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Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type

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ABSTRACT

Increased peripheral and central nervous system cortisol levels have been reported in Alzheimer's disease (AD) and may reflect dysfunction of cerebral components of the hypothalamic-pituitary-adrenal (HPA) axis. However, brain exposure to high cortisol concentrations may also accelerate disease progression and cognitive decline. The objectives of this study were to investigate whether HPA-axis dysregulation occurs at early clinical stages of AD and whether plasma and CSF cortisol levels are associated with clinical disease progression. Morning plasma and CSF cortisol concentrations were obtained from the subjects with AD dementia, mild cognitive impairment of AD type (MCI-AD), MCI of other type (MCI-O), and controls with normal cognition included in a multicenter study from the German Dementia Competence Network. A clinical and neuropsychological follow-up was performed in a subgroup of participants with MCI-AD, MCI-O, and AD dementia. CSF cortisol concentrations were increased in the subjects with AD dementia or MCI-AD compared with subjects with MCI-O or normal cognition. After controlling for possible confounders including CSF measures of amyloid beta1–42 and total tau, higher baseline CSF cortisol levels were associated with faster clinical worsening and cognitive decline in MCI-AD. The findings suggest that HPA-axis dysregulation occurs at the MCI stage of AD and may accelerate disease progression and cognitive decline.

1. Introduction

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased cortisol production has been consistently described in patients with Alzheimer's disease (AD) at the dementia stage and may reflect dysfunction of brain structures involved in the

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regulation of the HPA-axis activity (Jacobson and Sapolsky, 1991; Roozendaal et al., 2001). It is not known, however, whether HPA-axis dysregulation and consequent cerebral exposure to high cortisol concentrations occur at the prodromal stage of AD. Previous studies including small number of subjects with mild cognitive impairment (MCI) were inconclusive so far (Arsenault-Lapierre et al., 2010; Gil-Bea et al., 2010; Lind et al., 2007; Peavy et al., 2009; Popp et al., 2009; Souza-Talarico et al., 2010; Wolf et al., 2002).

Recent animal studies provided evidence that the central HPA axis is activated during the early stages of AD pathology and may precede cognitive impairment and behavioral symptoms (Hebda-Bauer et al., 2013). Early and prolonged exposure to high glucocorticoid levels may increase the vulnerability of cerebral neurons and promote the development of AD pathology (Catania et al., 2009; Dong and Csernansky, 2009; Green et al., 2006; Sotiropoulos et al., 2011; Wang et al., 2011). Damage to the structures involved in the control of HPA axis such as the hippocampus occurs at the early disease stages and may further disinhibit the HPA axis (Sapolsky et al., 1986). Accordingly, HPA axis hyperactivity with increased cortisol levels may be not only an early event in the course of AD but also a factor precipitating cognitive decline and clinical worsening over time. However, the role of hypercortisolism in the pathogenesis and progression of AD remains a subject of controversy (Bao et al., 2008; Notarianni, 2013; Swaab et al., 2005).

Only a few studies addressed the question whether increased cortisol levels may contribute to the clinical evolution of the disease in humans. Stressful life experiences, which may result in increased HPA-axis activity, but not salivary cortisol measures, were found in association with faster progression from MCI to dementia (Peavy et al., 2012), whereas higher plasma cortisol levels in association with increasing dementia symptoms were reported in subjects with AD (Csernansky et al., 2006). To our knowledge, no CSF studies on the relationship of HPA-axis function and cognitive decline in AD have been reported so far.

Here, we aimed at investigating whether circulating and CSF cortisol levels are increased at the predementia stage of AD. We further addressed whether higher baseline cortisol levels may predict cognitive decline and clinical disease progression over time in subjects with MCI and AD dementia.

