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Anatomical substrates and neurocognitive predictors of daily numerical abilities in Mild Cognitive Impairment

Benavides-Varela S. PhD.[1,2], Burgio F. MS.[1,3], Meneghello F. MD.[1], De Marco M. PhD.[4], Arcara G. PhD.[3], Rigon J. MS.[1], Pilosio C. MS.[1], Butterworth B. PhD. [5], Venneri A. PhD.[1,4], Semenza C. MD.[3]

[1]IRCCS San Camillo Hospital Foundation, Neuropsychology Unit, Lido-Venice, Italy
[2] Department of Developmental Psychology and Socialization, University of Padova, Italy
[3] Neuroscience Department, University of Padova, Italy.
[4] Department of Neuroscience, Medical School, University of Sheffield, United Kingdom.
[5] Institute of Cognitive Neuroscience, University College London, United Kingdom.

Corresponding author:
Silvia Benavides-Varela
silviabenavides@gmail.com
Via Alberoni 70, 30126
Lido-Venice
Italy
Tel. +39 3404586535

Authors' email list:
Butterworth: b.butterworth@ucl.ac.uk
Venneri: a.venneri@sheffield.ac.uk
Pilosio: cristina.pilosio@ospedalesancamillo.net
Rigon: jessica.rigon@ospedalesancamillo.net
Meneghello: francesca.meneghello@ospedalesancamillo.net
Burgio: francesca.burgio@ospedalesancamillo.net
Arcara: giorgio.arcara@gmail.com
De Marco: m.demarco@sheffield.ac.uk
Semenza: carlo.semenza@unipd.it

Abstract

Patients with mild cognitive impairment experience difficulties in mathematics that affect their functioning in the activities of everyday life. What are the associated anatomical brain changes and the cognitive correlates underlying such deficits? In the present study, 33 patients with Mild Cognitive Impairments (MCI) and 29 cognitively normal controls underwent volumetric MRI, and completed the standardized battery of Numerical Activities of Daily Living (NADL) along with a comprehensive clinical neuropsychological assessment. Group differences were examined on the numerical tasks and volumetric brain measures. The gray and white matter volume correlates were also evaluated. The results showed that relative to controls, the MCI group had impairments in number comprehension, transcoding, written operations, and in daily activities involving time estimation and money usage. In the volumetric measures, group differences emerged for the transcoding subtask in the left insula and left superior temporal gyrus. Among MCI patients, number comprehension and formal numerical performance were correlated with volumetric variability in the right middle occipital areas and right frontal gyrus. Money-usage scores showed significant correlations with left mesial frontal cortex, right superior frontal and right superior temporal cortex. Regression models revealed that neuropsychological measures of long-term memory, language, visuo-spatial abilities, and abstract reasoning were predictive of the patients' decline in daily activities. The present findings suggest that early neuropathology in distributed cortical regions of the brain including frontal, temporal and occipital areas leads to a breakdown of cognitive abilities in MCI that impacts on numerical daily functioning. The findings have implications for diagnosis, clinical and domestic care of patients with MCI.

Keywords: Numerical Deficits in Ecological Contexts; MCI mild Cognitive Impairment; Compensatory reorganization; Cognitive aging; Money usage and time estimation deficit.

1. Introduction

Deficits in mathematical abilities contribute to the difficulties experienced by patients with mild cognitive impairment (MCI) in everyday life activities (Nygård, 2003; Winblad et al., 2004). For instance, MCI patients have been recently shown to experience problems in understanding numerical information concerning health care (Delazer, Kemmler & Benke, 2013; Pertl et al., 2014). Moreover, impairments in tasks tapping financial capacities such as financial conceptual knowledge, bank statement management and bill payment have been also reported in these patients (Griffith et al., 2003 ; Griffith et al., 2010; Marson et al., 2009; Okonkwo, Wadley, Griffith, Ball & Marson, 2006; Sherod et al., 2009).

The numerical deficits in MCI may be primary or secondary to other cognitive difficulties. Griffith et al. (2003), in particular, related financial impairments to deficits in executive functions. Similarly, Zamarian et al. (2007a; 2007b) found that executive dysfunctions affect the patients' performance even on basic mathematical tasks. In particular, the studies of Zamarian and colleagues found that MCI patients who score within the normal range on basic arithmetic assessments show difficulties on arithmetic applied to daily-life by having to recruit additional, non-numerical resources. Accordingly, further studies have emphasized the relevance of age-associated attentional and executive decline in accounting for numerical difficulties in the elderly (Cappelletti, Didini, Stoianov & Zorzi, 2014; Duverne & Lemaire 2005; Lemaire & Arnaud, 2008). These studies have conjectured that such decline plays a role in those everyday numerical problems that show the typical features of a multistep problem, i.e. requiring focused attention, planning, reasoning and monitoring of the solution procedure.

