survival of hippocampal granule neuron (Sloviter et al., 1989), whereas chronically elevated levels are toxic to the hippocampus and are associated with memory deficits (de Kloet, Joëls, & Holsboer, 2005). Studies in the literature suggest the existence of an inverted U-shaped function to describe the effects of basal levels of circulating cortisol on memory where moderate levels enhance memory while high and low levels have an opposite effect (see de Kloet et al., 1999; Herbert et al., 2006; Lupien & McEwen, 1997; McEwen & Sapolsky, 1995 for reviews). For example, in rats, increasing MR levels in the granule cells of the dentate gyrus resulted in an enhancement of object recognition (Ferguson & Sapolsky, 2007). In another study (Roozendaal & McGaugh, 1997), the administration of a GR agonist enhanced hippocampal memory consolidation, while the administration of a GR antagonist impaired it. In humans, it was found that the administration of exogenous cortisol facilitated free recall of pictures and words (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003). A high dose of cortisol, however, resulted in a decrease in verbal declarative memory (Newcomer et al., 1999). Maheu, Joober, Beaulieu, and Lupien (2004) administered Metyrapone, a corticosteroid synthesis inhibitor, to participants, who exhibited an impairment in long-term declarative memory of a story. Thus, there are many lines of evidence showing that moderate ranges of cortisol are beneficial whereas too little or too much is detrimental to performance. Since our study showed that spatial learners have better memory than response learners on the RAVLT and the RO, we hypothesize that the cortisol levels of the spatial group are in the moderate range. The spatial group would thus be located closer to the peak of the inverted U-shaped curve for hippocampus-dependent memory performance compared to response learners. Response learners, with their lower basal cortisol levels, would be placed on the lower left end of the curve. Though we did not directly investigate stress in the current study, we hypothesize that individuals with stress-related basal cortisol levels that would be higher than those exhibited by spatial learners, such as people who are administered large doses of exogenous cortisol, would have impaired memory. Indeed, previous studies have shown that administering exogenous cortisol led to improved hippocampus-dependent episodic memory in individuals with low basal levels of cortisol and poorer memory in individuals with high basal levels of cortisol (Lupien and McEwen (1997). Schwabe et al. (2008) found that high chronic stress participants were more likely to use response strategies. Based on our hypotheses, we suggest that high chronic stress individuals using response strategies would exhibit worse performance than spatial learners if they were tested on neuropsychological tasks. Future experiments on chronic stress and cortisol and how they impact memory and navigation strategies are needed to clarify this issue.

The fact that spatial learners have more gray matter in the hippocampus than response learners (Bohbot et al., 2007) supports the hypothesis that their basal cortisol levels are in a healthy range. Our results suggest that spatial learners' basal cortisol levels are optimal with respect to their performance on standard neuropsychological tests of memory which is better than that of response learners. Accordingly, the cortisol levels of response learners seem to be too low. A study by Schwabe, Oitzl, Richter, and Schachinger (2009) supports this hypothesis. Exogenous cortisol administered to women increased the proportion of spatial strategy use at the expense of response strategies in finding the target card in a 3D model of a house. Though the mechanisms for the effects of endogenous and exogenous cortisol on the nervous system are different, our interpretation of these results are that, in the inverted U function, cortisol levels that are too low or too high may promote response strategies either because of reduced hippocampal plasticity when cortisol is too low (Joels, 1997), or hippocampal toxicity when it is too high (de Kloet et al., 1999).

Moderate levels of cortisol are thought to be beneficial to memory because of the associated ratio of mineralocorticoid receptor/glucocorticoid receptor (MR/GR) occupation in the hippocampus (de Kloet et al., 1999). Long-term potentiation (LTP), which enhances synaptic transmission during learning and memory, is optimal when glucocorticoid levels are moderate and the MR/GR ratio is high (Diamond, Bennett, Fleshner, & Rose, 1992). Conversely, when the MR/GR ratio is low, for example due to adrenalectomy in rats (Dubrovsky, Liquornik, Noble, & Gijsbers, 1987; Filipini, Gijsbers, Birmingham, & Dubrovsky, 1991) or too high, for example due to exogenous administration of glucocorticoids (Bennett, Diamond, Fleshner, & Rose, 1991; Pavlides, Watanabe, & McEwen, 1993), LTP is significantly decreased. Thus, low levels of MR occupancy or high levels of GR occupancy lead to a small MR/GR ratio and memory impairments.

A study found that aged rats exhibit decreased MR and GR synthesis along with decreased reuptake of their associated ligands, possibly due to hypocortisolism seen in aging (Hassan, Patchev, von Rosenstiel, Holsboer, & Almeida, 1999). They proposed that this may in turn cause disturbances in neuroendocrine responses to stress and lead to cognitive impairments. Interestingly, some studies have found that aged rats use response strategies to a greater extent than do younger rats (Barnes, Nadel, & Honig, 1980; Nicolle, Prescott, & Bizon, 2003). We hypothesize that increased response strategy use throughout the lifespan may lead to memory impairments observed in older age. We may thus draw a link between MR/GR ratios and strategies. Young adults who are spontaneously employing response strategies to the detriment of hippocampal-dependent spatial strategies, just as older adults are, may already show signs of memory impairments due to a lower MR/GR ratio. It is then possible that spatial learners, having more optimal levels of cortisol, have a higher MR/GR ratio than response learners, who may have lower GR occupancy or GR expression. This decreased ratio in response learners may in turn be due to the lower use of hippocampus-dependent spatial strategies in favor of caudate nucleus-dependent response strategies. This has implications with regards to the aging process. Young response learners, who already show impaired memory, may exhibit greater cognitive decline than spatial learners during normal aging. It is possible that their extended use of hippocampal-independent response strategies, along with their low endogenous cortisol levels, may lead to degeneration of the hippocampus and that this, in turn, may result in decreased MR/GR ratio and poorer memory. Alternatively, response learners may have a smaller hippocampus to begin with, which would push them to use response strategies and to have a lower MR/GR ratio. The causation in this instance needs to be further investigated.

Recent work has begun to explore the role that these receptors play in mediating the relationship between spatial and response strategies during acute stress. Schwabe, Schachinger, et al. (2010) demonstrated not only that glucocorticoids are involved in the stress-induced shift from spatial to response strategies on their learning task, but that this shift to response strategies actually rescued performance on their task and that the shift could be prevented with a pharmacological blockade of the MR. The effect of stress on multiple memory systems differs depending on whether stress is acute, chronic or baseline and on the degree of stress experienced (see Schwabe, Wolf, & Oitzl, 2010 for a review). Further studies are needed to explore the link between navigational strategies and the corticosteroid receptors as they relate to different degrees of stress.

The present study demonstrated an association between navigational strategies, memory, and endogenous cortisol levels. Participants who used spatial strategies on the 4/8 VM showed better memory on other hippocampus-sensitive neuropsychological tests of memory and higher basal cortisol levels compared to response learners. Further investigation is required to uncover where spatial and response learners fall on a putative inverted U-shaped curve and how basal cortisol levels in spatial and response learners relate to memory and hippocampal integrity. Experiments involving the administration of exogenous cortisol and the resulting effect on memory and navigation would furthermore be of great interest to reveal the underlying mechanisms of stress hormones on cognition.

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