2. Methods

2.1. Subject recruitment and diagnostic evaluation

One hundred forty-seven subjects with MCI, 105 subjects with AD dementia, and 37 controls with normal cognition were included in this study from the German Dementia Competence Network. The Dementia Competence Network includes a cross-sectional and longitudinal observational study investigating the diagnostic and prognostic power of clinical, laboratory, and imaging methods with regard to AD. The study was approved by the ethics review board of the coordinating center and by the local ethics committees and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent. The procedures for recruitment and assessment have been published previously (Kornhuber et al., 2009). Briefly, subjects 50 years or older were recruited at 11 participating University memory clinics and underwent a standardized set of clinical, neuropsychological, and laboratory assessments. The neuropsychological assessment included the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological (CERAD-NP) test battery and the Trail-Making Tests (TMTs) A and B (Morris et al., 1988). The Bayer Activities of Daily Living Scale was used to assess the performance of everyday activities (Hindmarch et al., 1998). Overall cognitive function was rated with the Clinical Dementia Rating (CDR) Scale. MCI was defined according to the recommendations of the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004). The diagnosis of MCI was established in an operationalized fashion. Subjects scoring >1 standard deviation below age- and education-adjusted norms in either tests of verbal memory, visual memory, word fluency, naming, visuoconstruction, processing speed, and executive functioning (CERAD-NP subtests and TMTs A and B) were considered as MCI cases, if they had a Bayer Activities of Daily Living Scale score of <4, and an individual (subjective) report on cognitive decline was given by the patient, informant, or referring clinician. According to the protocol of the CND, the MCI group was further divided in 2 subgroups: "MCI of AD type" (MCI-AD, $n = 102$) if memory impairment was present and if there was no evidence for significant cerebrovascular disease in clinical examination or magnetic resonance imaging and "MCI of other type" (MCI-O, $n = 45$) including all other cases, as previously described (Kornhuber et al., 2009). Diagnostic magnetic resonance imaging scans were read by neuroradiologists. The structured rating included the estimated quantity of vascular lesions (infarct zones, subcortical lacunes, and focal and diffuse white-matter lesions). The subjects with the diagnosis of AD dementia met clinical diagnostic criteria for probable AD from the National Institute of Neurological and Communicative Disorders and Stroke and Related Disorders Association (McKhann et al., 1984). The subjects with normal cognition were recruited from the inpatients scheduled for diagnostic lumbar puncture, for example, because of headaches, intervertebral disc disease, and so forth. They had a CDR Scale score = 0 or all cognitive subtests of the CERAD-NP and TMTs A and B within the normal range. All diagnoses and assignments of MCI subtypes were made by team conferences at the local study centers before the biological measurements.

2.2. Follow-up clinical and cognitive evaluations

Participants with MCI and AD dementia were invited to participate in annual follow-up clinical and neuropsychological examinations. In addition to the Mini-Mental State Examination (MMSE), the subtests of the CERAD-NP test battery, and the TMT, the neuropsychological assessment of the follow-up sample included the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-cog) (Rosen et al., 1984). The ADAS-cog word list and recognition were considered as additional verbal memory tasks and the ADAS-cog total score as a measure of overall cognitive performance. The CDR—sum of boxes (CDR-SOB) was used as a measure of the individual dementia severity and its changes over time (Morris, 1993). As neuropsychiatric symptoms may be related to psychological stress associated with the increased cortisol levels and HPA-axis hyperactivity has been described in subjects with depression (Sapolsky, 2000), we further assessed neuropsychiatric and depressive symptoms by the neuropsychiatric inventory (NPI) (Cummings et al., 1994) and by the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), respectively.

2.3. Blood and cerebrospinal fluid analyses

Venous and lumbar punctures were performed between 9 and 10 AM after overnight fasting. Blood samples were collected first, and CSF samples were obtained 15—45 minutes later. Standardized operating procedures for collecting, storing, and shipping blood and CSF were followed in all the participating centers (Lewczuk et al., 2006). Plasma and CSF cortisol concentrations were measured by using the serum cortisol rapid immunoassay (Coat-a-Count [J125] TKCO1,2,5; DPC/Siemens) according to the instructions of the manufacturer. The intra-assay and interassay coefficient of variations were 4.3%, and 5.2%, respectively. The CSF concentrations of amyloid beta (Aβ1—42) and tau were measured by enzyme-linked immunosorbent assay (ELISA;

Innogenetics, Ghent, Belgium). Leukocyte DNA was isolated with the Qiagen isolation kit (Qiagen, Hilden, Germany), and the apolipoprotein E (APOE) genotype was determined.