One interesting question is whether the mathematical difficulties experienced by MCIs are the result of specific regional anatomical changes. The hypothesis of the present study is that, if previously learned mathematical concepts and facts are deteriorating in MCI, then age-related compensatory mechanisms and functional reorganization might increasingly be more salient. Thus, for instance, a shift from parietal to frontal functioning, for which there is existing evidence in aging (Lövdén, Bäckman, Lindenberger, Schaefer & Schmiedek, 2001) is expected, independently of whether these changes lead to effective compensation. Such functional reorganization is likely to reflect increasing load on frontal executive functions. Parallel deterioration of linguistic and visuospatial abilities might also modulate this process. In order to investigate these neural changes, the present study will explore the pattern of association between numerical abilities assessed with neuropsychological instruments, and volumetric properties of the brain, both in patients diagnosed with MCI and in healthy controls.

Between-group qualitative differences in these maps would provide a rationale for the presence of both subjective and objective impairment of numerical processing in the MCI population.

2. Methods

2.1. Participants

Sixty-two elderly adults were invited to undertake a comprehensive clinical, neuropsychiatric, and neuropsychological examination at the IRCCS San Camillo Hospital (Lido-Venice, Italy). After completing a full neurological and neuropsychological assessment, participants were divided in two groups according to the

Petersen et al., criteria for diagnosing Mild Cognitive Impairment (Petersen et al., 2001). Thirty-three participants were diagnosed as having MCI (20 males), and twenty-nine (11 males) were enrolled in the control group because they showed no sign of cognitive impairment. Other sources of cognitive impairment such as focal lesions were ruled out by visual inspection of MRI scans, carried out by an experienced neuroradiologist. All participants were right-handed and none of them had a history of psychiatric disorder, drugs or alcohol abuse. There were no significant differences between MCI patients (M= 9.5y, SD= 4.3) and the control group (M= 11.1y, SD= 4.7) in scholastic attainment estimated in years of education ($p > 0.05$). Significant differences between the two groups were instead found in age $t(60) = 3.83$, $p < 0.001$, $d = 0.98$ (controls M= 67.1y, SD= 8.4; MCI M=74.4, SD= 6.0) and in the Mini Mental State Examination scores (MMSE (Folstein, Folstein & McHugh,1975) $t(60) = 5.23$, $p < 0.001$, $d = 1.31$ (controls M= 29.1, SD= 1.3; MCI M=26.5, SD= 2.5). As a consequence, these two variables were included as covariates in all analyses. Written informed consent was obtained from all participants after the nature of the study was fully explained. The study was approved by the Institutional Review Board of the IRCCS Fondazione Ospedale San Camillo (Venice, Italy).

2.2. Measures

2.2.1 Cognitive Assessment

A comprehensive neuropsychological battery was administered to all participants as part of their clinical evaluation. This battery included measures of attention, executive functions, reasoning, language, memory, and visuospatial abilities. The tests used to assess each domain (See Supplementary Material) were chosen on the basis of theoretical and clinical considerations. The aim was to obtain cognitive profiles which could be clinically informative and sensitive to the impact of early-stage neurodegeneration.

2.2.2 Numerical Assessment

All participants completed three sub-sections of the Numerical Activities of Daily Living test-NADL (Semenza et al., 2014). NADL measures the impact of specific numerical abilities on participants' everyday life. The sub-sections administered to the participants included:

1) A brief Interview with the participant, which assesses the patient's awareness of their possible numerical deficits in everyday life. This interview consists of ten simple questions enquiring about how well the participant uses numbers in everyday life. (e.g., "Do you shop by yourself?"; "Do you make your own telephone calls unaided, do you dial them yourself?")

2) An Informal test of numerical competence that measures the participants' numerical competence in everyday tasks. It encompasses questions in the domains of Time (e.g. current date), Measure (e.g. amount of pasta or rice in an average portion), Transportation (e.g. distance between home and hospital), Communication (e.g. own telephone number), General Knowledge (e.g. number of days in a week?) and Money (e.g. estimating the price of a new car).

3) A Formal Test of Numerical Abilities, which assesses the patients' scholastic numerical abilities using brief sub-tests graded for difficulty. It includes the following domains: Number comprehension, Transcoding (reading and writing Arabic numerals), Mental calculation, Knowledge of rules and principles of calculation, and Written

operations.

Number comprehension comprises three subtests that assess the patient's ability to relate number words and digits to numerical magnitudes: Number line marking (the participant is asked to mark a number on a line defined by its end points), Numerosity comparison (comparing the number of squares in two displays presented simultaneously, up to nine squares per panel), and Digit comprehension (ten displays are presented one at a time along with a list of digits from 1 to 10. For each display, the participant is requested to point at the appropriate number).

