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ORIGINAL ARTICLE

Predictors of subjective cognitive deficits in patients with mild cognitive impairment

Lorenz LOESSNER,[1] Claudia MATTHES,[1] Robert HAUSSMANN,[1] Moritz D. BRANDT,[2,3] Cathrin SAUER,[1] Melanie ESPIN,[4] Felix NOPPES,[1] Annett WERNER,[3,5] Jennifer LINN,[5] Thomas HUMMEL,[4] Antje HAEHNER[4] and Markus DONIX[1,3]

Department of [1]Psychiatry, University Hospital Carl Gustav Carus, [2]Neurology, University Hospital Carl Gustav Carus, [4]Otorhinolaryngology, University Hospital Carl Gustav Carus and [5]Neuroradiology, University Hospital Carl Gustav Carus, Technische Universität Dresden and [3]German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany

Correspondence: Prof Markus Donix, MD, PhD, Department of Psychiatry, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany. Email: markus.donix@ukdd.de

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Abstract

Background: Detailed examination of cognitive deficits in patients with mild cognitive impairment (MCI) yields substantial diagnostic and prognostic value, specifically with respect to memory. Magnitude and characteristics of subjective cognitive deficits, however, often receive less attention in this population at risk for developing dementia.

Methods: We investigated predictors of subjective cognitive deficits in patients with MCI, using a detailed assessment for such impairments associated with different cognitive domains, as well as demographic and clinical variables including magnetic resonance imaging data.

Results: The strongest predictor for subjective memory deficits was depressed mood, whereas subjective performance issues associated with attention or executive functions also corresponded to measurable impairments in the respective cognitive domains. Reduced hippocampal thickness and hemispheric entorhinal cortex thickness asymmetry were associated with objective memory impairment but not with subjective deficits or symptoms of depression.

Conclusions: Whereas low objective memory performance and reduced cortical thickness within medial temporal lobe subregions could be associated with neurodegeneration, greater subjective memory deficits in patients with MCI may indicate psychological burden.

INTRODUCTION

The risk of developing dementia among patients with mild cognitive impairment (MCI) is about 10% per year.[1] This estimate varies considerably depending on the research setting or individual genetic risk. Furthermore, progression to dementia is only one possible outcome, and up to 30% of patients with MCI may later revert to normal cognition.[1] However, dementia conversion estimates rise in the case of memory deficits,[2] as they represent a prodromal feature of Alzheimer's disease, the most common neurodegenerative disorder. It is therefore clinically important to detect such an amnestic impairment, whether it occurs alone (single domain MCI) or accompanied by deficits in other cognitive domains (multiple domain MCI).[3] This illustrates why basic screening tests are insufficient to establish a nuanced and therefore clinically meaningful neurocognitive

profile, and why comprehensive testing batteries are challenging enough and ultimately necessary to do so. From a clinical perspective, an amnestic impairment would be perceived in line with hippocampal atrophy, a potent predictor for an imminent conversion of MCI to Alzheimer's dementia.[4] It could also trigger obtaining additional biological markers of Alzheimer's disease from cerebrospinal fluid (CSF) or positron emission tomography in select patients.

Subjective cognitive deficits are associated with an increased risk for developing MCI or dementia among otherwise healthy older people without measurable cognitive impairment.[5,6] In patients with MCI, it remains unclear whether a detailed examination of their subjective cognitive deficits would also yield clinically meaningful information. A simple question regarding the presence of subjective memory deficits may address the respective MCI diagnostic criterion,[3] but could leave certain aspects of the subjective deficits undetected, for example deficit severity. Furthermore, subjective complaints that are not associated with memory could be underrepresented in a clinical interview, since the patient may not be able to allocate subjective changes to different cognitive domains.