2.4. Statistical analysis

Differences in the age and years of education between the diagnostic groups were compared by 1-way analysis of variance. Pearson χ^2 test was used for group differences in gender and APOEε4 status (carrier vs. noncarrier of at least 1 APOEε4 allele). Correlations between plasma and CSF cortisol levels were analyzed with Pearson correlation. To compare plasma and CSF cortisol concentrations between the groups, we used analysis of covariance including age, gender, years of education, and the APOEε4 status as further factors followed by post hoc tests with Bonferroni correction for multiple testing.

To evaluate the effects of cortisol levels on cognitive decline and clinical disease progression, we considered in further analyses all the participants with MCI-O, MCI-AD, and AD dementia with follow-up evaluation and complete data for the previously mentioned neuropsychological tests and for CDR-SOB, MADRS, and NPI. Individual mixed-model analyses of variance for each clinical and neuropsychological variable of interest over all time points were separately constructed for each diagnostic group. The neuropsychological variables of interest were CERAD-NP verbal immediate and delayed recall, TMTs A and B, and ADAS-cog word list and recognition. Further variables of interest included in the analyses were MMSE, ADAS-cog total score, CDR-SOB, MADRS, and NPI. Fixed factors were cortisol level group (high vs. low baseline cortisol groups defined by using a median split separately for each diagnostic group) and the potential modifiers of cognitive decline age, sex, years of education, and individual follow-up time. As carrying the APOEε4 allele has been reported to influence the relationship between cortisol levels and cognition (Gerritsen et al., 2011; Gil-Bea et al., 2010; Lee et al., 2008), we included the APOEε4 status as a further factor. In additional steps, the CSF concentrations of Aβ1–42 and tau were added as factors to assess whether cortisol effects may be independent of these markers of AD pathology. The random factor was the individual participant. The effect of time and the interaction of time with cortisol level group were the effects of interests and are reported.

3. Results

3.1. Cross-sectional analyses

Subjects' characteristics and cortisol concentrations in plasma and CSF by diagnostic group are given in Table 1. There were no differences between the MCI-AD, the MCI-O, and the control group regarding age and years of education. Participants with AD dementia were older than those with MCI-AD, MCI-O, or normal cognition ($F = 16.736$, degrees of freedom [df] $= 3$, $p < 0.001$, respectively) and had less years of education than those with MCI-O ($F = 3.843$, df $= 3$, $p = 0.005$). The percentage of women was higher in the AD dementia group compared with the MCI-O ($\chi^2 = 12.198$, $p = 0.001$) and the MCI-AD ($\chi^2 = 7.335$, $p = 0.008$) groups. As expected, the proportion of APOEε4 carriers significantly differed between groups with lowest percentage in the control and highest in the AD dementia group (controls < MCI-O: $\chi^2 = 4.214$, $p = 0.048$; MCI-O < MCI-AD: $\chi^2 = 4.440$, $p = 0.044$; MCI-AD < AD dementia: $\chi^2 = 9.770$, $p = 0.002$).

Plasma cortisol correlated with CSF cortisol concentrations ($r = 0.305$, $p < 0.001$). There were no diagnostic group differences regarding plasma cortisol levels ($F = 1.326$, df $= 3$, $p = 0.266$). Mean CSF cortisol levels differed between groups after controlling for age, gender, education, and APOEε4 status ($F = 8.702$, df $= 3$, $p < 0.001$). CSF cortisol levels were higher in AD dementia and MCI-AD compared with the subjects with normal cognition ($p = 0.002$ and $p = 0.013$, respectively) and compared with MCI-O ($p < 0.001$ and $p = 0.002$, respectively). There was difference in CSF cortisol levels neither between AD dementia and MCI-AD patients nor between MCI-O patients and controls (Fig. 1).

