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

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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 x 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.

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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; Rimele 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
2.2. Procedures

Study to the subjects, written informed consent was obtained by the local ethics committee. After complete description of the medical examination, the study was carried out in accordance with (BDI). Symptoms were assessed by the self-report Beck Depression Inventory (MINI); 2) serious medical conditions, especially those associated with adrenal dysfunctions, steroid use, or well-known impacts on 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 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.

2.3. 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.
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