In this study we used a detailed assessment for subjective cognitive deficits to investigate them in patients with MCI. We were primarily interested in examining whether the subjective changes associated with memory, attention, and executive functions would be predicted by demographic, clinical, or neurobiological measures. In cognitively unimpaired individuals, there could be education and gender effects in the perception of cognitive decline; a patient's age or mood could also modulate subjective deficits.[7–9] In patients with MCI, however, the individual weight of these predictors may change. Symptoms of depression are particularly frequent in this population,[10] but despite the associated risk for future cognitive decline,[11] depressive mood among patients with MCI does not correlate with CSF or neuroimaging markers of Alzheimer's disease.[12,13] Subtle changes in brain morphology, such as regional cortical thinning or regional hemispheric asymmetry, likely associated with early neurodegeneration, are detectable with magnetic resonance imaging (MRI) in patients with cognitive impairment, particularly in Alzheimer's disease and its prodromal stages.[14–18] We therefore hypothesized that when compared with other potentially modulating variables, the impact of depressive mood changes on subjective cognitive deficits would be more important in patients with MCI. We also hypothesized that reduced cortical thickness or hemispheric asymmetry in medial temporal lobe subregions would be associated with objective but not with subjective cognitive deficits.

METHODS

Patients

We recruited 37 patients with mild cognitive impairment (mean age 70.9 ± 6.1 years) who underwent detailed clinical and neurocognitive examination, as well as brain MRI. In addition to obtaining whole brain data, our patients were invited to specific MRI scans focusing on the medial temporal lobe and the olfactory bulb. The primary aim of the superordinate project was to investigate the impact of an olfactory training using four different odors[19] over the course of 4 months on cognitive performance and brain measures at baseline and follow-up examinations. Here, we only report baseline data unrelated to the olfactory intervention. All subjects were identified through our university memory clinic between 2018 and 2021 and participated after providing written informed consent. We conducted the study in accordance with the ethical principles of the Declaration of Helsinki and after our university's ethics committee approval (EK 136032015). All patients met the most frequently used criteria for mild cognitive impairment, which include (i) memory complaint, preferably qualified by an informant; (ii) memory impairment for age; (iii) preserved general cognitive function; (iv) intact activities of daily living; and (v) being not demented.[3] Diagnostic procedures prior to study participation included a clinical examination by an experienced physician, neurocognitive and laboratory testing, as well as brain imaging. No patient reported a psychiatric or neurological disease that could have explained the cognitive impairment otherwise. Patients also did not report or show (e.g., laboratory) signs of any systemic disease possibly affecting brain functioning; they also did not receive any psychotropic medication. One of the subjects did not participate in MRI scanning.

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Neurocognitive testing

For the objective cognitive examination of memory we used word list learning as well as the word list delayed recall and visual memory delayed recall items of the Consortium to Establish a Register for Alzheimer's Disease-Neuropsychological (CERAD-NP) test battery.[20] We examined the objective attention performance with the digit span forward test from the Wechsler Memory Scale-Revised (WMS-R)[21] and the Trail Making Test (TMT) Part A.[22] Executive functions were investigated with the TMT Part B, corrected for performance on Part A (TMT B-A),[23] and the Stroop Test (interference).[24]

We examined subjective cognitive deficits with the 'Questionnaire for complaints of cognitive disturbances, FLei'.[7,25] This assessment is comprised of 35 questions targeting subjective deficits associated with memory, attention, and executive functions. Three domain subscales consist of 10 items per scale, accompanied by five control questions. Individuals are invited to rate their performance in everyday situations using 5-point scales (e.g., for 'It is difficult for me to follow a conversation between several individuals', responses range from 0 = never to 4 = very often). The FLei questionnaire does not define an impairment threshold.

Neuroimaging

We used a Siemens Magnetom Verio 3-Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) and a 12-channel receive only head coil to obtain oblique coronal T2-weighted fast-spin echo scans (repetition time: 5200 ms; echo time: 105 ms; slice thickness: 3 mm; spacing: 0 mm; 19 slices; in-plane voxel size: 0.39 × 0.39 mm; field of view: 200 mm). To investigate cortical thickness within the medial temporal lobe, we analysed our MRI data with a cortical unfolding technique.[26–28] The method allows cortical thickness measurements within subregions of the hippocampus and its adjacent structures, thus, the cornu ammonis fields 1–3 including the dentate gyrus, the subiculum, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and the fusiform gyrus. These regions of interest are flattened into two-dimensional space based on metric multidimensional scaling after the manual masking of CSF and white matter. Before their mathematical projection to the flattened cortical maps, regional boundaries are specified using histological and MRI atlases.[29,30]

