Cognitive Dysfunction, Hippocampal Atrophy and Glucocorticoid Feedback in Alzheimer's Disease

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Background: *The hippocampal formation is damaged early in Alzheimer's disease (AD). An association between temporal lobe volume and cognitive function has been shown in several studies. Increased limbic-hypothalamic-pituitary-adrenal (LHPA) axis function has been suggested to be related to hippocampal atrophy and cognitive impairment. Our hypothesis was that there is a clear link between hippocampal volume – notably of the CA1 region - memory (episodic and visuospatial) and decreased feedback sensitivity in the LHPA axis in AD.*

Methods: *Sixteen medication-free outpatients with mild to moderate AD were included. Hippocampal volume was measured with magnetic resonance imaging. Dexamethasone suppression tests were performed using .5 mg and .25 mg dexamethasone. Three different components in the neuropsychological battery – Rey 15 item memory test, Alzheimer's Disease Assessment Scale (ADAS) word recall and spatial span from Wechsler Adult Intelligence Scale – Revised neuropsychological instrument (WAIS-R NI) – were found to represent episodic and visuospatial memory.*

Results: *Low hippocampal CA1 volume and high post-dexamethasone cortisol levels in combination were significantly associated with Rey 15 item memory and spatial span test outcomes. No association was found between LHPA feedback and hippocampal volume.*

Conclusions: *Low hippocampal volume and a disturbed negative feedback in the LHPA axis link to specific cognitive impairments in Alzheimer's disease.*

Key Words: Alzheimer's disease, cognition, memory, hippocampus, hypercortisolism, MRI

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that affects millions of individuals. It accounts for more than 60% of cases of dementia (Fratiglioni et al 2000). A progressive decline in brain functions is typical for AD with memory impairment as a cardinal symptom. However, all memory functions are not equally affected. A broad distinction can be made between declarative and nondeclarative long-term memory (Squire 1993). Within the domain of declarative memory, a distinction can be made between memory for facts (semantic memory), and memory for events (episodic memory) (Tulving 1993). Episodic memory is markedly affected in the early course of the disease (Hodges 1998). Visuospatial functions are also affected in an early clinical stage (Almkvist 1996).

Regions that are known to be critical for episodic memory and also visuospatial memory, i.e. hippocampus (notably the CA1 subregion) and anatomically related structures in the medial temporal lobe (Burgess et al 2002; Squire 1993), show signs of dysfunction at an early stage of Alzheimer's disease (Almkvist and Backman 1993; Bobinski et al 1998; Scheltens et al 2002; West et al 1994).

The hippocampal formation also forms part of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis (Figure 1); a negative feedback loop where increased glucocorticoid (mainly cortisol in humans) levels are "shut-off" by activation of receptors at one or several levels of this axis. Activation of these receptors influence neurochemistry, neuronal excitability and structural plasticity (McEwen 2000). Notably, excessive glucocorticoid exposure to hippocampal neurons impairs neuronal plasticity and may contribute to/worsen neurodegeneration. This has been suggested to result in a vicious circle, where loss of neurons in the hippocampus leads to further loss of feedback inhibition leading to hypercortisolism with progressive hippocampal damage, etc. (Sapolsky et al 1986; Seckl and Olsson 1995). However, data are conflicting on the role of the hippocampus as a sensor for feedback in the LHPA (Tuvnes et al 2003). Notably, other brain sites including the prefrontal cortex, the lateral septum, the bed nucleus of the stria terminalis may be important for LHPA axis feedback function (Tuvnes et al 2003).

Short-term treatment with glucocorticoids decreases memory performance (Newcomer et al 1994; Sapolsky et al 1990; Wolkowitz et al 1990) and patients exposed to high circulating cortisol levels for extended periods of time, i.e. patients with Cushing's syndrome, have significant cognitive dysfunction (Starkman et al 2001). This excessive hypercortisolism has been linked to a decrease in hippocampal volume which seems at least partially reversible after treatment of the hypercortisolism (Starkman et al 2003). Increasing cortisol levels in old age has also been shown to predict memory impairment and a decrease in hippocampal volume (Lupien et al 1998).

In earlier studies we have found an increased glucocorticoid production rate in the early phase of Alzheimer's disease (Rasmuson et al 2001). In addition, we have shown a decrease in negative feedback, using low-dose dexamethasone suppression tests (Näsman et al 1995). Notably, in patients with AD, abnormal cortisol responsiveness to glucose has been linked to hippocampal atrophy (de Leon et al 1988), and a study using an overnight 1 mg dexamethasone suppression test suggested a link between post-dexamethasone cortisol levels and total hippocampal atrophy (O'Brien et al 1996).

A putative association between abnormal shut-off of the LHPA axis (linked to increased cortisol secretion), hippocampal atrophy, and cognitive impairment thus emerges from different strands of research. Our hypothesis, in this cross-sectional study, was that there is an association between hippocampal volume (notably of the CA1 region) episodic and visuospatial memory impairment and decreased feedback sensitivity of the LHPA axis in AD.

