Identification of subgroups in amnestic mild cognitive impairment

Abstract—The DMS48 is a visual recognition memory test designed to detect memory changes in early Alzheimer disease (AD). Patients with amnestic mild cognitive impairment (aMCI) who succeeded on this task exhibited frontal hypoperfusion on SPECT. In contrast, failure was associated with temporomesial and temporoparietal hypoperfusion, a pattern usually described in the early stages of AD. It may possible to detect patients at high risk for AD within a population of aMCI.

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E. Guedj, MD; E.J. Barbeau, PhD; M. Didic, MD; O. Felician, MD, PhD; C. de Laforte, MD; M. Ceccaldi, MD, PhD; O. Mundler, MD, PhD; and M. Poncet, MD

The initial site of neuropathologic change in most patients with Alzheimer disease (AD) involves the anterior subhippocampal region.[1,2] Animal and human studies suggest that this brain region is critical for successful performance on visual recognition memory tasks.[3,4] We designed a visual recognition memory test, the DMS48, to detect dysfunction of anterior subhippocampal structures and thereby contribute to the early diagnosis of AD.[5] In a preliminary study, all patients with mild and moderate probable AD were impaired on the DMS48, whereas patients with Parkinson disease (PD) performed at the level of control subjects.[5] Patients with amnestic mild cognitive impairment (aMCI) were impaired, their performance being intermediate between that of control subjects and patients with mild AD. However, a large dispersion was observed in the aMCI group: some patients scored below controls on the task, whereas others succeeded. Although all aMCI patients presented with an objective isolated memory impairment, because this was an inclusion criterium,[6] we suggested that different mechanisms may be involved. Memory dysfunction of aMCI patients with normal scores on the DMS48 could be related to frontal or subcorticofrontal dysfunction that affects recall but not recognition,[7] whereas impaired performance on this task may be related to lesions of the medial temporal lobes affecting storage. However, imaging data that could have supported this hypothesis were not available at that time.

In this study, we hypothesized that, if performance on the DMS48 reflected different patterns of lesions in patients with aMCI, different perfusion patterns would be found on SPECT.

Methods. *Subjects.* We included 26 patients meeting strict criteria for aMCI.[6] Patients were included if their performance was 1.5 SD below the mean of matched control subjects on the delayed free recall of a verbal memory task. Brain imaging, routine biologic survey, detailed neuropsychological evaluation, assessment of daily activities, psychiatric interview, and physical examination excluded patients with nondegenerative diseases or multidomain impairment. The local ethics committee approved this study, and all patients signed informed consent.

DMS48. The DMS48 is a test of visual recognition memory.[5] Stimuli to be learned consist of 48 colored drawings. After a 1-hour delay, each target is shown simultaneously with a distractor, and the subject is asked to identify the target. Patients with aMCI were divided into two subgroups, according to their Z score on the DMS48. Thirteen patients obtained a Z score of −1.5 or greater (DMS48+ group), and 13 obtained a Z score below −1.5 (DMS48− group). Mean MMSE score and mean age did not differ between the two groups (table 1).

SPECT procedure. Each patient was injected with 740 MBq of ^{99m}Tc-ECD, at rest, in a quiet surrounding, with eyes closed. Acquisition was performed on a double-head rotating gamma camera (ECAM, Siemens, Erlangen, Germany) equipped with a fan beam collimator. Tomographic slices were reconstructed using a filtered back projection algorithm with Chang attenuation correction.

Statistical analysis. A voxel-by-voxel group study was performed using SPM2. The data were standardized on the Montreal Neurologic Institute (MNI) atlas by using a 12-parameter affine transformation, followed by nonlinear transformations and a trilinear interpolation. Dimensions of the resulting voxels were 2 × 2 × 2 mm. Standardized data were then smoothed by a gaussian filter (full width at half maximum = 12 mm). We compared DMS48+ and DMS48− groups using the "compare-populations one scan/subject" routine, which performs a fixed-effects simple *t* test for each voxel. Global normalization was performed using proportional scaling. The SPM {T} maps were obtained at a height threshold of $p = 0.05$, corrected for multiple comparisons for the cluster. MNI coordinates were finally converted into Talairach coordinates using Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Results. The figure shows the SPM intergroup comparisons. Figure A shows the regions for which the voxel counts in the DMS48+ group were significantly lower than in the DMS48− group, whereas figure B shows the regions for which the voxel counts in the DMS48− group were significantly lower than those in the DMS48+ group.

From Service Central de Biophysique et de Médecine Nucléaire, AP-HM Timone, Marseille, France (E.G., C.d.L., O.M.); Centre de Recherche Cerveau et Cognition, CNRS UMR-5549 and Université Paul Sabatier Toulouse 3, Toulouse, France (E.J.B.); and Service de Neurologie et de Neuropsychologie AP-HM Timone and Laboratoire de Neurophysiologie et de Neuropsychologie, INSERM U751, Marseille, France (M.D., O.F., M.C., M.P.).