Statistical analyses

We estimated multiple linear regression models to investigate the influence of several predictors on subjective cognitive deficits associated with memory, attention, and executive functions. In each model there was a set of fixed predictors (age, sex, years of education, symptoms of depression using the Beck Depression Inventory (BDI) total score,[31] and hippocampal cortical thickness as an average measure across both hemispheres' hippocampal regions) as well as domain-specific predictors for objective performance in memory, attention, and executive functions performance as outlined above in Section 2.2. In order to limit the number of predictors, we focused on the CERAD-NP wordlist learning for memory, the WMS-R digit span forward for attention, and the TMT B-A for executive functions. However, calculating the same models with the CERAD-NP verbal or visual delayed recall items for memory, TMT A for attention or Stroop test interference for executive functions did not change the overall results. We further conducted bivariate Spearman correlation analyses to investigate the possible associations of symptoms of depression with subjective and objective cognitive performance. We conducted bivariate Pearson correlation analyses to investigate the possible associations between subjective and objective cognitive performance, and between hippocampal thickness and objective or subjective memory performance. We utilized an analysis of variance to detect any hemispheric asymmetry in entorhinal cortex thickness or hippocampal thickness, modelling objective and subjective cognitive deficits as covariates. We used a significance level of $P < 0.05$ in all statistical analyses.

RESULTS

Demographic and clinical characteristics of our participants are detailed in Table 1. The multiple linear regression models yielded the following results. For memory (adjusted $R^2 = 0.289$, $P = 0.024$), only the BDI total score (B = 0.5; SE = 0.186; 95% confidence interval (CI) = [0.117, 0.883]; $P = 0.013$) predicted subjective memory deficits; thus, participants experiencing more severe symptoms of

Table 1 Demographic and clinical characteristics

Characteristics and measures		SD
Participants (*N*)	37	
Female sex (*N*)	20	
Age (years)	70.9	±6.1
Education (years)	14.8	±2.9
BDI (score range 0–63)	9.5	±9.1
MMSE (0–30)	28.1	±1.8
Memory		
FLei-G (subjective memory) (0–40)	17.8	±8.8
CERAD-NP word list learning total score (0–30)	18.6	±3.4
CERAD-NP word list delayed recall (0–10)	5.2	±2.3
CERAD-NP visual memory delayed recall (0–40)	21.5	±11.6
Attention		
FLei-A (subjective attention) (0–40)	13.0	±8.6
WMS-R digit span forward (0–10)	7.2	±1.7
TMT A (sec)	42.2	±11.8
Executive functions		
FLei-E (subjective executive functions) (0–40)	10.1	±7.5
TMT B-A (sec)	127.5	±66.4
Stroop test, interference (quotient)	24.1	±19.4

BDI, Beck depression inventory; CERAD-NP, Consortium to Establish a Register for Alzheimer's Disease-Neuropsychological test battery; FLei, Questionnaire for complaints of cognitive disturbances; MMSE, Mini-Mental State Examination; SD, standard deviation; TMT A/B-A, Trail Making Test part A and B-A; WMS-R, Wechsler Memory Scale-Revised.

depression reported greater memory impairment. For attention (adjusted $R^2 = 0.521$, $P < 0.001$), significant predictors were BDI total score (B = 0.453; SE = 0.145; 95% CI = [0.154, 0.753]; $P = 0.005$) and WMS-R digit span forward (B = −1.58; SE = 0.659; 95% CI = [−2.937, −0.222]; $P = 0.024$). In addition to symptoms of depression, objective deficits in attention were associated with subjective deficits in this domain. For executive functions (adjusted $R^2 = 0.675$, $P < 0.001$), significant predictors were BDI total score (B = 0.572; SE = 0.107; 95% CI = [0.352, 0.793]; $P < 0.001$) and TMT B-A (B = 0.083; SE = 0.018; 95% CI = [0.046, 0.120]; $P < 0.001$). This means that symptoms of depression as well as objective deficits in executive functions were associated with greater subjective deficits in the respective cognitive domain.

