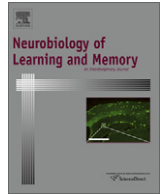




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Caudate nucleus-dependent response strategies in a virtual navigation task are associated with lower basal cortisol and impaired episodic memory

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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.

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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, Thorndyrcraft, 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 back-up 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.

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