Aus der Klinik für Psychiatrie und Psychotherapie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Effects of Mineralocorticoid Receptor Stimulation on Spatial Learning and Spatial Memory in Healthy Young Adults: A Study Using the Virtual Morris Water Maze Task

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Dr. med. univ. Dominique Piber

aus Graz, Österreich

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INHALTSVERZEICHNIS

1. ABSTRACT (deutsch)

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Einleitung: Stresshormone, wie zum Beispiel Kortisol, beeinflussen eine Vielzahl kognitiver Funktionen einschließlich Hippocampus-basierter räumlicher Gedächtnisleistungen. Die Stresseffekte des Kortisols werden im menschlichen Gehirn über zwei unterschiedliche Rezeptoren vermittelt: den Glukokortikoid-Rezeptor (GR) und den Mineralokortikoid-Rezeptor (MR). Da der MR eine besonders hohe Dichte im Hippocampus aufweist, untersuchte die vorliegende Studie die Effekte von pharmakologischer MR-Stimulation auf die räumliche Lern- und Gedächtnisleistung.

Methoden: Achtzig gesunde, junge Probanden (40 Frauen, 40 Männer, mittleres Alter = 23.9 Jahre ± *SD* = 3.3) führten den virtuellen Morris Water Maze (vMWM) task nach der Einnahme von 0.4 mg Fludrocortison, einem MR-Agonisten, oder eines Placebos durch. Beim vMWM task handelt es sich um ein Computer-basiertes Paradigma, das der Untersuchung der räumlichen Encodierung und des räumlichen Gedächtnisabrufs dient.

Ergebnisse: Wir fanden keinen Effekt von MR-Stimulation auf die räumliche Encodierung im vMWM task. Allerdings zeigten Probanden, die Fludrocortison erhielten, verbesserte Leistungen des räumlichen Gedächtnisabrufes im vMWM task. Dabei fand sich weder ein Geschlechtseffekt noch eine sex-by-treatment-Interaktion.

Zusammenfassung: MR-Stimulation führt bei gesunden, jungen Erwachsenen zu einer Verbesserung des Hippocampus-basierten räumlichen Gedächtnisabrufes im virtuellen MWM task. Die vorliegende Studie bestätigt nicht nur die Relevanz der MR-Funktion bei räumlichen Gedächtnisprozessen, sondern weist auch auf einen möglichen Vorteil einer akuten MR-Stimulation bei humanem Gedächtnisabruf räumlicher Inhalte hin.

2. ABSTRACT (englisch)

ABSTRACT (englisch)

Objectives: Stress hormones such as cortisol influence a broad variety of cognitive processes, including hippocampal based spatial memory. In the brain, cortisol effects are mediated via two different receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). As the MR shows high density in the hippocampus, a region well-known to be involved in spatial memory, we examined the effects of pharmacological MR stimulation on spatial memory.

Methods: Eighty healthy young participants (40 women, 40 men, mean age = 23.9 years ± *SD* = 3.3) completed the virtual Morris Water Maze (vMWM) task after receiving 0.4 mg fludrocortisone, a MR agonist, or placebo. The vMWM is a computer-based paradigm that tests spatial encoding and spatial memory retrieval.

Results: We found no effect of MR stimulation on spatial encoding during the vMWM task. However, participants who received fludrocortisone showed improved spatial memory retrieval performance. We found no main effect of sex nor a sex-by-treatment interaction.

Conclusion: In healthy young adults, MR stimulation leads to improved hippocampal based spatial memory retrieval in a virtual Morris Water Maze task. This study not only confirms the importance of MR function in spatial memory, but also suggests beneficial effects of acute MR stimulation on human spatial memory retrieval.

3. EIDESSTATTLICHE VERSICHERUNG

EIDESSTATTLICHE VERSICHERUNG

„Ich, Dominique Piber, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „*Effects of Mineralocorticoid Receptor Stimulation on Spatial Learning and Spatial Memory in Healthy Young Adults: A Study Using the Virtual Morris Water Maze Task*" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer angegeben sind. Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Berlin, 12. Oktober 2016

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Dr. med. univ. Dominique Piber

Promovend

4. ANTEILSERKLÄRUNG AN DER ERFOLGTEN PUBLIKATION

ANTEILSERKLÄRUNG AN DER ERFOLGTEN PUBLIKATION

Publikation:

Piber D, Schultebraucks K, Mueller SC, Deuter C, Wingenfeld K, Otte C. *Mineralocorticoid receptor stimulation effects on spatial memory in healthy young adults: a study using the virtual Morris Water Maze task*. Neurobiol Learn Mem. 2016;136:139-46.
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Beitrag im Einzelnen:

In dieser in Erstautorenschaft erstellten experimentellen biobehavioralen Arbeit werden die Effekte der pharmakologischen Stimulation des Mineralokortikoid-Rezeptors (MR) mit dem MR-Agonisten Fludrocortison auf die Encodierung und den Gedächtnisabruf von räumlicher Information bei gesunden, jungen Erwachsenen unter besonderer Berücksichtigung von Geschlechtseffekten untersucht.