Correlation analyses revealed significant associations between symptoms of depression and subjective cognitive deficits in memory (ρ (Spearman's Rho) = 0.625, $P < 0.001$), attention (ρ = 0.662, $P < 0.001$), and executive functions (ρ = 0.663, $P < 0.001$), but not between symptoms of depression and objective performance in any of these cognitive domains (Fig. 1). Objective and subjective cognitive

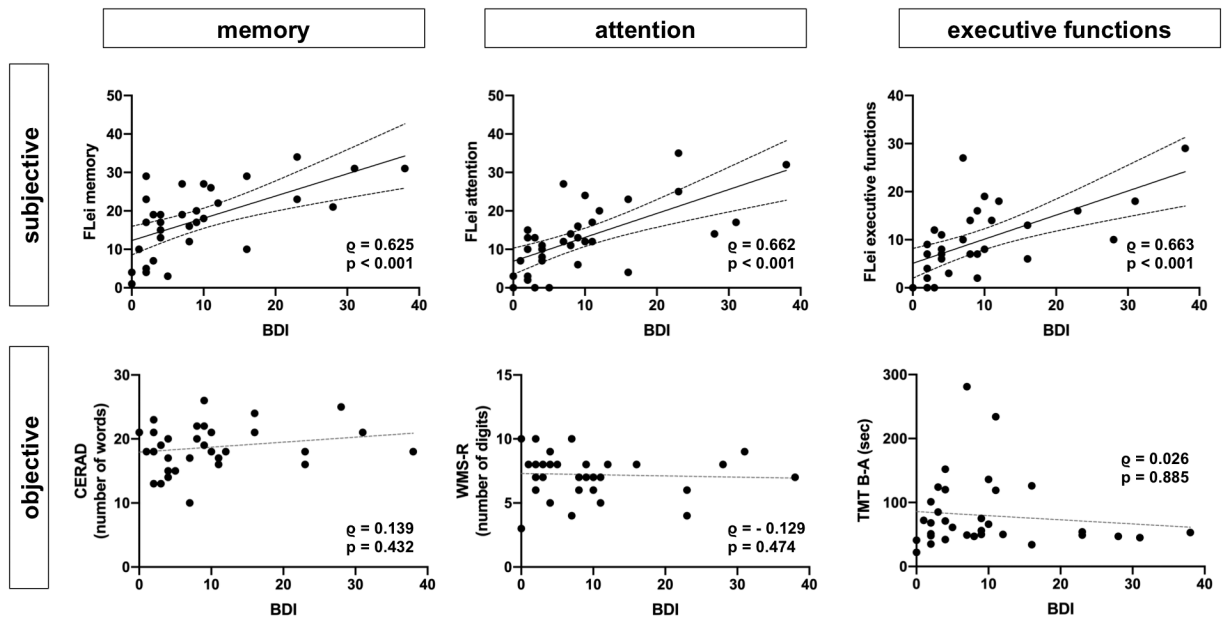

Figure 1 Symptoms of depression and cognitive performance. Symptoms of depression show significant associations with subjective but not with objective cognitive deficits in memory, attention and executive functions. We provide Spearman correlation coefficients (ρ), and for significant associations the 95% confidence intervals. BDI, Beck Depression Inventory; CERAD-NP, Consortium to Establish a Register for Alzheimer's Disease-Neuropsychological test battery; FLei, Questionnaire for complaints of cognitive disturbances; TMT B-A, Trail Making Test part B-A; WMS-R, Wechsler Memory Scale-Revised.

