

Mini-Mental State Examination Is Sensitive to Brain Atrophy in Alzheimer's Disease

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Key Words

Alzheimer's disease · Mini-Mental State Examination · Brain atrophy · Neuroimaging · Hippocampus

Abstract

Background/Aims: Screening instruments such as the Mini-Mental State Examination (MMSE) are useful for the early identification of Alzheimer's disease (AD). We tested whether macrostructural differences in brain volume are related to the MMSE. **Methods:** The MMSE was related to cortical thickness and the volume of 19 brain structures in 96 patients with mild to moderate AD. In addition, the patients were compared to 93 healthy elderly controls. **Results:** The MMSE was related to the volume of the total brain, cerebral cortex, accumbens, cerebral white matter, inferior lateral ventricles and hippocampus. Positive correlations with cortical thickness were found for 41% of the brain surface, and 58% of this area was significantly thinner in AD. **Conclusion:** The MMSE is sensitive to macrostructural brain atrophy in AD, but also to morphometric variation not specifically related to AD.

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Introduction

The Mini-Mental State Examination (MMSE) [1] is one of the simplest and most widely used screening instruments for Alzheimer's disease (AD), both in clinical

settings and research [2, 3]. However, relatively little is known about the degree to which such screening instruments are sensitive to brain changes in AD. Substantial macrostructural brain changes are seen even in early stages of AD [4], and in a recent position paper, abnormal structural MRI findings were proposed as a research criterion for AD [5]. It is necessary to have screening measures which are sensitive to the disease, and which are applicable for nonspecialist medical practitioners as well. Further, it would be of great interest to know how such screening measures are associated with disease-related brain changes. Relationships of MMSE score and hippocampal volume with atrophy in mild cognitive impairment and AD [6–10] have been established. However, AD also affects large areas of the brain outside the hippocampus, especially within the temporoparietal episodic memory network [11]. In addition to the hippocampus, this network includes parahippocampal, entorhinal, retrosplenial, posterior cingulate and precuneus cortices [12–15]. We have virtually no knowledge about the sensitivity of the MMSE to nonhippocampal changes. Measures of whole brain atrophy have been shown to correlate with the MMSE [10, 16, 17], but only few studies have explored restricted regions outside the hippocampus. In one study, the hippocampal but not the entorhinal cortex volume correlated with the MMSE in mild cognitive impairment patients [18].

The purpose of the present study was to test the relationship between the MMSE and regional brain chang-

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es measured by MRI. We especially wanted to explore to what extent the brain areas that showed a relationship between morphometry and MMSE score overlapped with the areas typically showing atrophy in AD. It was hypothesized that the MMSE would be related to the reduced volume/thickness of the temporoparietal episodic memory network described above, as well as to the expansion of the ventricular system. However, since the MMSE is a nonspecific test with regard to neuropsychological functions, some kind of relationship with brain morphometry in areas not affected by AD was expected.

Methods

Sample

Raw data were drawn from the Open Access Series of Imaging Studies (OASIS; <http://www.oasis-brains.org/>) database, and previous studies using this database have contrasted AD patients with healthy elderly controls [12, 19–23]. To our knowledge, analyses of MMSE results, which are included in the present paper, have not previously been reported, and all MR data were processed locally and exclusively for the present study. Marcus et al. [23] described the details of the recruitment, screening and MR acquisition procedures. All participants underwent the Washington University Alzheimer Disease Research Center's full clinical assessment, yielding clinical dementia ratings (CDR) for all participants [24]. A global CDR of 0 was taken to indicate no dementia, and a CDR of ≥ 0.5 to indicate mild or moderate AD. Participants were excluded if they suffered from other active neurological or psychiatric illnesses or serious head injury, had a history of clinically meaningful stroke, used psychoactive drugs or had gross anatomical abnormalities evident on MRI. Four of the 100 patients in the database were excluded due to a less than optimal scan quality, and the remaining 96 patients had a mean age of 76.6 years (range: 62–96 years); 59% were females. Ninety-three healthy and age-matched elderly controls with high-quality MR scans were selected (mean age: 76.7 years; range: 61–94 years; 74% females). Education was better in the healthy group ($p < 0.05$), with 3.3 versus 2.8 points (2 = high school, 3 = some college, 4 = college graduation). Socioeconomic status did not differ significantly (2.8 in the AD patients vs. 2.5 in the healthy subjects, where a high score indicates low status). The mean MMSE score was significantly lower ($p < 0.05$; mean: 24.4; range: 14–30) in the AD patients than in the controls (mean: 28.9; range: 25–30).