Der Arbeitsanteil des Promovenden war dabei die Konzeptualisierung des Experiments, die Entwicklung des Studienaufbaus sowie die Implementierung und Durchführung des Computer-basierten Paradigmas mit anschließender Datenanalyse. Der Promovend etablierte im Rahmen dieser Studie das verwendete Computer-basierte Paradigma, den virtuellen Morris Water Maze (vMWM) task, an der Klinik für Psychiatrie und Psychotherapie der Charité im Rahmen einer wissenschaftlichen Kooperation mit Herrn Prof. Dr. Sven Müller von der Psychologischen Fakultät der Universität Gent, Belgien. Dies umfasste auch die Programmierung des vMWM task, den Aufbau der Testumgebung mit dem entsprechenden EDV-Equipment sowie den Entwurf der Studienskripte für diese und zukünftige Arbeiten. Die Supervision dieser experimentellen Studie erfolgte durch Herrn Prof. Dr. Christian Otte und Frau Prof. Dr. Katja Wingenfeld, die beide bereits eine Vielzahl von wissenschaftlichen Arbeiten zur humanen Kognition bei Manipulation der Hypothalamus-Hypophysen-Nebennieren-Achse durchgeführt und publiziert haben.

Die durchgeführte Arbeit wurde als doppelblinde, Placebo-kontrollierte, randomisierte Studie mit einem *between-group*-Design konzipiert. Insgesamt wurden achtzig gesunde, junge Erwachsene rekrutiert (40 Frauen, 40 Männer, mittleres Alter = 23.9, ± *SD* = 3.3), die randomisiert 0.4 mg Fludrocortison (*Florinef®)* oder Placebo erhielten und danach den vMWM task durchliefen. Neben der kognitiven Testung erfolgten auch repetitive Messungen vegetativer Parameter und des Speichelkortisols. Die biobehavioralen Daten wurden unter der Supervision von Frau Prof. Dr. Katja Wingenfeld statistisch aufbereitet.

Von Beginn der Planungsphase erfolgten wöchentliche Lab-Meetings mit Herrn Prof. Dr. Christian Otte und Frau Prof. Dr. Katja Wingenfeld. Im Einzelnen dienten diese Treffen zur Klärung von Fragen bei der Konzeptualisierung, Rekrutierung, Datenerhebung und statistischen Berechnung. Die wissenschaftliche Kooperation mit Herrn Prof. Dr. Sven Müller erfolgte in regelmäßigen Web-gestützten Meetings und Telefonaten sowie in mehreren Lab-Meetings in Berlin und in Belgien.

Weitere Arbeitsanteile des Promovenden waren das Zusammentragen und die graphische Darstellung der Ergebnisse, der Entwurf des Manuskripts mit der erforderlichen Literaturrecherche sowie die Bearbeitung des Review-Prozesses im Rahmen der Veröffentlichung im Journal *Neurobiology of Learning and Memory*.

Berlin, 12. Oktober 2016

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Dr. med. univ. Dominique Piber

Promovend

5. AUSZUG AUS DER JOURNAL SUMMARY LIST (ISI WEB OF KNOWLEDGE^{SM})

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6. DRUCKEXEMPLAR DER PUBLIKATION

DRUCKEXEMPLAR DER PUBLIKATION

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Mineralocorticoid receptor stimulation effects on spatial memory in healthy young adults: A study using the virtual Morris Water Maze task

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ABSTRACT

Objectives: Stress hormones such as cortisol are known to influence a wide range of cognitive functions, including hippocampal based spatial memory. In the brain, cortisol acts via two different receptors: the glucocorticoid (GR) and the mineralocorticoid receptor (MR). As the MR has a high density in the hippocampus, we examined the effects of pharmacological MR stimulation on spatial memory.
Methods: Eighty healthy participants (40 women, 40 men, mean age = 23.9 years ± *SD* = 3.3) completed the virtual Morris Water Maze (vMWM) task to test spatial encoding and spatial memory retrieval after receiving 0.4 mg fludrocortisone, a MR agonist, or placebo.
Results: There was no effect of MR stimulation on spatial encoding during the vMWM task. However, participants who received fludrocortisone exhibited improved spatial memory retrieval performance. There was neither a main effect of sex nor a sex-by-treatment interaction.
Conclusion: In young healthy participants, MR stimulation improved hippocampal based spatial memory retrieval in a virtual Morris Water Maze task. Our study not only confirms the importance of MR function in spatial memory, but suggests beneficial effects of acute MR stimulation on spatial memory retrieval in humans.

1. Introduction

Stress and glucocorticoids influence a broad variety of cognitive processes, such as memory encoding, consolidation and retrieval (Roozendaal, McEwen, & Chattarji, 2009; Sandi & Haller, 2015; Vogel, Fernandez, Joels, & Schwabe, 2016). These effects are mediated via two different receptors, which differ in various characteristics, such as expression, density and binding behavior: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) (de Kloet, 2013). The GR binds glucocorticoids with a 10-fold lower affinity, as compared to the MR (Reul & de Kloet, 1985). The GR is expressed throughout the brain, while the MR shows a high density in limbic brain areas, including the hippocampus (de Kloet, Joels, & Holsboer, 2005), a region well-known to be involved in spatial and declarative memory (Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000; Maguire et al., 1998). Besides nuclear receptor variants, MR and GR also occur as low affinity membrane-associated receptor variants mediating rapid non-genomic actions in response to glucocorticoids (Karst et al., 2005; Vogel et al., 2016).

