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Cognitive function in older adults with major depression: Effects of mineralocorticoid receptor stimulation

Christian Otte [a, *], Katja Wingenfeld [a], Linn K. Kuehl [a], Steffen Richter [a], Francesca Regen [a], Dominique Piber [a], Kim Hinkelmann [b]

[a] Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany
[b] Department of Psychosomatic Medicine, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany

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ABSTRACT

Memory and executive function are often impaired in older adults with major depression. Mineralocorticoid receptors (MR) are abundantly expressed in the hippocampus and in the prefrontal cortex, brain areas critical for memory and executive function. In both aging and depression, MR expression in the brain is reduced. Therefore, diminished MR function could contribute to impaired cognition in older adults with depression and might be a promising target for pharmacological intervention.

Twenty-three older adults with major depression (mean age 61.6 yrs ± 8.1, n = 13 women) without medication and 24 age-, sex- and education-matched healthy participants received the MR-agonist fludrocortisone (0.4 mg) or placebo in a randomized, double-blind, within-subject cross-over design. We measured psychomotor speed, executive function, verbal learning and memory, and visuospatial memory.

Compared to controls, depressed patients performed worse in psychomotor speed (group effect $p = 0.01$), executive function (group effect $p < 0.01$), verbal learning (group effect $p = 0.02$), and verbal memory (group effect $p < 0.01$) but not in visuospatial memory. There were no significant treatment effects. However, we found a group × treatment interaction in verbal learning ($p = 0.04$) and visuospatial memory ($p = 0.02$) indicating that depressed patients performed worse after fludrocortisone whereas controls performed better after fludrocortisone.

Our data suggest that –in contrast to younger depressed patients-older adults with depression do not benefit from MR stimulation but deteriorate in cognitive function.

1. Introduction

Older adults with major depression often exhibit cognitive deficits compared to healthy individuals in the same age group. Memory and executive function are among those domains that are most consistently impaired (Kohler et al., 2010). Importantly, studies have found impaired cognition to be associated with altered cortisol secretion in older patients with major depression (Fiocco et al., 2006; O'Brien et al., 2004).

Cortisol exerts its effects in the brain via two different nuclear receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GR are distributed throughout the brain, while MR are expressed primarily in limbic areas. Both receptors are abundantly expressed in the hippocampus and in the prefrontal cortex, brain areas critical for memory and executive function.

Indeed, animal studies have consistently shown a role for MR in memory performance and executive function (Joels et al., 2008). For example, blockade of MR impairs spatial learning and memory (Arp et al., 2014; Ter Horst et al., 2014) and working memory (Berger et al., 2006). In contrast, overexpression of MR improved memory in animals (ter Heegde et al., 2015). In healthy humans, blockade of the MR impaired memory and executive function in young healthy men (Cornelisse et al., 2011; Otte et al., 2007; Rimmele et al., 2013; Schwabe et al., 2013).

Importantly, there is evidence of decreased MR expression in the hippocampus and prefrontal cortex in depressed patients (Klok et al., 2011; Medina et al., 2013). Furthermore, polymorphisms of the MR gene have been associated with depression (DeRijk et al., 2008), dysfunction of the MR has been demonstrated in

* Corresponding author. Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany.
E-mail address: christian.otte@charite.de (C. Otte).

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treatment-resistant depression (Juruena et al., 2010; 2009b, 2013), and administration of a MR agonist as add-on to standard antidepressants accelerated the response to antidepressants (Otte et al., 2010). Furthermore, preclinical studies have demonstrated that MR expression in the brain is reduced in aging (Choi et al., 2008; Reul et al., 1991). Finally, studies in humans have shown diminished MR function in aging (Otte et al., 2003).

In sum, there is a plethora of data suggesting an important role of MR function on cognition in healthy individuals (Joels et al., 2008) and first evidence of impaired MR function in major depression and in aging (ter Heegde et al., 2015). Recently, we have demonstrated improved cognitive function after fludrocortisone compared to placebo in young depressed patients (Otte et al., 2015) and in healthy individuals (Hinkelmann et al., 2015). However, so far no study directly examined a potential therapeutic effect of MR stimulation in older adults with major depression. Therefore, we examined the acute effects of the MR agonist fludrocortisone on memory and executive function in older adults with major depression and age-, sex-, and education-matched healthy controls. We hypothesized that fludrocortisone would improve memory and executive function in depressed patients.