3.2. Longitudinal analyses

Subjects' characteristics, cortisol concentrations in plasma and CSF, and concentrations of Aβ1–42 and tau in the CSF of the follow-up sample are given in Table 2. Complete data from at least 1 follow-up visit were available from 113 study participants with MCI-O, MCI-AD, or AD dementia. Subjects with normal cognition were not included in the follow-up study. There were no differences between the follow-up sample and the sample used for the cross-sectional analyses regarding age, gender, years of education, and the proportion of APOEε4 carriers and between the measures of cognitive function, neuropsychiatric symptoms, depression, and global functioning. A clinical and neuropsychological follow-up assessment of the disease progression over up to 42 months (mean follow-up time, 25.8 months, mean visit number, 3.01) was performed.

In the MCI-AD group, mixed-effects models revealed significant interactions of follow-up time by CSF cortisol level group (high vs. low levels) for measures of immediate verbal recall, delayed verbal recall, verbal recognition, psychomotoric speed, global cognition (MMSE and ADAS-cog total score), and dementia severity (CDR-SOB score) (Table 3). After controlling for effects of the CSF concentrations of Aβ1–42 and tau, the interactions of time by cortisol levels

Table 1
Subject characteristics and cortisol concentrations in plasma and CSF by diagnostic group

	Cognitively normal	MCI-O	MCI-AD	AD dementia
No.	37	45	102	105
Age, y	64.35[a] (8.08)	66.22[a] (8.16)	67.35[a] (7.92)	72.95 (7.42)
Gender (F), *n* (%)	16 (43.2)	13[b] (28.9)	42[b] (41.2)	63 (60.0)
Education, y	12.14 (2.16)	13.31[b] (3.13)	12.28 (2.88)	11.63 (2.79)
MMSE	28.67[a] (1.09)	27.02[a] (2.37)	26.70[a] (2.59)	22.70 (3.06)
ApoEε4 carriers, *n* (%)	1[a] (2.7)	12 (26.7)	46[b] (45.1)	70 (66.7)
Plasma cortisol, μg/dL	16.34 (7.64)	14.95 (6.26)	16.63 (5.67)	15.16 (6.19)
CSF cortisol, μg/dL	0.252[a,c] (0.251)	0.239[a,c] (0.218)	0.493 (0.480)	0.555 (0.387)

Unless otherwise noted, values shown are mean (standard deviation).
Key: AD, Alzheimer's disease; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; F, female; MCI, mild cognitive impairment; MCI-AD, MCI of AD type; MCI-O, MCI of other type; MMSE, Mini-Mental State Examination.
[a] $p < 0.001$ compared with AD dementia.
[b] $p < 0.01$ compared with AD dementia.
[c] $p < 0.01$ compared with MCI of Alzheimer's type.

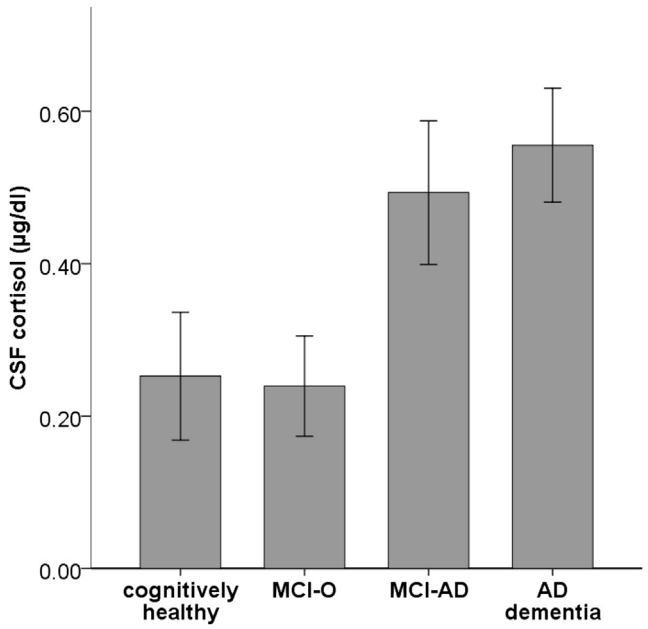

Fig. 1. Mean cerebrospinal fluid (CSF) cortisol levels of cognitively healthy participants ($n = 37$), subjects with mild cognitive impairment of other type (MCI-O, $n = 45$), subjects with MCI of AD type (MCI-AD, $n = 102$), and subjects with AD dementia ($n = 105$). The CSF cortisol levels were significantly higher in subjects with AD dementia and with MCI-AD compared with controls with normal cognition and subjects with MCI-O. Error bars depict confidence interval (95%).

remained significant for all measures excepting for CERAD delayed verbal recall (Supplementary Table 1).