Accordingly, several animal studies have shown that the MR mediates spatial encoding (Arp et al., 2014; Ter Horst et al., 2013). For assessing spatial memory performance in rodents, researchers have used the Morris Water Maze (MWM) task intensively throughout the last decades (D'Hooge & De Deyn, 2001; Morris, 1984; Morris, Garrud, Rawlins, & O'Keefe, 1982). In this task, rodents have to search for a hidden platform in a circular pool after a series of learning trials. Eventually, rodents undergo a probe trial, which measures spatial memory retrieval by calculating the time spent in the correct quadrant of the pool while still searching for the hidden platform. Interestingly, a number of animal studies found that a blockade of the MR leads to an impairment of spatial memory in a MWM (Oitzl & de Kloet, 1992; Qiu et al., 2010; Yau, Noble, & Seckl, 1999). In particular, it has been shown that rats spent up to 20% less time searching in the correct quadrant of the MWM task probe trial (Yau et al., 1999). Moreover, transgenic MR-deficient mice, that carry a genetic deletion of the MR in the

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forebrain, show significant impairment in their exploratory searching behavior (Arp et al., 2014) and spatial encoding processes (Berger et al., 2006; Ter Horst et al., 2013), as compared to their wild-type littermates. In turn, transgenic mice with forebrain-specific or hippocampal MR gene overexpression show improved spatial searching behavior (Arp et al., 2014) and improved spatial memory retrieval, seen in an increase of time spent in the correct quadrant of the MWM task probe trial (Ferguson & Sapolsky, 2008; Harris, Holmes, de Kloet, Chapman, & Seckl, 2013; Lai et al., 2007; Yau, Olsson, Morris, Meaney, & Seckl, 1995).

However, while the animal model has been studied extensively, studies addressing the role of the MR in humans are sparse. There is some evidence from human studies that MR blockade impairs visuospatial, verbal, and working memory in healthy adults (Cornelisse, Joels, & Smeets, 2011; Otte et al., 2007; Rimmele, Besedovsky, Lange, & Born, 2013). Conversely, recent human studies have shown that the stimulation of the MR in healthy individuals leads to an improvement in various neuropsychological domains, such as verbal memory and executive function (Otte, Wingenfeld, Kuehl, Kaczmarczyk, et al., 2015), as well as visuospatial memory and working memory (Hinkelmann et al., 2015).

The limited number of human studies, which investigated the effect of MR stimulation on spatial memory, have used the Rey-Osterrieth and modified Taylor complex figure tests to measure visuospatial memory (Hubley & Tremblay, 2002). In order to maximize extrapolation of findings from the animal literature and increase comparability of results, we used the virtual Morris Water Maze (vMWM) task for the present study. The vMWM is an analogue of the original research tool that has been translated from an animal task to a validated virtual testing instrument for human studies (Astur, Ortiz, & Sutherland, 1998; Hamilton, Johnson, Redhead, & Verney, 2009). Prior work that investigated spatial encoding and memory retrieval in humans using this task has shown highly consistent and reliable findings. For example, the vMWM has been used to examine spatial encoding and memory processes in patients with traumatic brain injury (Livingstone & Skelton, 2007; Skelton, Bukach, Laurance, Thomas, & Jacobs, 2000), transient global amnesia (Bartsch et al., 2010), and hippocampal damage (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Daugherty, Bender, Yuan, & Raz, 2015; Driscoll et al., 2003; Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010). Furthermore, this task has been used to examine the influence of psychiatric conditions, such as schizophrenia (Folley, Astur, Jagannathan, Calhoun, & Pearlson, 2010; Hanlon et al., 2006) or post-traumatic stress disorder (Astur et al., 2006), as well as the impact of sex hormones (Astur, Tropp, Sava, Constable, & Markus, 2004; Burkitt, Widman, & Saucier, 2007; Chamizo, Artigas, Sansa, & Banterla, 2011; Mueller, Jackson, & Skelton, 2008; Mueller, Verwilst, Van Branteghem, T'Sjoen, & Cools, 2016; Mueller, Temple, et al., 2008; Nowak, Diamond, Land, & Moffat, 2014; van Gerven, Schneider, Wuitchik, & Skelton, 2012) on spatial encoding and spatial memory.

Therefore, the present study sought to examine to which extent MR stimulation in humans can alter encoding of a spatial map and spatial memory retrieval processes. Based on prior studies on human cognition (Arp et al., 2014; Hinkelmann et al., 2015; Otte, Wingenfeld, Kuehl, Kaczmarczyk, et al., 2015; Otte, Wingenfeld, Kuehl, Richter, et al., 2015; Wingenfeld et al., 2015) and data from animal studies (Arp et al., 2014; Berger et al., 2006; D'Hooge & De Deyn, 2001; Ferguson & Sapolsky, 2008; Harris et al., 2013; Lai et al., 2007; Oitzl & de Kloet, 1992; Qiu et al., 2010; Yau et al., 1995, 1999) we hypothesized that the MR agonist fludrocortisone would lead to improved spatial memory retrieval in healthy adults. Since several human studies report a sex effect on spatial memory in terms of behavioral strategies (Mueller, Jackson, et al., 2008; Ross, Skelton, & Mueller, 2006) and recruitment of brain regions in virtual mazes (Gron et al., 2000), we also controlled our analyses for sex.