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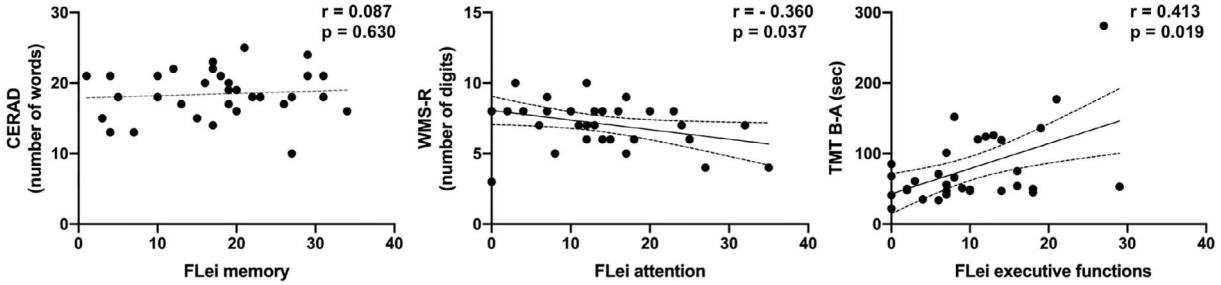

Figure 2 Objective and subjective cognition. Subjective deficits in attention and executive functions correlate with objective deficits in the respective domains, whereas this association cannot be observed in the memory domain. We provide Pearson correlation coefficients (*r*), and for significant associations the 95% confidence intervals. CERAD-NP, Consortium to Establish a Register for Alzheimer's Disease-Neuropsychological test battery; FLei, Questionnaire for complaints of cognitive disturbances; TMT B-A, Trail Making Test part B-A; WMS-R, Wechsler Memory Scale-Revised.

performance correlated in the attention (*r* (Pearson's *r*) = −0.360, *P* = 0.037) and executive functions (*r* = 0.526, *P* = 0.002) domains, but not in the memory domain (Fig. 2). Further correlation analysis also showed a significant moderate association between hippocampal thickness and objective memory performance (CERAD-NP word list learning; *r* = 0.409, *P* = 0.013) but not between hippocampal thickness and subjective memory performance (*r* = 0.024, *P* = 0.896).

Investigating all subjects as a group using an analysis of variance, we further detected hemispheric asymmetry in the entorhinal cortex (left hemispheric thickness (mean/SD) = 2.41 mm/0.26 mm; right = 2.61 mm/0.25 mm; $F(1, 29) = 9.402$, $P = 0.005$) but not in the hippocampus (left = 2.39 mm/0.15 mm; right = 2.35 mm/0.15 mm; $F(1, 29) = 0.848$, $P = 0.365$). We used objective and subjective memory performance as covariates, and we only detected a significant influence of objective cognitive performance on entorhinal cortex asymmetry.

DISCUSSION

We show that symptoms of depression are the most important predictor for subjective cognitive deficits in patients with MCI. Whereas reduced objective performance in attention and executive functions also corresponds with subjective deficits in these cognitive domains, mood changes were the strongest predictor for all domains and the only predictor for subjective memory deficits. Reduced cortical thickness in the hippocampus, associated with poorer objective memory performance but not with subjective deficits or symptoms of depression, as well as a hemispheric entorhinal cortex thickness asymmetry, may indicate the association of these imaging biomarkers with early neurodegeneration. Medial temporal cortical thinning and volume loss, specifically within the hippocampal region, are well-known biological markers associated with neurodegeneration in Alzheimer's disease and its prodromal stages.[4,17] Different temporal trajectories of neurodegeneration within the brain's hemispheres contribute to changes in hemispheric asymmetry in this disease spectrum,[18] although other variables, such as carrying the apolipoprotein E e4 risk allele, may also modulate this feature.[16]

In contrast to differentiating objective neurocognitive test results, e.g., establishing neurocognitive profiles, our data suggest that a detailed assessment of subjective cognitive changes does not yield comparable information in the aetiological classification of cognitive decline among patients with MCI. However, our data still indicate a clinical value of investigating the subjective deficits in these patients, and how this may differ from cognitively healthy people. In cognitively unimpaired individuals, the presence of subjective cognitive deficits is associated with a risk of subsequent decline and developing dementia.[5,6] These deficits are modulated by various predictors such as age, education, gender, and mood changes.[8] In our patients with MCI, the subjective cognitive deficits may primarily point to symptoms of depression, and could therefore guide physicians to identify and treat these patients. The prevalence of depression among patients with MCI is high, up to 40% in clinical settings.[10] Although there is a 28% higher risk of