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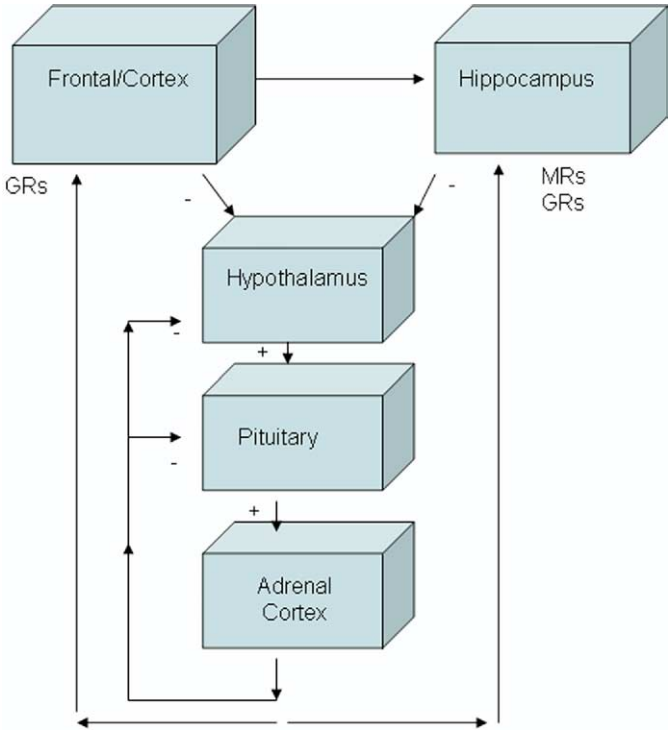

Figure 1. Schematic representation of the limbic hypothalamic pituitary adrenal axis. Modified after Lupien and Lepage (2001). GR, glucocorticoid receptor; MR, mineralocorticoid receptor.

Methods and Materials

Subjects

Sixteen outpatients with mild to moderate AD were included in the study (Table 1). They were referred to the psychogeriatric clinic, Umeå University Hospital, Sweden, for investigation of dementia. This included a medical history obtained from interviews with the patients and their families or caregivers and a physical examination. Inclusion criteria were a diagnosis of AD, no concomitant disease, and no medication. Exclusion criteria were acute medical illness, endocrine disorders, depression, renal dysfunction, prostate hyperplasia, gynecological disorders, smoking, and excessive alcohol intake. All patients met the criteria of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKann 1984).

Methods

Blood was drawn for routine laboratory analyses including plasma glucose, serum albumin, vitamin B12, folate, thyroid hormones and tests for human immunodeficiency virus (HIV), borrelia and the Venereal Disease Research Laboratory test (VDRL) in order to exclude patients with memory deficits caused by infections or metabolic diseases. Serum creatinine levels did not exceed 120 μmol/L. Electroencephalograms (EEG) and CT scans were performed to exclude focal central nervous system (CNS) pathology. The Montgomery-Åsberg Depression Scale (MADRS) (Montgomery and Asberg 1979) was used to exclude depression (range 0–30); none of the patients scored more than six points. Two neuropsychological evaluations were performed at two different occasions, one for diagnostic purpose and one for research purpose (data from the latter were used in this study). The cognitive level was estimated with Mini-Mental State Examination (MMSE) (Folstein et al 1975), the Clinical Dementia Rating scale (CDR) (Hughes et al 1982) and the first neuropsychological investigation.

Study Design

This study was a cross-sectional design with no control group.

Neuropsychological Assessment

The neuropsychological tests concentrated on verbal and nonverbal episodic memory, visuospatial function and attention. The memory tests were auditory-verbal learning test (AVLT) (Ivnik et al 1990; Rey 1964), word recall from Alzheimer's disease assessment scale (ADAS) (Rosen et al 1984), logical memory and verbal paired associates from Wechsler memory scale (WMS) (Wechsler 1987), Rey 15 item memory test (RMT) (Bernard and Fowler 1990), spatial span from Wechsler Adult Intelligence Scale – Revised neuropsychological instrument (WAIS-R NI) (Kaplan 1991) and a nonverbal memory test where the subjects were shown, one by one, 15 nonfigurative pictures and later asked to recognize those among 15 new pictures (Elgh and Nyth, unpublished). Visuospatial function was tested with Block Design, a test of visuospatial organization (Lezak 1995) and attention was tested with Digit Symbol from WAIS-R (Wechsler 1981).

A principal component analysis, varimax with Kaiser normalization (SPSS Inc., Chicago, Illinois), was used to reduce the number of variables in the testing of hypothesis and to find indicator variables for further analysis. It revealed that there were probably three main components in the test battery. The first component consisted of four cognitive tests with high component loadings: block design, ADAS word recall, AVLT and the nonverbal memory test. ADAS word recall had the highest component score and was thus chosen to represent the first component. The second component consisted of RMT and verbal paired associates from WMS. RMT had the highest component score and was chosen to represent the second component. The third component consisted of spatial span and digit symbol. Spatial span had the highest component score and was chosen to represent the third component (Table 2). All components reflect different aspects of either episodic or visuospatial memory; none of them is purely verbal or nonverbal.

Dexamethasone Suppression Test

Over-night dexamethasone suppression tests (DST) were performed using .25 mg and .5 mg dexamethasone (DEX), respectively. The patients started with either .25 mg or .5 mg. After an over-night fast, blood was drawn at 8 am for basal serum cortisol analyses. At 10 pm the same day, .25 or .50 mg DEX, was given orally under supervision (Decadron®, Merck Sharp & Dohme Internat; Rathway, New Jersey). The following day at 8

Table 1. Subject Characteristics

Variables	
Sex (Male/Female)	5/11
Age (years) (mean (SD), range)	75.3 (7.1), 61–83
MMSE (mean (SD), range)	20.5 (5.8), 11–29
BMI (kg/m^2) (mean (SD), range)	24.2 (2.8), 19.7–28.1
CDR 1, *n* (M/F)	9 (3/6)
CDR 2, *n* (M/F)	7 (2/5)

MMSE, Mini-Mental State Examination (Folstein et al 1975); BMI, Body mass index (weight in kilograms divided by the square of height in meters); CDR, Clinical Dementia Rating scale (Hughes et al 1982).