2. Experimental procedures

2.1. Participants

Eighty healthy volunteers (40 women, 40 men, age range 18–30 years, mean age = 23.9 ± *SD* = 3.3), all undergraduate students from the Humboldt University and the Free University, Berlin, participated in our study. All participants received a monetary compensation of 40 €. None of the participants reported neurological, psychiatric, or psychological disorders, acute or persistent medical disease. No participant took any medication. Female participants were in their luteal cycle phase or on oral contraceptives during time of testing. Exclusion criteria were psychiatric disorders, neurological diseases, previous traumatic brain injury, malignant tumors, chronic or acute infections, autoimmune diseases, cardiovascular diseases, metabolic or endocrine diseases, allergies and pregnancy. All participants fulfilled a screening for previous or current psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders – DSM-IV. All participants showed normal weight (mean BMI = 22.9 ± 2.9). The extent of having experiences in playing computer games and its influence on the performance in three-dimensional (3D) games has been shown repeatedly. Therefore, participants completed a questionnaire regarding their experience with playing computer games and using joysticks prior to the experiment phase (Mueller, Jackson, et al., 2008). Our study was approved by the Ethics Committee of the German Psychology Association, and was in line with the World Medical Association Declaration of Helsinki. Participants signed a written informed consent before participation.

2.2. Procedure

We used a double-blind, placebo-controlled, randomized between-group design. Participants were randomly assigned to either 0.4 mg fludrocortisone (*Florinef*®) or placebo condition. Fludrocortisone or placebo were administered at 1 p.m., the experimental testing started two hours after drug intake at 3 p.m. in a quiet testing surrounding. Participants were abstinent from alcohol and caffeinated drinks and were not allowed to engage in any form of sport or strenuous physical activity on the day of testing or to drink liquids 60 min prior to testing. Since blood pressure can be influenced by MR stimulation, we measured blood pressure at five different measuring times throughout the study protocol: 0 min (baseline – immediately before fludrocortisone or placebo intake), 90 min, 120 min, 180 min, and 210 min after drug intake. Salivary cortisol was collected at the same measuring times. In our study protocol, the virtual Morris Water Maze task was part of a larger battery of computer-based paradigms (see also Schultebraucks et al., 2016).

2.3. Hormonal assessment

Salivary cortisol was collected in synthetic swabs and stored at room temperature. Upon completion of the experiment, the swabs were stored at −80 °C (−112 °F) until they were ready for further biochemical analyses. The concentration of saliva cortisol was measured in the Neurobiology Laboratory of the Department of Psychiatry, Charité University Hospital Berlin, Germany, as described in greater detail elsewhere (Duesenberg et al., 2016).

2.4. Assessment of spatial memory: the virtual Morris Water Maze task

We used the virtual Morris Water Maze task, an analogue of the original research tool that has been translated from a task for animals to a validated virtual testing instrument for human studies

(Astur et al., 1998; Hamilton et al., 2009). A 24-in. PC monitor was used, which showed the virtual environment from a first-person perspective. Participants used a commercially acquired joystick, which allowed them to control their speed and swimming direction. Following previous studies (Skelton et al., 2000), the virtual environment consisted of a round pool, placed in the middle of a square room with one abstract painting on each wall. The experiment consisted of a total number of 22 trials. Participants started with the familiarization/exploration trial, during which they were given a total of 180 s time to get used to the environment and the handling of the joystick. In this trial no platform occurred. In a next step, participants had to undergo 4 visible platform trials, during which the platform was introduced and participants had to swim towards the visible platform as fast as possible. The performance during the visible platform trials is a measure for motor control. Subsequently, participants had to undergo 16 experimental/hidden platform trials, during which the platform was transferred to a new location, lowered underneath the pool's surface, and was invisible to the participants (see Fig. 1). During these 16 experimental/hidden trials, the platform did not change its location. The starting position alternated in each trial in a pseudo-randomized order at four different locations on the side of the pool (North, South, East, West). The performance during the experimental/hidden trials is a measure for spatial encoding. Lastly, the participants performed a probe trial for a total time of 60 s, during which the platform remained hidden. During the probe trial the platform's location was identical to the prior experimental/hidden trials. However, unlike during the previous experimental/hidden trials, the platform did not reveal itself during the 60 s of the probe trial, even when participants swam over the correct location. The time spent in the correct quadrant during the probe trial is a measure for spatial memory retrieval. Therefore, the total amount of time [in %] spent in the correct quadrant during the 60 s was calculated. As outcome measures for spatial memory encoding we defined the following variables: Latency (1), which describes the time [in seconds] that was spent to determine the correct location of the platform. Path length (2), which is defined as the distance relative to the pool diameter covered to reach the platform. Heading error (3), that represents the angle [in degrees] between an ideal heading direction and the actual heading direction. First move latency (4), which is a measure for initial movement and initial reaction.

2.5. Statistical analyses

We used SPSS version 22.0 for all statistical analyses. Demographic data were analyzed with *t*-test (continuous data) or χ^2 test (categorical data). Data from the vMWM task were analyzed as follows: adhering to the original testing method (Morris, Garrud, Rawlins, & O'Keefe, 1982), the pool was divided into 4 quadrants on an invisible N-S and E-W axis. Resembling the method of previous studies (Mueller, Verwilst, Van Branteghem, T'Sjoen, & Cools, 2016; Mueller et al., 2009), the 16 experimental/hidden platform trials were separated into 4 blocks of 4 trials each (block 1: trial 1–4, block 2: trial 5–8, block 3: trial 9–12, block 4: trial 13–16). A 2 × 4 rmANOVA with the main factor time (repeated measurement, block 1–4) and treatment (fludrocortisone vs. placebo) was used for each performance variable: latency (1), path length (2), heading error (3), and first move latency (4). We used a *t*-test to compare performances of the vMWM task probe trial between the placebo and the fludrocortisone group. In a second step we introduced sex as an additional group factor and repeated all analyses. Cohen's *d* was used as a measure of effect size and alpha was set at 0.05, two-tailed. For the statistical analyses of salivary cortisol and blood pressure we used a rmANOVA with time (0 min, 90 min, 120 min, 180 min, and 210 min after drug intake) as within-subject factor and treatment (fludrocortisone vs. placebo) as between-subject factor.