In the MCI-O group, the mixed-effects models revealed significant interactions of follow-up time by CSF cortisol level group for measures of immediate verbal recall in the CERAD-NP but not the ADAS-cog word list learning task. Interactions of follow-up time by cortisol level were also observed for measures of global cognition (MMSE and ADAS-cog total score) but not for CDR-SOB. There were no significant interactions of follow-up time by CSF cortisol level for any neuropsychological measures and the CDR-SOB score in the AD dementia group (Supplementary Table 2). Measures of depressive (MADRS score) and neuropsychiatric (NPI score) symptoms did not show a subgroup difference by cortisol level in any diagnostic group.

Table 2
Follow-up sample ($n = 113$)

	MCI-O	MCI-AD	AD dementia
No.	30	37	46
Age, y	65.93[b] (7.88)	65.59[a] (8.27)	71.52 (7.97)
Gender (F), %	23.3[b]	32.4[b]	56.5
Education, y	13.40[b] (2.85)	12.59 (2.97)	11.87 (3.05)
MMSE	27.17[a] (2.12)	26.70[a] (1.89)	23.59 (2.73)
ApoEε4 carriers, *n* (%)	10[b] (33.3)	18 (48.6)	31 (67.4)
Plasma cortisol, µg/dL	13.49 (4.92)	16.06[c] (5.60)	15.67 (7.45)
CSF cortisol, µg/dL	0.244 (0.204)	0.566[c] (0.508)	0.652 (0.387)
CSF Aβ1–42, pg/mL	746.3[a] (231.2)	716.8[a] (284.2)	522.9 (215)
CSF tau, pg/mL	432.0 (264.0)	424.2[b] (200.2)	543.7 (242.3)
Number of visits	3.03	3.14	2.89
Follow-up interval, mo	26.33	27.19	24.28

Subject characteristics and cortisol concentrations in plasma and CSF by diagnostic group. Missing cases for CSF concentrations of Aβ1–42 and tau: MCI-O, $n = 7$; MCI-AD, $n = 3$; and AD dementia, $n = 2$. Unless otherwise noted, values shown are mean (standard deviation).
Key: Aβ, amyloid beta AD, Alzheimer's disease; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; F, female; MCI, mild cognitive impairment; MCI-AD, MCI of AD type; MCI-O, MCI of other type; MMSE, Mini-Mental State Examination.
[a] $p < 0.001$ compared with AD dementia.
[b] $p < 0.05$ compared with AD dementia.
[c] $p \leq 0.05$ compared with MCI of other type.

Table 3
Interactions of follow-up time by CSF cortisol level

	Interaction effect time by CSF cortisol level		
	MCI-AD		
	High vs. low cortisol levels	SE	*p*
Memory measures			
CERAD verbal immediate recall	−0.148	0.048	0.003
CERAD verbal delayed recall	−0.055	0.025	0.033
CERAD visual delayed recall	0.006	0.042	0.881
ADAS-cog immediate recall	0.062	0.024	0.012
ADAS-cog recognition	0.123	0.047	0.010
Other measures			
TMT A	1.777	0.597	0.004
TMT B	1.063	0.616	0.090
MMSE	−0.124	0.051	0.018
ADAS-cog sum	0.331	0.096	0.001
CDR-SOB	0.077	0.033	0.024
NPI sum	0.114	0.123	0.335
MADRS sum	−0.017	0.087	0.842

Controlled for age, sex, and years of education. Higher values in ADAS-cog, CDR-SOB, NPI, and trail-making variables represent worse performance.
Key: AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CDR-SOB, CDR—sum of boxes; CSF, cerebrospinal fluid; F, female; MCI, mild cognitive impairment; MCI-AD, MCI of AD type; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory; SE, standard error; TMT, Trial Making Test.