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The DMS48, a test designed for research purposes, can be downloaded at the following address: http://www.sf-neuro.org (Greco file; compulsory free registration).

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Address correspondence and reprint requests to Dr. Eric Guedj, Service Central de Biophysique et de Médecine Nucléaire, Assistance Publique des Hôpitaux de Marseille, Centre Hospitalo-Universitaire de la Timone, 264, rue Saint Pierre, 13385 Marseille Cedex 5, France; e-mail: eric.guedj@ap-hm.fr

Table 1 *Characteristics of amnestic MCI subgroups*

	DMS48−	DMS48+	*p*
n	13	13	
Age, mean ± SD (range), y	68.8 ± 7.9 (53 to 80)	72.4 ± 9.0 (52 to 82)	0.1742
Women/men	7/6	8/5	
MMSE score, mean ± SD (range)	27.3 ± 1.0 (26 to 29)	27.5 ± 1.7 (25 to 30)	0.8334
DMS48 Z-score, mean ± SD (range)	−4.8 ± 2.3 (−1.8 to −9.0)	−0.5 ± 0.7 (−1.5 to 0.5)	<0.0001

p calculated using a nonparametric Mann–Whitney *U* test.

MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; DMS48− = patients failing the test; DMS48+ = patients succeeding on the test.

The DMS48+ group showed relative hypoperfusion of the left prefrontal cortex, which included orbitoventral and dorsolateral areas. In marked contrast, the DMS48− group showed bilateral relative hypoperfusion of the temporal lobes including bilateral entorhinal, perirhinal, hippocampal, and temporobasal cortices, extending to the temporo-occipital junctions. In this group, bilateral hypoperfusion of the temporoparietal cortices, the right occipital cortex, the bilateral posterior cingulum, and the left insula were also observed (table 2).

Discussion. Distinct patterns of cerebral hypoperfusion were found when comparing two subgroups of aMCI patients, based on their performance on the DMS48, a visual recognition memory task. aMCI patients with normal performance on the DMS48 showed relative left prefrontal hypoperfusion and no perfusion defect in the temporal or parietal lobes. This contrasted with bilateral relative hypoperfusion of the medial temporal lobe, including rhinal cortices on both sides, as well as hypoperfusion of the posterior cingular and temporoparietal cortices in the aMCI group with impaired visual recognition memory. These brain perfusion patterns could not be explained by a difference in severity of cognitive decline, because mean MMSE scores did not differ. Mean age did not differ either.

All aMCI patients were impaired on the free recall of a verbal memory test, which was the inclusion criterion. However, the different SPECT patterns observed suggest that their memory impairment may be subsequent to distinct mechanisms. The frontal hypoperfusion suggests that the DMS48+ group failed this verbal task because of poor recall related to frontal or subcorticofrontal dysfunction. The left frontal hypoperfusion in this group may therefore reflect a recruitment bias related to the use of a verbal memory task as an inclusion criterion. Intact performance on the DMS48 in this group is probably related to the fact that this task does not require recall, because targets are shown during recognition. This is in line with a previous study in which patients with PD, a disorder affecting subcorticofrontal loops, performed at the level of control subjects on the DMS48. In this study, performance on the DMS48 was also found to be independent of executive functioning.[5]

In contrast, medial temporal lobe hypoperfusion in the DMS48− group suggests that these subjects failed the task because of poor storage, a pattern that is usually associated with medial temporal lobe dysfunction. The DMS48 is a test of visual recognition memory that was designed because studies in monkeys demonstrated that lesions of anterior sub-