MRI Acquisition

Three to 4 individual T_1 -weighted MP-RAGE (magnetization-prepared rapid gradient-echo) sequences were obtained with a Vision 1.5T MRI scanner (Siemens, Erlangen, Germany) in a single imaging session with the following parameters: TR = 9.7 ms, TE = 4.0 ms, flip angle = 10° , TI = 20 ms, TD = 200 ms, sagittal orientation, thickness = 1.25 mm, gap = 0 mm, 128 slices, with 256×256 pixels (1×1 mm) resolution. Head movement was minimized by cushioning and a thermoplastic face mask. Positioning was low in the head coil (toward the feet) to optimize the imaging

of the cerebral cortex. MP-RAGE parameters were empirically optimized for gray-white contrast [23].

MRI Analysis

The sequences were averaged, and all datasets processed and analyzed with FreeSurfer 4.01 (<http://surfer.nmr.mgh.harvard.edu/>) at the Neuroimaging Analysis Laboratory, Center for the Study of Human Cognition, University of Oslo, with the additional use of computing resources from the $\sim 4,000$ -CPU Titan grid cluster (<http://hpc.uio.no>) run by the Research Computing Services Group at Universitetets senter for informasjonsteknologi (USIT), University of Oslo. For subcortical structures, a neuroanatomical label was automatically assigned to each voxel, based on probabilistic information automatically estimated from a manually labeled training set [25], yielding results comparable in accuracy to manual labeling [25, 26]. As part of this procedure, a measure of the cortical gray matter (GM) volume was estimated, which was included in the subcortical volume analyses. The estimated intracranial volume (ICV) was calculated by use of an atlas-based normalization procedure [19]. Cortical thickness measurements were obtained by reconstructing representations of the GM-WM (white matter) boundary and the cortical surface [27, 28], and the distance between these surfaces at each point across the cortical mantle was calculated. This method uses both intensity and continuity information from the entire 3-D MR volume in segmentation and deformation procedures to construct representations of cortical thickness. The maps produced are capable of detecting submillimeter differences between groups [29], which is validated by using histology and MR [30, 31]. The maps were smoothed, using a circularly symmetric gaussian kernel across the surface with a full width at half maximum of 15 mm, and averaged across participants by using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns [32]. This procedure provides an accurate matching of morphologically homologous cortical locations among the participants on the basis of each individual's anatomy while minimizing metric distortion. As we expected large and widespread cortical effects, a relatively coarse smoothing level was chosen. An optimal smoothing level equals the size of the effects, and thus a full width at half maximum of 15 mm was chosen as a reasonable approximation. A limitation of using a wide smoothing kernel is that smaller effects may be reduced or even wiped out. In addition to the continuous cortical analyses, we used an automated labeling system [33, 34] to divide the cortex into 33 different gyral-based areas in each hemisphere. The thickness estimation procedure was automated, but the accuracy of the spatial registration and the WM and GM segmentations were checked for all scans and routinely corrected for minor inaccuracies. The types of errors that most often require user intervention are insufficient removal of nonbrain tissue (typically dura in superior brain areas) and inclusion of vessels adjacent to the cortex (especially in the temporal lobes).

Statistical Analyses

Due to a very low variance in MMSE scores in the controls, and due to large roof effects, analyses involving the MMSE were done within the AD sample only. However, for interested readers, we have provided this information as online material (online supplementary table 1, www.karger.com/doi/10.1159/000241878). Volumes were estimated separately for each hemisphere, and the mean of left and right was used in the analyses. The volumetric

Table 1. Volume measures

Structure	Pearson's r
Total brain volume	0.36
Cerebral cortex	0.36
Accumbens	0.31
Cerebral WM	0.29
Inferior lateral ventricle	-0.27
Hippocampus	0.21
Amygdala	0.17
Lateral ventricle	-0.14
Brain stem	0.13
Pallidum	0.12
ICV	0.10
Cerebrospinal fluid	-0.09
Cerebellum cortex	0.08
Thalamus	0.08
3rd ventricle	-0.07
4th ventricle	0.06
Putamen	0.04
Caudate	0.04
Cerebellum WM	0.01

Correlations between MMSE score and the volume of each of the measured structures, sorted by (absolute) coefficient size. Characters in italics indicate $p < 0.05$.

variables were regressed on the ICV and the residuals used in the analyses. Volumetric analyses were done using Pearson's correlations, while a statistical comparison of the surface maps was generated by computing a general linear model for each vertex [28, 35]. The false discovery rate (FDR; <0.05) was used to control for familywise errors.