4. Discussion

The presented results show an increase of CSF cortisol levels in subjects with MCI of AD type of similar magnitude as in participants with AD dementia suggesting that HPA-axis dysfunction in AD (Gil-Bea et al., 2010; Laske et al., 2009; Popp et al., 2009) precedes the dementia disease stages. Furthermore, the findings show that increased baseline CSF cortisol levels in subjects with AD at the MCI stage are associated with faster cognitive decline and progression of dementia severity over time.

By measuring salivary (Souza-Talarico et al., 2010; Wolf et al., 2002), plasma (Csernansky et al., 2006), or CSF (Gil-Bea et al., 2010; Popp et al., 2009) cortisol levels in different body fluids as a proxy of HPA-axis activity, most previous studies did not find differences between patients with MCI and cognitively healthy subjects. In contrast, others reported higher salivary cortisol levels (Arsenault-Lapierre et al., 2010) and increased saliva cortisol awakening response in subjects with MCI but no differences in basal cortisol levels (Lind et al., 2007). Overall, these studies, however, were limited by small numbers of included participants. Besides further methodological differences such as the measurement of cortisol in different fluids, an important aspect possibly explaining inconsistencies of previous reports is that subjects diagnosed with MCI are a heterogeneous group regarding the underlying cerebral pathologies and their clinical manifestations (Winblad et al., 2004). Only a part of the subjects with MCI can be considered as being at a prodromal stage of AD. In a previous single-center study including a relatively small number of participants, we found similar CSF cortisol levels in patients with MCI and cognitively healthy controls (Popp et al., 2009). In the present study, separating the MCI group in the MCI-AD and MCI-O subgroups revealed a marked increase of CSF cortisol of similar magnitude in MCI-AD and AD dementia but no increase in MCI-O compared with the subjects with normal cognition. These findings strongly suggest that HPA-axis dysregulation takes place at predementia stages of the disease and may reflect damage of brain structures that are both involved in the HPA-axis regulation and early affected by neurodegeneration in AD. HPA-axis dysfunction may be specifically

related to MCI because of AD and less common in MCI of other etiologies. In addition, the finding of similar levels of CSF cortisol in MCI-AD and AD dementia suggests that in AD, cortisol concentrations remain at a high level but stable despite disease progression and clinical worsening from MCI to dementia.

Most studies focusing on HPA axis and cortisol in patients with AD have measured plasma or salivary cortisol levels. The assessment of CSF cortisol, however, may better reflect the cortisol concentrations to which the brain structures are exposed. In blood, the unbound, biologically active form of cortisol represents only a minor part of the total plasma levels, whereas in the CSF, cortisol is for the most part unbound (Predine et al., 1984). Moreover, after stimulation of the HPA axis, CSF cortisol increases rapidly and remains longer at higher levels than plasma cortisol (Martensz et al., 1983). In our study, plasma cortisol levels did not differ between the diagnostic groups and were not associated with cognitive decline or clinical changes over time. We found significant but moderate correlations between plasma and CSF cortisol concentrations, which is in line with the previous reports (Peskind et al., 2001; Predine et al., 1984) and suggests that single plasma cortisol measures as performed in our study does not accurately reflect cortisol levels in the central nervous system. It is also noteworthy that not the biologically active but the total cortisol was measured in the plasma samples, whereas mainly unbound cortisol was measured in the CSF.

High levels of cortisol in early AD may have particularly deleterious effects on affected brain structures, contribute to the pathophysiological process, and accelerate clinical disease progression. Prolonged exposure to high glucocorticoid levels impairs cognitive function and increases the vulnerability of cerebral, in particular of hippocampal neurons for toxic events (Sapolsky, 2000). Furthermore, exposure to high glucocorticoid levels may contribute to the early development of Alzheimer's pathology and related cognitive impairment (Dong et al., 2008; Green et al., 2006; Sotiropoulos et al., 2011). In the animal studies, chronic stress and glucocorticoid administration have been shown to increase cerebral Aβ formation and induce tau hyperphosphorylation in the hippocampus and prefrontal cortex, with concomitant cognitive impairment in learning and memory tasks (Catania et al., 2009; Dong et al., 2008; Sotiropoulos et al., 2011; Srivareerat et al., 2009). Conversely, treatment with the glucocorticoid receptor antagonist mifepristone reduced cerebral Aβ, tau pathologies, and cognitive impairment in an AD mouse model, pointing to a potential therapeutic role for interventions to counteract HPA-axis hyperactivity (Baglietto-Vargas et al., 2013).