2. Material and methods

2.1. Participants

We recruited 23 older adults with major depression (mean age 62.5 years, age range 51–77 years) according to DSM-IV criteria from a specialized depression clinic at the Department of Psychiatry and Psychotherapy, Charité University Medical School, Berlin. Inclusion criteria were 1) a diagnosis of major depressive disorder, single or recurrent according to DSM-IV criteria, 2) a minimum baseline score of 18 points on the Hamilton Rating Scale for Depression, 17-item version (HDRS − 17); 3) age >50 years; and 4) a period of at least 3 days free from antidepressants, antipsychotics, mood stabilizers, and other medications influencing HPA activity. Only sleep medication and benzodiazepines as needed were allowed.

Criteria for exclusion were 1) dementia, schizophrenia spectrum disorder, bipolar disorder, substance dependence within the last six 6 months according to the Mini-International Neuropsychiatric Interview (MINI); 2) serious medical conditions, especially those associated with adrenal dysfunctions, steroid use, or well-known impact on HPA activity (e.g., diabetes mellitus) or cognitive function; and 3) pregnancy and nursing.

A control group of 24 healthy subjects matched for age, sex, and years of education were enrolled in the study. Healthy subjects were free of former and present DSM-IV Axis I disorders according to the MINI. In patients and healthy individuals, depressive symptoms were assessed by the self-report Beck Depression Inventory (BDI).

All participants underwent a screening procedure consisting of a medical and psychiatric history questionnaire, and a routine medical examination. The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Procedures

Participants ingested four fludrocortisone (0.1 mg each) pills (Astonin H, Merck Serono GmbH, Germany) or four identical looking placebo pills in a randomized order and a double-blind, cross-over design with three days in between test days. The order of fludrocortisone and placebo administration was balanced. All subjects were tested in the afternoon between 14:00 h and 17:00 h with fludrocortisone being administered at 14:00 h. After a 90-min break following drug administration, participants underwent cognitive testing. Blood pressure was assessed at 14:00 h (baseline), 16:00 h, and 17:00 h by an automatic device (Carescape V100, GE Healthcare).

2.3. Neuropsychological assessment

2.3.1. Trail Making Test (TMT)

Psychomotor speed was assessed with the TMT part A. In this task, the subject has to connect encircled numbers in ascending order as quickly as possible. Part B assesses aspects of executive function, i.e. cognitive set shifting and requires the alternation between numbers and letters, again in ascending order.

2.3.2. Rey–Osterrieth complex figure test (RCFT) and Taylor complex figure test (TCFT)

These tests measure visuospatial memory. The participant is first required to copy a complex figure. Immediately thereafter (direct recall) and 20 min later (delayed recall) the figure has to be re-drawn from memory.

2.3.3. Auditory verbal learning test (AVLT)

The AVLT is a measure of short-term and long-term verbal memory. The experimenter reads a list of 15 words (list A), which the participant is requested to repeat in loose order. After list A has been presented five times, the subject is asked to reproduce words from a newly presented list (list B). Following this, the subject is instructed to recall the words from list A without renewed presentation. After 30 min, the subject is again asked to repeat the words from list A (delayed recall).

2.4. Hormonal assessment

Salivary cortisol was determined by radioimmunoassay (DRG, Marburg, Germany). Interassay and intra-assay coefficients of variation were below 8% and the detection limit was 0.5 ng/ml.

2.5. Statistical analyses

Demographic characteristics between depressed patients and healthy participants were compared using t-tests for continuous variables and chi-square tests for dichotomous variables. Separate repeated-measures analyses of variance (rm-ANOVA) with treatment (fludrocortisone vs. placebo) as within-subject factor and group (depressed patients vs. healthy controls) as between-subject factor were conducted to examine differences in cognitive function and blood pressure. We also calculated partial eta squared-values as a measure of the effect size.

Cortisol values were analyzed by repeated-measures ANOVA controlling for baseline cortisol values.

3. Results

There were no significant differences between depressed patients and healthy controls on demographic variables (Table 1).

3.1. Psychomotor speed: TMT A

Rm-ANOVA with treatment (fludrocortisone vs. placebo) as within-subject factor and group (depressed vs. healthy controls) as between subject factor did not reveal a treatment effect ($F = 0.6$, $p = 0.42$) but a group effect ($F = 7.2$, $p = 0.01$, partial eta-squared 0.16) indicating slower psychomotor speed in depressed patients