Results

Correlations between the MMSE score and the brain volumes in the AD sample are presented in table 1. The MMSE score did not correlate with age ($r = 0.01$; $p = 0.96$), and age was thus not regressed out in subsequent analyses. The MMSE score correlated negatively with the inferior lateral ventricles and positively with the total brain volume as well as the volumes of the cerebral cortex, accumbens, cerebral WM and hippocampus. For cortical thickness, significant ($FDR < 0.05$) positive relationships were found in several areas including the bilateral medial parietal (i.e. precuneus and retrosplenial), supramarginal, lateral parietal and fusiform cortices, in addition to parts of the superior, middle frontal and inferior lateral temporal cortices, and the left entorhinal cortex (fig. 1, 2). Correlations between MMSE and mean thick-

Table 2. Cortical areas

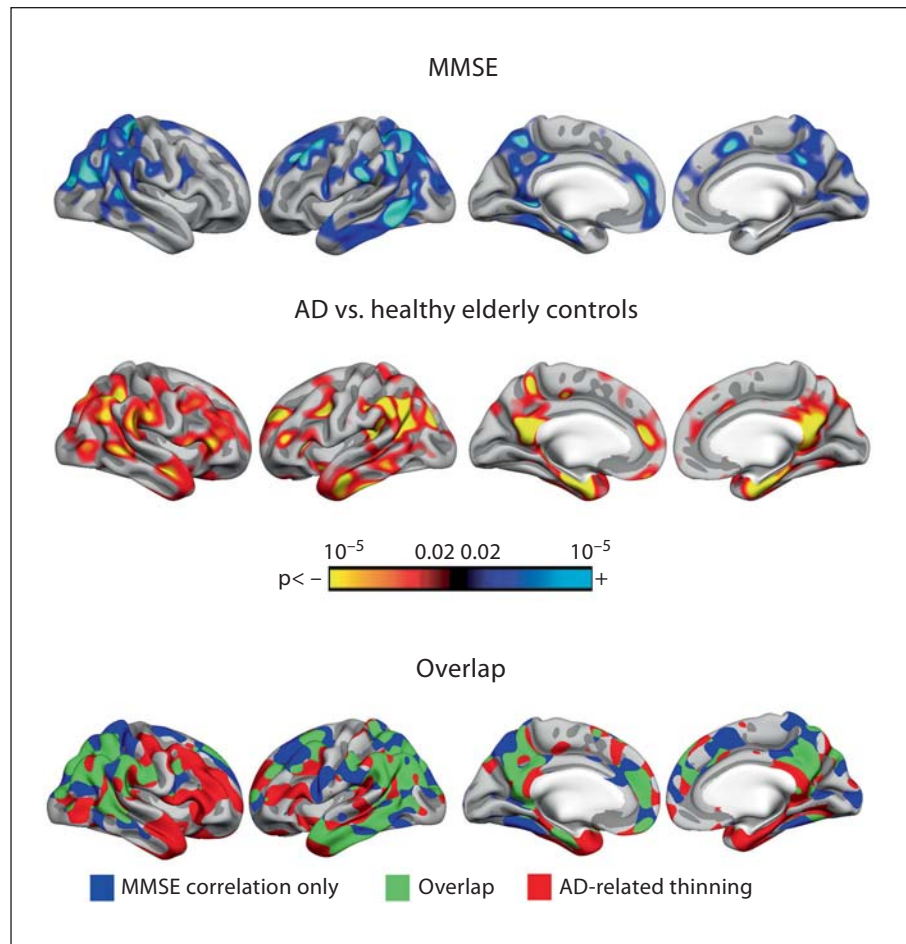
	Pearson's r
Inferior parietal	0.46
Supramarginal	0.45
Superior parietal	0.41
Precuneus	0.38
Postcentral	0.37
Middle temporal	0.36
Superior frontal	0.35
Caudal middle frontal	0.33
Fusiform	0.32
Lateral occipital	0.31
Inferior temporal	0.30
Pericalcarine	0.28
Banks superior temporal sulcus	0.27
Entorhinal	0.27
Superior temporal	0.26
Caudal anterior cingulate	0.24
Rostral middle frontal	0.23
Posterior cingulate	0.22
Pars opercularis	0.22
Frontal pole	0.21
Precentral	0.21
Lingual	0.20
Parahippocampal	0.19
Medial orbitofrontal	0.18
Transverse temporal	0.18
Paracentral	0.16
Pars triangularis	0.14
Cuneus	0.13
Lateral orbitofrontal	0.13
Rostral anterior cingulate	0.11
Temporal pole	0.10
Pars orbitalis	0.10

Correlations between MMSE score and mean thickness in each of the automatically parcellated cortical areas, sorted by coefficient size. Characters in italics indicate $p < 0.05$.

ness in 33 automatically defined cortical areas are presented in table 2. Significant and positive correlations were found for 21 areas. Similar analyses for the controls are reported in online supplement table 1.