3. Results

3.1. Demographic data

The two treatment groups (fludrocortisone vs. placebo) did not differ significantly in sex, age, body mass index, smoking or their psychological state. There was no significant difference regarding the intake of oral contraceptives in female participants. Furthermore, the two groups did not differ significantly in their experiences with games and joysticks (Likert scale: 1 = never, 2 = sometimes, 3 = monthly, 4 = weekly, 5 = every few days, 6 = daily). The demographic characteristics are summarized in Table 1.

3.2. Blood pressure

There was no significant effect of treatment on systolic or diastolic blood pressure values. We found a significant effect of time on the systolic ($F(4,78) = 13.70$, $p < 0.001$) and diastolic blood pressure values ($F(4,78) = 5.68$, $p < 0.001$) but no time × treatment interaction effect, indicating a decrease of blood pressure over time. The results are shown in Table 2.

3.3. Salivary cortisol secretion

We found no significant main effect of treatment on salivary cortisol secretion. There was a significant main effect of time and a significant time × treatment interaction. *Post hoc* tests revealed significant differences between the cortisol values of the placebo and the fludrocortisone group at 180 min and 210 min after drug intake. Cortisol delta values (*i.e.*, baseline value at 0 min minus

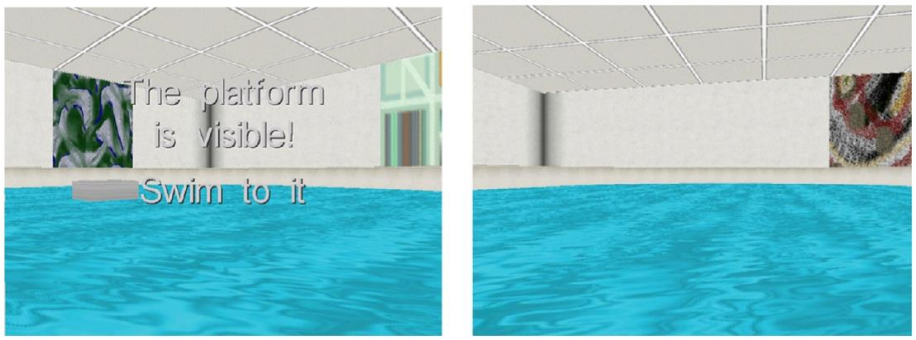

Fig. 1. (a and b) Visible platform trial and experimental/hidden platform trial of the virtual Morris Water Maze task.

the last value 210 min after drug intake) showed a significant difference between the placebo and the fludrocortisone group, indicating greater cortisol suppression after fludrocortisone intake compared to placebo. The results of the salivary cortisol secretion during testing are described in details elsewhere (Schultebraucks et al., 2016).

3.4. Virtual Morris Water Maze results

3.4.1. Visible platform trials (motor control condition)

In the visible platform trials we found no significant effect of treatment, indicating that fludrocortisone had no effect on the participants' motor control.

3.4.2. Hidden platform trials (spatial encoding)

Concerning latency we found a significant main effect of time ($F(3,234) = 31.53$, $p < 0.001$), indicating better task performance, *i.e.*, faster determination of the hidden platform location over time. The main effect of treatment and the time × treatment interaction were not significant. For the variables heading error, path length and first-move latency we also found significant main effects of time (heading error: $F(3,234) = 18.91$, $p < 0.001$; path length: $F(3,234) = 37.9$, $p < 0.001$; first move latency: $F(3,234) = 2.22$, $p = 0.086$). Thus, task performance increased over time, suggesting effective learning over time. There was no significant main effect of treatment and no significant time × treatment interaction for heading error, path length and first move latency, respectively. The results are presented in Fig. 2. After repeating the analysis with sex as additional factor the results did not change (main effect sex: all p-values > 0.05 for latency, heading error, path length, and first move latency).

3.4.3. Probe trial (spatial memory retrieval)

In the probe trial we found a significant effect of treatment ($t(78) = 2.12$, $p = 0.037$, $d = 0.47$), indicating that the participants who received fludrocortisone searched longer in the correct quadrant for a hidden platform (mean: 65.67% (*SD* 18.07)), as compared to participants who received placebo (mean: 56.79% (*SD* 19.43)). This main effect of treatment remained significant after controlling for sex (main effect sex: $p = 0.28$). The results are shown in Fig. 3.

4. Discussion

We examined whether stimulating the MR with fludrocortisone improves encoding of a spatial map and spatial memory retrieval in healthy young adults. Consistent with our hypothesis, we found that fludrocortisone leads to improved spatial memory retrieval. This was shown in an increase of time spent in the correct quadrant during the vMWM task probe trial. In contrast, stimulating the MR did not lead to improved learning over time, nor did it improve motor control. The treatment effect on memory retrieval was stable after controlling for sex, but no significant differences between men and women were seen.

Our results support the findings of earlier human studies, which examined the influence of MR stimulation on various neuropsychological domains, such as visuospatial memory, working memory, and verbal memory in healthy participants (Hinkelmann et al., 2015; Otte, Wingenfeld, Kuehl, Kaczmarczyk, et al., 2015; Otte, Wingenfeld, Kuehl, Richter, et al., 2015). Still, the literature on the role of MR on spatial memory performance is sparse. So far, it has been shown that MR blockade with the antagonist spironolactone impairs working memory (Cornelisse et al., 2011). Furthermore, blockade of the MR leads to an impairment of recalling texts and

Table 1
Demographic data.