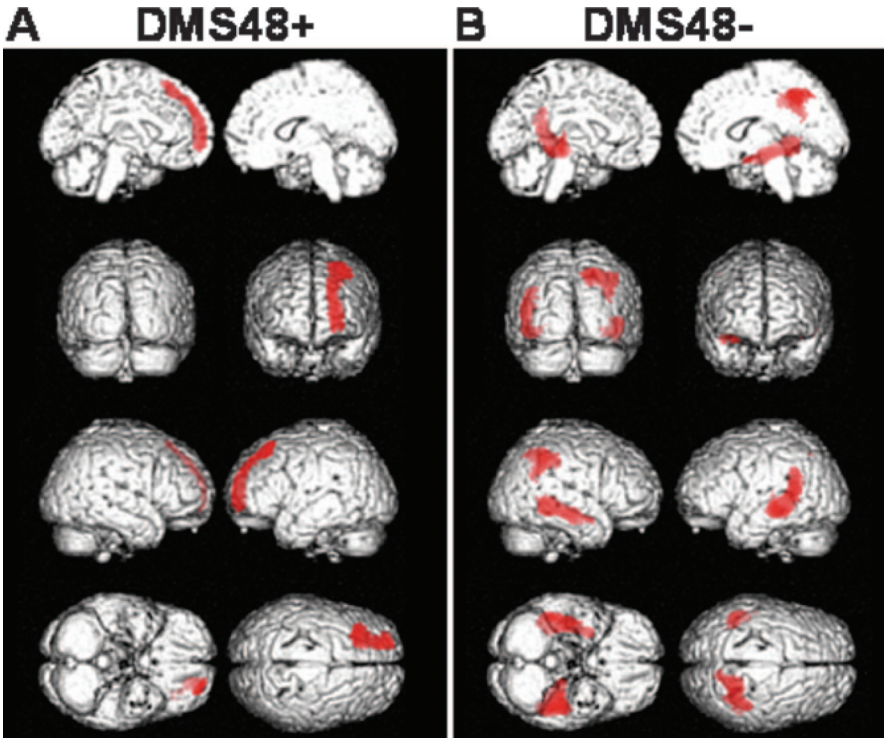

Figure. Anatomic localization of peaks of hypoperfusion when comparing DMS48− and DMS48+ groups on SPM2 surface rendering ($p_{cluster\text{-}level} < 0.05$; corrected for multiple comparisons). (A) SPM analysis demonstrating regions where cerebral perfusion is lower in the DMS48+ group as compared with the DMS48− group. Note that the significant region is the left prefrontal lobe. (B) SPM analysis demonstrating regions where cerebral perfusion is lower in the DMS48− group as compared with the DMS48+ group. Note that the significant regions are the temporoparietal cortex and the cingulum.

Table 2 *Talairach coordinates of relative hypoperfusions ($p_{cluster\text{-}level} < 0.05$; corrected for multiple comparisons) when comparing DMS48− and DMS48+ groups*

$p_{corrected}$ (cluster-level)	*k*	Z	Coordinates x, y, z (mm)	BA	Regions
DMS48−					
0.004	1,233*	4.32	−38,−31, −7	L BA36	L PHG
		3.93	−32,−27, −4		L hippocampus
		3.90	−46,−44, 6	L BA22	L MTG
0.040	802†	3.89	38,−14,−13	R BA21	R MTG
		3.78	40,−22, −9	R BA13	R insula
		3.76	32, −3,−17	R BA34	R PHG
0.033	837‡	3.88	22,−43, 43	R BA7	R SPL
		3.12	40,−49, 34	R BA40	R IPL
DMS48+					
0.044	785§	3.75	−32, 30, 48	L BA8	L SFG
		3.28	−30, 35, 42	L BA8	L MFG
		3.21	−18, 52, 27	L BA9	L SFG

Results obtained with SPM2 are listed by clusters and in decreasing order of peak Z score values. Cluster size is indicated by the *k* value, which represents the number of significant voxels in the particular cluster.
These large clusters also include (in decreasing order of peak Z score value):

* L BA13, L BA41, L BA27, L BA37, L BA39, L BA28, L BA40.
† R BA36, R hippocampus, R BA22, R BA19, R BA37, R BA20, R BA39.
‡ R BA31, R BA39, R BA2.
§ L BA10.

DMS48− = patients failing the test; DMS48+ = patients succeeding on the test; BA = Brodmann area; L = left; R = right; PHG = parahippocampal gyrus; MTG = middle temporal gyrus; SPL = superior parietal lobule; IPL = inferior parietal lobule; SFG = superior frontal gyrus; MFG = middle frontal gyrus.

hippocampal structures severely impair performance on this type of task.[3] The results obtained in the current study are in agreement with our hypothesis, because patients who failed this test show hypoperfusion of these structures bilaterally. Furthermore, this group of patients also showed hypoperfusion of parietotemporal and posterior cingulate cortices, a pattern that has been reported in neuroimaging studies of prodromal AD.[8,9]

aMCI patients who succeed on the DMS48 have different patterns of cerebral perfusion from those who fail on this task, providing further evidence that the syndrome of aMCI includes patients with distinct memory deficits corresponding to distinct patterns of brain dysfunction and probably to different diseases. Furthermore, hypoperfusion of the medial temporal lobes, as usually reported in AD, was observed in aMCI patients with impaired visual recognition memory. They also displayed relative hypoperfusion of parietotemporal and posterior cingulate cortices as in prodromal AD. These findings could suggest that aMCI patients with impaired performance on the DMS48 are at high risk of AD. However, follow-up data will be necessary to determine the predictive value of these results.

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