In humans, only a few observational studies have investigated whether increased salivary or plasma cortisol levels predict a more rapid disease progression in AD, reporting inconclusive results (Csernansky et al., 2006; Peavy et al., 2009, 2012). In our study, high CSF cortisol levels were associated with faster cognitive decline in MCI-AD but not in the AD dementia group. Participants with MCI-AD having higher baseline CSF cortisol levels showed a more rapid decline in tasks of episodic memory and psychomotoric speed compared with MCI-AD subjects with lower cortisol levels. Further, higher cortisol concentrations predicted faster worsening in measures of global cognition and increasing dementia severity in this subgroup. The associations remained significant after controlling for multiple possible confounders including CSF markers for AD pathology. These results are in line with the previously reported higher plasma cortisol levels in association with more rapidly increasing dementia symptoms and decreasing performance in tests associated with temporal lobe function in subjects with early clinical stages of AD (Csernansky et al., 2006). They support the hypothesis that in AD, exposure of brain structures to increased cortisol concentrations at the MCI stage may contribute to the AD-related pathophysiological process and accelerate cognitive decline. Brain regions playing a central role for the episodic memory function and early affected in the course of AD such as the hippocampus may be particularly vulnerable to deleterious effects of increased cortisol levels. These effects may be more relevant for clinical disease progression at the predementia than at the dementia stages of AD. The putative MCI stage–dependent vulnerability may be explained by advanced damage of the involved cerebral structures and loss of related cognitive functions resulting in weaker effects of increased cortisol levels on the clinical disease progression at the dementia stages of AD. This hypothesis is supported by our findings and by previous reports suggesting that HPA-axis disturbance and basal hypercortisolemia remain stable during mild-to-moderate AD stages (Notarianni, 2013).

Our data also provide evidence that higher cortisol levels may accelerate cognitive decline not only in MCI-AD but also in MCI of other type. In the MCI-O group, higher CSF levels were associated with a more rapid decline in one of the performed tests of verbal immediate recall and in measures of global cognition but not with changes in dementia severity. Of note, the mean CSF cortisol levels in the MCI-O group were similar to those in the subjects with normal cognition suggesting that even at lower levels, differences in CSF cortisol concentrations may be relevant for further cognitive decline.

The strengths of this study include the large sample size, the multicenter design, and the broad inclusion criteria for MCI allowing for separate analyses in MCI subgroups and consideration of possible confounders. The fact that the cognitively healthy participants were patients with neurologic complaints undergoing diagnostic lumbar puncture should be considered as a limitation. Maladaptive stress responses may occur in patients with chronic pain (Vachon-Presseau et al., 2013), and patients with headache, intervertebral disc disease, and other medical conditions experienced as stressful may have excessive levels of cortisol. Therefore, higher cortisol levels in this control group than in healthy volunteers cannot be excluded. As a consequence, subjects with MCI-O could also have increased cortisol levels, but the magnitude of this increase would be significantly lower than in the MCI-AD and the AD dementia. Finally, including patients and not healthy volunteers in the group of cognitively healthy subjects suggest higher specificity of the findings of elevated cortisol levels in MCI-AD and the AD dementia. As we chose to include only participants with complete data in the longitudinal analysis, the sample used was rather small. However, this sample did not differ from the sample used for the cross-sectional analyses regarding demographics, the proportion of APOEε4 carriers, and cognitive performance.

5. Conclusions

According to the results in this study, HPA-axis hyperactivity may be not only an early event in the course of AD but also a factor contributing to further cognitive decline and clinical worsening over time. In future studies, longer follow-up in larger samples of participants with MCI may reveal further long-term consequences of high cortisol levels. If confirmed, our results would support approaches for early detection of HPA-axis dysfunction and for interventions to counteract effects of increased cortisol levels at the predementia AD stages.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.031.

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