	Fludrocortisone ($n = 40$)	Placebo ($n = 40$)	Statistics
Age in years (*SD*)	24.1 (3.1)	23.8 (3.6)	$t(78) = 0.44$, $p = 0.67$
Sex (male/female)[a]	20/20	20/20	$\chi^2(1) = 0.00$, $p = 1$
Body mass index (*SD*)	22.9 (3.1)	23.1 (2.6)	$t(78) = 0.29$, $p = 0.77$
Smoker[a]	10	9	$\chi^2(1) = 0.07$, $p = 0.99$
Oral contraceptive[a]	12	12	$\chi^2(1) = 0.00$, $p = 1$
Handedness[a] (L/R)	3/36	3/34	$\chi^2(1) = 0.005$, $p = 0.95$
Navigation questionnaire[b]			
Dizziness	1.6 (0.78)	1.6 (0.63)	$t(77) = 0.25$, $p = 0.80$
Game experience in youth	3.6. (0.26)	3.7 (0.27)	$t(77) = 0.25$, $p = 0.80$
Game experience in last year	2.1 (1.29)	2.3. (1.54)	$t(77) = 0.41$, $p = 0.68$
3D game experience	1.8 (1.36)	1.7 (1.19)	$t(77) = -0.28$, $p = 0.78$
2D game experience	2.1 (1.36)	2.0 (1.04)	$t(77) = -0.27$, $p = 0.78$
Joystick experience	1,6 (0.78)	1.7 (0.77)	$t(77) = 0.53$, $p = 0.60$

[a] Number of participants.
[b] Likert scale.

Table 2
Systolic and diastolic blood pressure.

	Fludrocortisone ($n = 40$)	Placebo ($n = 40$)	Statistics
Systolic blood pressure (mmHg)			
0 min. (baseline)	122.6 (14.0)	126.1 (11.6)	$F(4,78) = .27$, $p = .89$
+ 90 min.	116.2 (15.3)	118.4 (10.2)	
+ 120 min.	117.0 (14.9)	120.2 (12.9)	
+ 180 min.	117.5 (13.5)	120.2 (11.5)	
+ 210 min.	117.5 (13.6)	119.0 (12.2)	
Diastolic blood pressure (mmHg)			
0 min. (baseline)	76.5 (7.0)	77.2 (8.5)	$F(4,78) = .63$, $p = .64$
+ 90 min.	72.6 (7.7)	74.3 (8.1)	
+ 120 min.	73.2 (8.4)	75.3 (10.0)	
+ 180 min.	74.8 (8.1)	75.9 (7.6)	
+ 210 min.	76.2 (9.7)	76.0 (8.6)	