progression to dementia among patients with MCI and depression when compared to those without symptoms of depression,[11] the interrelationship may be complex. Mourao and colleagues hypothesize that MCI and depression share abnormalities in neurobiological cascades. Irrespective of whether depression could be perceived as a state or trait marker for the development of dementia in patients with MCI, the authors discuss symptoms of depression beyond the reaction to simply recognizing one's own cognitive deficits.[11] It remains an active debate whether depression is a risk factor for and/or a symptom of early dementia.[32,33] Preuss and colleagues mention potentially different clinical characteristics of depression in patients with dementia and cognitively healthy people.[34] With respect to the possible aetiological factors for symptoms of depression among the cognitively impaired, these authors and others highlight the importance of a high cognitive reserve for the recognition of individual cognitive deficits.[35] It is intuitively accessible that the potential for such symptom awareness is generally greater among patients with MCI than in those already suffering from dementia. Given the high prevalence of depression in patients with MCI,[10] a psychological burden could be a relevant factor. This would be in line with higher rates of depression after the onset of cognitive impairment among demented individuals with the mildest cognitive deficits.[36] However, Palmer and colleagues show that apathy and not depression predicted the development of dementia in patients with MCI.[37] Martin and Velayudhan also reviewed different neuropsychiatric symptoms in patients with MCI and their associations with future cognitive decline. They point to methodological issues in assessing and differentiating these clinical features, which could contribute to the heterogeneous results in the literature.[38]

We previously showed extrahippocampal but not hippocampal cortical thinning in younger patients with major depression.[13] Others also reported reduced parahippocampal and fusiform gyrus cortical thickness associated with vulnerability for mood disorders,[39] although there are contrasting results with respect to the involvement of hippocampal subfields in major depression.[40] In our sample we did not find an association between symptoms of depression and cortical thickness measures across the medial temporal lobe. When compared with our previous data in young people with major depression,[13] issues related to statistical power are unlikely to be the primary reason for this. Taken together with our neuroimaging findings, we may therefore speculate that the symptoms of depression in our patients with MCI do not indicate advanced neurodegeneration. The correlation of objective memory impairment with reduced hippocampal thickness as well as the entorhinal cortex thickness asymmetry suggest neurodegeneration within the Alzheimer's disease clinical spectrum, independent of subjective cognitive deficits or symptoms of depression. The association of the latter clinical features, however, could still reflect a psychological disease burden[41] as well as it suggests therapeutic avenues for targeting symptoms of depression in patients with MCI. The effectiveness of psychological interventions[42] that recognize disease burden is in line with the distinct characteristics of depressive symptoms in patients with MCI,[34] as is the limited effect of sertraline treatment in these patients.[43]

It is a limitation of this study that we only investigated patients with MCI. Although the characteristics and frequency of subjective cognitive deficits may differ between patients with MCI and other populations, such as individuals without a measurable cognitive impairment, we did not directly test these differences. We also cannot rule out the possibility of a bidirectional relationship between symptoms of depression and subjective memory deficits in our patients with MCI. However, the dissociation between objective and subjective memory deficits does not suggest that recognizing objective changes is sufficient to elicit depressed mood in these patients. Furthermore, the directionality of the association would not limit intervention strategies. Additional study limitations include the possible aetiological heterogeneity in prodromal stages of Alzheimer's disease and other dementias. Although all subjects met standard criteria for MCI,[3] and despite a thorough clinical characterization and the availability of neuroimaging data, we did not perform CSF analyses. Using cross-sectional data we cannot investigate whether increased subjective cognitive deficits or symptoms of depression would be associated with faster cognitive decline or greater rates of conversion to dementia, irrespective of a neurodegenerative aetiology. Greater subjective cognitive deficits in patients with MCI may be associated with psychological burden rather than with neurodegeneration. The

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association of objective but not subjective cognitive deficits with reduced hippocampal thickness and hemispheric entorhinal cortex asymmetry is in line with this hypothesis, although we did not investigate the long-term trajectories of mood changes, cognitive abilities and their possible interactions. Raising awareness for the high prevalence of depression among patients with MCI,[10] and how affected individuals may present, could open therapeutic avenues to improve the patients' mental and cognitive health.

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