Cortical thickness in AD versus healthy controls was contrasted. In order to perform a conjunction analysis, the p value surface maps derived from the group comparison and the MMSE analysis were binarized at $p = 0.02$ ($FDR \leq 0.05$). The degree of overlap between the results was color-coded and projected onto the average brain (fig. 1). The results showed that the thickness in several of the atrophic areas in AD was also related to the MMSE score, e.g. in the precuneus, lateral parietal corti-

Fig. 1. Cortical thickness analyses. Top panel: general linear models with the MMSE score as an independent, and cortical thickness per vertex as a dependent variable were run, and the results displayed as color-coded p value maps projected onto the semi-inflated average brain of the sample (blue-green: positive relationship). The lower p value threshold was set to equal an FDR of 0.05. Middle panel: p value maps derived from contrasting the thickness at each vertex between the AD patients and healthy controls (red-yellow: thinner in AD). Bottom panel: The p value maps from the MMSE analysis and from the contrast between AD patients and normal controls were binarized at $p = 0.02$, and the degree of overlap between the results was color-coded and projected onto the average brain.



ces and left entorhinal cortex. Naturally, several areas affected by AD were not related to the MMSE score. Bilaterally, this was the case for the temporal pole, parts of the isthmus of the cingulate, the parahippocampal cortex and parts of the inferior and middle frontal gyrus.

Finally, scattered areas were found where thickness correlated with MMSE but not with AD. This was true, bilaterally, for the fusiform gyrus, in addition to scattered areas in the superior frontal gyrus, the right middle and inferior frontal gyrus, the postcentral gyrus, the inferior parietal gyrus, a smaller section of the precuneus, and the middle and inferior temporal gyrus. The number of statistically significant vertexes in each category was counted. Seventeen percent of the total surface area was related to the MMSE alone, 27% to AD alone and 24% to both. Thus, >50% of the brain surface showed thinning in AD, >40% was related to the MMSE score, and 58% of the vertices where the MMSE was related to thickness were also related to AD.

Discussion

The MMSE was related to macrostructural brain changes in AD, but also to morphometric variation not associated with AD. While it has previously been established that MMSE and hippocampal volume are related [6–10], the present study showed that the MMSE is sensitive to AD-related atrophy in large cortical and subcortical brain areas outside the hippocampus as well. However, the results also showed that the MMSE is not exclusively sensitive to AD-related brain morphometry as >40% of the cortical regions that correlated with the MMSE score were not related to AD. AD-related atrophy was especially evident in the medial temporoparietal network including the hippocampus and entorhinal cortex and, to some extent, the parahippocampal cortex, retrosplenial cortex/posterior cingulate and parts of the precuneus. In addition, lateral anterior parts of the temporal lobe, supramarginal gyrus and parts of inferior parietal