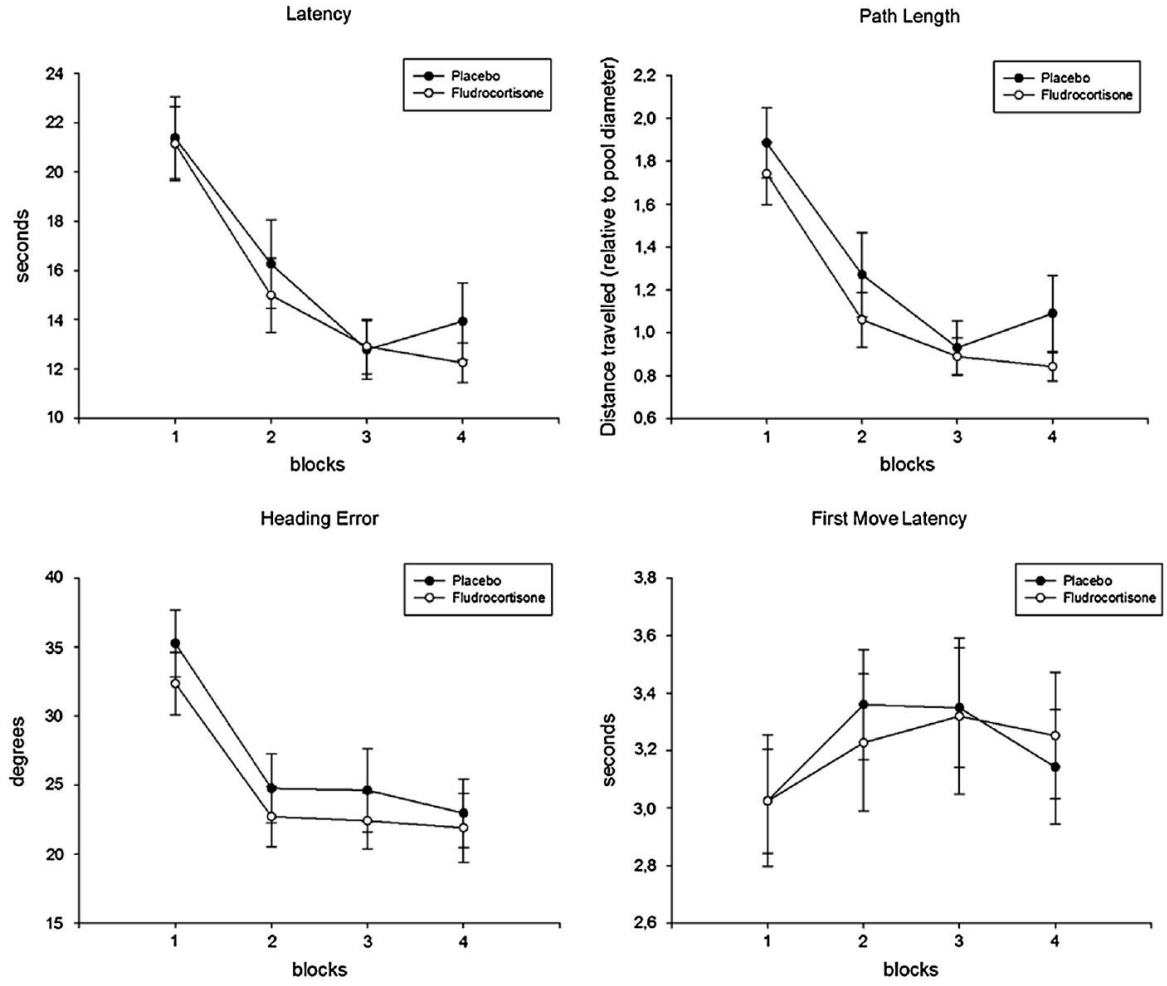

Fig. 2. These figures show performance for the placebo group (black), and the fludrocortisone group (white) for latency, path length, heading error and first move latency. Error bars denote standard error of the mean.

pictures, particularly of emotional material (Rimmele et al., 2013), and to impaired selective attention and visuospatial memory in healthy young males (Otte et al., 2007). However, few studies in humans have investigated the effect of MR stimulation on cognition. One study showed that MR stimulation leads to improved visuospatial memory and working memory, as compared to placebo in healthy individuals (Hinkelmann et al., 2015).

Overall, these human studies demonstrate that the MR plays a crucial role in memory retrieval and their results are in line with various animal studies that focused on hippocampus-dependent encoding and memory processes in rodents (Arp et al., 2014; Berger et al., 2006; D'Hooge & De Deyn, 2001; Ferguson & Sapolsky, 2008; Harris et al., 2013; Lai et al., 2007; Oitzl & de Kloet, 1992; Ter Horst et al., 2013; Yau et al., 1995, 1999). So far, there is evidence that forebrain-specific (Harris et al., 2013; Lai et al., 2007) and hippocampal MR (Ferguson & Sapolsky, 2008; Yau et al., 1995) gene overexpression improves spatial memory in rodents, whereas MR-deficiency significantly impairs it (Ter Horst et al., 2012, 2013). Beyond these findings, there is also evidence that the MR plays an important role in memory performances in psychiatric diseases. This is important, because a range of psychiatric disorders show significant hippocampal impairment. Particularly in the last years, studies have addressed MR function in patients with Major Depressive Disorder (MDD) and have found that MR stimulation leads to improved verbal memory and executive function (Otte, Wingenfeld, Kuehl, Kaczmarczyk, et al., 2015) in young depressed patients. However, there seems to be an age-dependent effect: another study suggested that older adults with MDD perform worse in verbal learning and visuospatial memory tasks after fludrocortisone compared to placebo and therefore do not benefit from MR stimulation (Otte, Wingenfeld, Kuehl, Richter, et al., 2015).

Data from human studies (Buss, Wolf, Witt, & Hellhammer, 2004; Het, Ramlow, & Wolf, 2005; Kuhlmann, Kirschbaum, & Wolf, 2005; Wolf, Convit, et al., 2001) as well as results from animal studies (Coluccia et al., 2008; Roozendaal, Griffith, Buranday, De Quervain, & McGaugh, 2003) suggest that glucocorticoids have impairing effects on memory retrieval. Nevertheless, the literature on these glucocorticoid effects on human memory is equivocal (de Kloet et al., 2016; de Quervain, Aerni, Schelling, & Roozendaal, 2009). For example, stress has been found to enhance declarative memory processes (Domes, Heinrichs, Reichwald, & Hautzinger, 2002; Nater et al., 2007; Payne et al., 2007; Schwabe, Bohringer, Chatterjee, & Schachinger, 2008; Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007), while other studies report an opposite effect (Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001; Zoladz et al., 2011). Additionally, the impact of stress on the GR and the MR also depends on the time of exposure: acute stress exposure increases hippocampal MR (Gesing et al., 2001; Veenema, Meijer, de Kloet, Koolhaas, & Bohus, 2003), while chronic stress exposure leads to hippocampal MR down-regulation (Lopez, Chalmers, Little, & Watson, 1998; Schmidt et al., 2010; Veenema, Meijer, de Kloet, & Koolhaas, 2003). Particularly, chronic states of elevated glucocorticoid levels show impaired cognitive

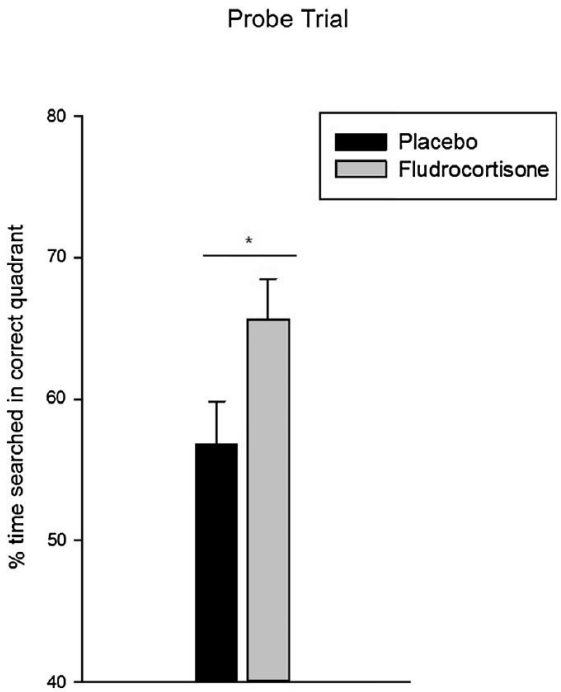

Fig. 3. This figure shows performance for the placebo group (black), and the fludrocortisone group (grey) for the probe trial. Error bars denote standard error of the mean.

