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Mild cognitive deficits in patients with primary adrenal insufficiency

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ABSTRACT

Background: The brain is a major target organ for cortisol considering its high density of glucocorticoid receptors. Several states of hypothalamus–pituitary–adrenal dysregulation point towards impairments in cognitive functioning. However, there is a very limited body of research on the effects of hypocortisolism on cognitive functioning.
Aim: To evaluate cognitive functioning in patients with hypocortisolism (i.e., primary adrenal insufficiency (PAI)) and to examine the possible effect of postponing early-morning hydrocortisone intake on cognitive functioning.
Methods: Thirty-one patients with PAI on regular morning hydrocortisone intake and 31 healthy matched controls underwent nine neuropsychological tests, evaluating memory and executive functioning. In addition, the effect of normal timing and postponement of morning hydrocortisone intake on neuropsychological tests were assessed in an additional 29 patients with PAI.
Results: Compared to controls, patients with PAI performed worse on auditory and visual memory tasks (all $P \leq 0.024$) and executive functioning tasks (all $P \leq 0.012$). In contrast, patients performed better on a concentration and an attention task (both $P < 0.05$). Postponement of hydrocortisone intake in the morning did not affect the outcomes of neuropsychological tests.
Conclusion: Patients on long-term hydrocortisone replacement for PAI show mild cognitive deficits compared to controls. There was no effect of postponement of regular hydrocortisone intake on cognition.

1. Introduction

In the human brain, the effect of cortisol is mediated via two types of receptors: the mineralocorticoid receptors (MRs) and the glucocorticoid receptors (GRs). MR is highly expressed in the hippocampus, a brain structure involved in memory and learning processes, while GR is widely expressed throughout the whole brain. Cortisol has a tenfold higher binding affinity for the MR than for the GR. Consequently, MRs are activated first when cortisol levels increase, followed by GR activation when cortisol levels increase further (Reul and De Kloet, 1985). Activation of the MR leads to retrieval of previously learned tasks and behavioural responses to new situations, while GR activation is responsible for the consolidation of new information (De Kloet et al., 1998).

The mediating functions of MR and GR activation regarding behaviour have been studied in animal models. Long-term-potentiation (LTP, reinforcement of synaptic contacts contributing to storage of information) is enhanced when cortisol levels are mildly elevated, resulting in activation of all MRs and some of the GRs. When GRs are extensively activated because of high levels of cortisol, LTP was impaired while long-term-depression (reduction of synaptic contacts causing the opposite effect of LTP) was enhanced (De Kloet et al., 1999). In accordance, it has been postulated that cortisol levels follow an inverted u-shaped dose response curve, with very low cortisol levels (predominantly activating the MRs), as well as very high cortisol levels (activating MRs and a large amount of GRs) negatively affecting the mediating function of these receptors on information processing. This work has been elaborated further in humans by Lupien et al. (2005), who showed that memory performance can be modulated by pharmacological manipulations of glucocorticoid levels, with too low, as well as too high glucocorticoid levels resulting in impaired memory function.

The negative effects of exposure to cortisol excess on the human brain and cognition have been shown in patients with Cushing's

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Table 1
Literature overview of studies reporting on cognitive functioning in patients with adrenal insufficiency.

	N	GenderM/F	Age yr	Design	Controls	Cognitive measures	Cognitive domains	Outcomes
Tytherleigh et al. (2004)	9	NA	Mean: 37.9	P	NA	Forward and backward digit span Item recognition HVLT Names Test Doors Test Letter Naming Speed of comprehension Category naming	Working memory Episodic and semantic components of declarative memory	Patients performed better on the digits backward task when GR and MR were activated compared to only GR activation. They performed better on the HVTL when both receptors were activated compared to only MR or GR activation
Harbeck et al. (2009)	14	3/11	Range: 29–70	P	NA	WISC DST LCT VIG STM TMT-A/B	Intellectual functioning Mental flexibility Focused attention Vigilance Short-term memory Executive functioning	Mimicking the physiological rise in cortisol secretion during the night did not affect cognitive functioning compared to cognitive functioning during normal HC intake. A significant negative correlation was found between cortisol levels and short-term memory performance.
Klement et al. (2009)	8	2/6	Mean: 52.6 SEM: 3.2	C–S	Gender-, age-, BMI matched healthy controls	Stroop-cwt Word list	Selective attention Short-term memory	Patients performed worse on the word-reading and color-naming subtest (attention).
Henry et al. (2014)	27	7/20	Mean: 48.7 SD: 15.36	C–S	Age-, education-, gender-and race matched healthy controls	BTACT	Episodic memory Working memory Executive functioning Reasoning Speed of processing	Patients performed worse onepisodic memory and speed of processing.
Schultebraucks et al. (2015)	30	9/21	Mean: 52.4 SD: 14.4	C–S	Age-, education-, and gender matched healthy controls	ZVT Stroop-cwt Digit span AVLT ROCF AMT	Executive functioning Concentration Verbal memory Visual memory Working memory Autobiographical memory	Patients performed worse on verbal learning. There were no significant differences in the other domains.
Werumeus et al. (2015)	47	29/18	Mean: 51 SD: 14	Randomized double blind cross-over study	Intervention study: 10 weeks low dose HC (0.2–0.3 mg/kg body weight/day) vs. 10 weeks high dose HC (0.4–0.6 mg/kg body weight/day)	RBMT 15 Words test Digit span RCFT 15 Figures test TAP: vigilance, divided attention, visual scanning, alertness Verbal fluency tests TMT Reading the Mind in the Eyes test	Memory Attention Executive functioning Social cognition	There were no significant differences in cognitive functioning between the low dose and the high dose regimen.
Present study	60	23/37	Mean: 49.0 SD: 12.4	C–S	Age-, gender-, education matched healthy controls Patients with PAI who postponed HC intake References values of patients with remission of CD	WMS RAVLT RCFT FAS TMT-A/B LDST Stroop-cwt SART GIT-2	Verbal intelligence Working memory Short-term memory Mental flexibility Verbal fluency Psychomotor speed Speed of processing Executive functioning Sustained attention	Patients performed worse on memory and executive functioning tasks, but better on a concentration task and made fewer errors during a focused attention task. No differences were observed compared to patients who postponed HC intake, except for fewer repeats during a verbal fluency task.