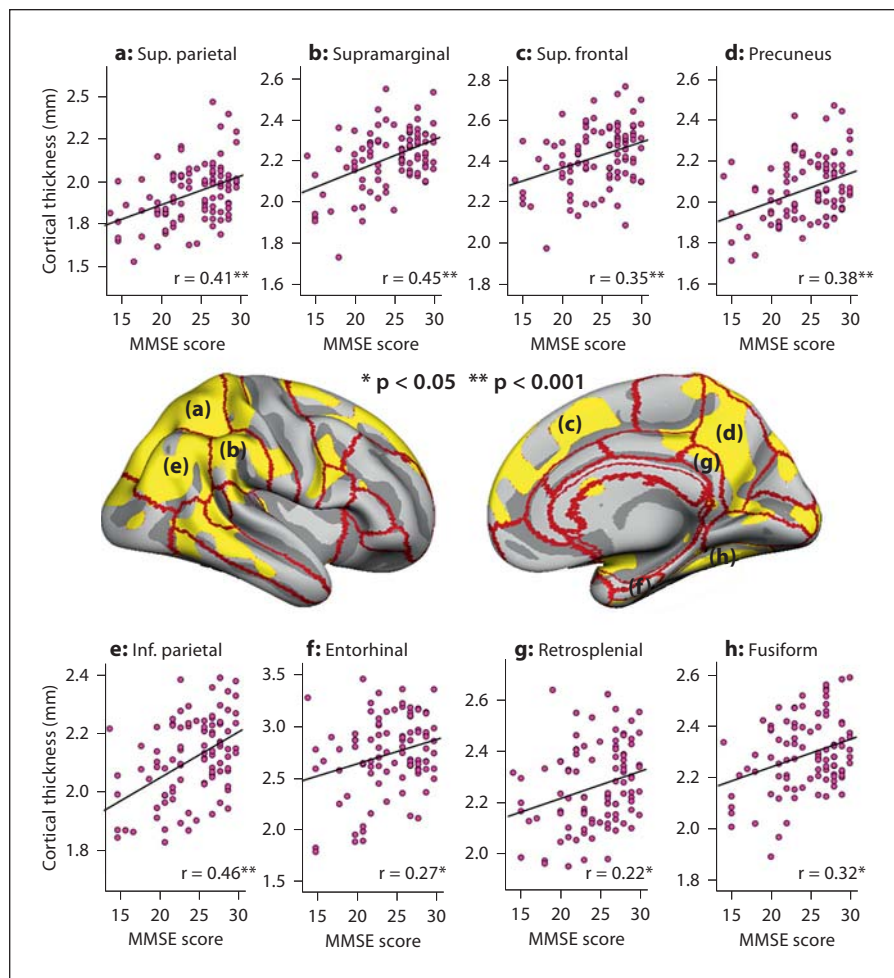


Fig. 2. Scatterplots of selected regions of interests. The cortex was parcellated into 33 gyral-based areas based on an automated procedure [33, 34]. Correlations between MMSE score and mean thickness in 8 selected areas are shown. No thickness was calculated in corpus callosum and the medial wall.

cortex were affected, while scattered smaller areas with AD-related atrophy were found in the frontal cortex. Areas that were relatively spared included most of the superior frontal gyrus, cuneus, lingual and fusiform gyrus, occipital cortex and the areas around the central sulcus.

The total brain volume and cerebral cortex were the volumetric measures that correlated the strongest with the MMSE score in the AD sample. This fits with previous research showing relationships between MMSE score and measures of global atrophy [10, 16, 17]. As expected from previous research [6–10], a relation to hippocampal volume was also seen. However, this relationship was considerably weaker than the relationships with the larger structures. The cortical thickness analyses allowed for more detailed tests of the topographical pattern of MMSE correlations. A substantial overlap between effects of AD and relationships with MMSE was seen. Fifty-eight percent of the vertices that were related to the MMSE score

showed thinning in AD. This indicates that the MMSE is sensitive to AD-related brain changes. However, the overlap is not much larger than one would expect by chance. Thus, it seems that the MMSE is not specifically related to the medial temporal lobe atrophy seen in AD. This was expected since the MMSE is not related to specific neurocognitive abilities. Instead, the MMSE appears to be an unspecific measure related to gross macroscopic brain changes.

The present results indicate that the MMSE is related to brain changes in mild to moderate AD. However, the conclusions are based on cross-sectional analyses and should be verified by longitudinal data. We do not know whether the MMSE-morphometry correlations which do not overlap with AD effects could, in part, be due to incipient undiagnosed degenerative disorders. Indeed, this could be the case at least for parts of the effects. It would be important to test how gradual changes in MMSE score

follow gradual changes in brain morphometry in the same patients. Further, the present study includes only a single method for measuring cerebral characteristics. It is necessary to know more about the interactions between different measures and biomarkers for cognitive decline in AD. Thus, the inclusion of positron emission tomography imaging and cerebrospinal fluid biomarkers (e.g. tau and $A\beta_{42}$), and possibly genetic testing for APOE would be beneficial for a better understanding of the relationship between macrostructural brain changes and cognitive function in AD.

The present results indicate that, even though the MMSE is regarded as a tool for the rapid evaluation of behavioral dementia, the test is also sensitive to macrostructural brain changes in mild to moderate AD. Brain morphometry has not been established as the gold standard for AD pathology, but the observed relationship be-

tween MMSE scores and brain atrophy still contributes to a validation of the use of such short screening instruments in the examination of cognitive deficits in elderly individuals. This highlights the importance of the clinical use of such simple screening measures. Still, the low specificity of the MMSE-brain relationships versus the AD-related changes means that subsequent investigations with MR will be necessary to establish to what degree brain morphometric changes that are consistent with AD are present in individual patients.

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