performance (McEwen, 2001; Sapolsky, 2000). Thus, there is evidence that the GR has a divergent role in memory processes, as compared to the MR.

For the future, MR stimulation could be interesting as a therapeutic outlook to alleviate memory deficits in psychiatric diseases, such as MDD, or in other conditions that go along with neurocognitive impairment. For example, it would be interesting to investigate the effect of MR stimulation on spatial memory in people suffering from mild cognitive symptoms. To investigate this therapeutic thought further studies are needed.

The previous published literature on spatial memory after MR stimulation is limited and has predominantly used pencil-and-paper paradigms (*e.g.*, Rey-Osterrieth Complex Figure). In the current study, we used the vMWM task, since this paradigm is arguably more ecologically-valid than paper-and-pencil tasks and offers more precise measurements of numerous memory variables, which are comparable to the same variables used in animal versions of the task.

While examining the role of the MR in spatial memory, one must be aware that there are various factors that can influence the process and performance of spatial memory. There is evidence that spatial memory can be impaired by non-pharmacological stressors, such as the socially evaluated cold pressor test (SECPT) (Guenzel, Wolf, & Schwabe, 2014). Furthermore, a recently published study showed that acute stress, induced by the Paced Auditory Serial Addition Task (PASAT), has an impact on navigational strategies (van Gerven, Ferguson, & Skelton, 2016). Thus, future studies should try to disentangle MR and GR mediated effects on spatial memory and should also evaluate the effects of other mediating factors, such as autonomic response to stress, the role of norepinephrine and psychological stress reactivity.

Strengths and limitations: Our study consisted of a homogenous group of healthy young adults, which show a high degree in terms of comparability and high levels of cognitive functioning. Our study size, with a total of 80 participants, as well as the well-controlled design are both strengths of our study. However, we could not replicate sex differences in spatial memory performance, which might be due to a lack of power. We are aware that healthy individuals show undisturbed performances in spatial encoding and spatial memory per se. For our research approach we tried to increase the degree of difficulty of the vMWM task as much as possible by reducing discriminative external cues to avoid ceiling effects. This could be an explanation and a potential reason why we did not find a significant effect of treatment on spatial encoding.

The two separate experiment phases of the MWM animal task, namely *spatial encoding* and *spatial memory retrieval*, have been validated since its introduction in the 1980s (Morris, 1984; Morris, Garrud, Rawlins, & O'Keefe, 1982). Although this conceptual division and standard procedure of the animal task has been subsequently transferred to the human paradigm in analogous manner, it does present a problem. Namely, that having a probe trial immediately after the hidden platform trials makes it difficult to monitor whether spatial memory for the platform location has entered short-term or long-term storage (Vorhees & Williams, 2006). Previously, the probe trial in the human version has been defined as "testing the location of a target allocentrically" (Livingstone & Skelton, 2007). To ensure that spatial memory has entered long-term storage, a 24-h recall testing would be required. Furthermore, the pharmacological manipulation is present during both encoding and retrieval. Again, it would be important to clearly separate learning and memory retrieval to better differentiate related effects of MR stimulation.

Moreover, the present study was designed as a proof-of-concept that MR stimulation would improve spatial learning and/or memory. However, the precise way in which participants solved the present task was not assessed. Indeed, studies addressing the effects of stress on human spatial navigation strategies, whether subjects choose an ego- or an allocentric strategy, are sparse and their results have not always been consistent with data from animal studies. A recently published study tested participants in a forced allocentric task and in a forced egocentric task (Guenzel et al., 2014) and showed, contrary to findings with rodents, that stress does not have an impact on navigational efficiency in either task. There is evidence that acute stress can also shift from one navigation strategy to another, presumably based on a switch from hippocampus-based to caudate-based navigation effect (Schwabe, Schachinger, de Kloet, & Oitzl, 2010). In humans, stress increases the likelihood of choosing a stimulus-response strategy, although high salivary cortisol levels produce the opposite (Schwabe, Oitzl, Richter, & Schachinger, 2009). Furthermore, a recently published study showed that a social stressor leads more often to an allocentric navigation strategy in humans (van Gerven et al., 2016). However, investigating the choice of the navigation strategy (egocentric/stimulus-response vs. allocentric/bird-perspective) was not a specific aim of this study and represents a limitation.

5. Conclusion

The present study examined the effect of MR stimulation on spatial memory by using the virtual Morris Water Maze task. We found significant improvement of MR stimulation on hippocampus-based spatial memory retrieval but not on spatial encoding over time. In line with previous published data, our study supports the importance of the MR function in spatial memory. Further studies are needed to evaluate and replicate the findings of this study.

Conflict of interest

All authors declared no conflicts of interest with respect to the authorship or the publication of this article.

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7. LEBENSLAUF

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Dissertation nicht veröffentlicht.

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