Transcoding consists of two sub-tests: Reading Numbers Aloud (including two-digit numbers, e.g. 12, up to five-digit numbers, e.g., 65300), and Writing Numbers to Dictation (including two-digit up to five-digit numbers).

Mental Calculation encompasses three subtests: Mental Addition (e.g., 5+7), Mental Subtraction (e.g., 13-4), and Mental Multiplication. (e.g., 9×6).

Knowledge of Arithmetical Rules and Principles assesses the ability to use basic rules (e.g. the commutativity of addition, or managing operations with 0) in written form. It consists of sub-tests of Arithmetical Rules (e.g., 0+9; 1×7), Addition Principles (e.g., if 26+37 = 63 then 37+26 = ?), and Multiplication Principles (if 94×5 = 470 then 93×5= ?).

Written Operations included complex Addition (e.g., 463+659), Subtraction (548-231), and Multiplication (429×53).

2.3. Statistical Analysis of Behavioral Data

Non-parametric Wilcoxon rank-sum tests were used to assess continuous variables, including the clinical, demographic and performance scores in the NADL battery. In an initial analysis, the scores of the two groups in the three sub-sections of the NADL were compared setting Bonferroni's correction for multiple comparisons (alpha = .01). In a second analysis, each domain of the Informal and Formal assessments was compared between groups, adjusting the significance level according to the number of comparisons carried out within each sub-section (alpha = .008). Additionally, given that the two groups differed in age (see section 2.1), a further Pearson's correlation analysis was carried out to evaluate the association between age and scores on each sub-test and domain of the NADL battery.

Finally, participants' raw scores on the neuropsychological tests were converted into z scores and averaged to form the composite variable representing each cognitive domain (see Supplementary Material for additional details). The neuropsychological composites were entered into separate stepwise regression models to determine the cognitive correlates of numerical abilities showing between-group differences. The use of composite scores allowed us to reduce sensibly the risk of multicollinearity and potential instability of single variables.

2.4. MRI Acquisition, Preprocessing and Analysis

Three-dimensional (3D) T1-weighted MR images were acquired using a 1.5 T Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1.1×1.1×0.6 mm and the field of view was 250 mm with a matrix size of 256×256×124. In addition, a T2-weighted axial scan and a coronal fluid attenuated inversion recovery (FLAIR) scan were also acquired to detect the presence of significant vascular pathology or microbleeds, which might either be not compatible with the diagnosis of MCI prodromal to AD or induce a suboptimal segmentation of the T1-weighted images. A number of pre-processing steps were followed to obtain the gray matter (GM) and white matter (WM) segments from the 3D T1-weighted structural scan before carrying out statistical analyses using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). To correct for global differences in brain shape, structural images were warped to a standard stereotactic space and segmented to extract maps of GM, WM and cerebral spinal fluid using the default segmentation procedure available in SPM8 (Ashburner & Friston, 2005). Modulated-normalized GM and WM images were then smoothed with an 8 mm FWHM Gaussian kernel to reduce variability between participants. Smoothed-modulated-normalized segments were entered into voxel-based multiple regression analyses to investigate linear correlations between GM and WM volumes and participants' scores on each sub-test of the NADL battery. Moreover, a factorial model was used to characterize the relationship between numerical abilities, diagnostic group and brain volumes. For this purpose the participants' performance on each NADL sub-test was turned into a categorical value using the median split method. Then, a 2×2 ANOVA with performance (below the median and above the median) and group (MCI and Controls) as independent variables was carried out to determine the main effect of group and the interactions. Age, years of education, MMSE scores, and total intracranial volume values were included as covariates in both the regression and the factorial models. Height threshold was set at $p < 0.001$ (uncorrected) for all analyses. Only cluster corrected areas (FWE) with a significance level of $p \leq 0.05$ and at least 200 voxels are reported. Anatomical regions were identified using the Talairach Daemon

Client (Lancaster et al., 2000), following conversion of the Montreal Neurological Institute coordinates extracted from the SPM output into Talairach coordinates using the Matlab function mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

3. Results

3.1. Behavioral results

A summary of the performance of the two groups on the NADL sub-sections and their corresponding domains is presented in Table 1. The first set of analyses comparing the scores of the two groups in the three NADL sub-sections (total scores) showed no significant differences between the groups in the Interview ($Z = 2.02$, $p = .043$), but there were significant differences in the Informal ($Z = 3.55$, $p = .0003$) and Formal assessments ($Z = 3.50$, $p = .0004$). The subsequent set of analysis carried out on the domains of the Informal Numerical competence test showed that MCI patients and controls significantly differed in Time estimation ($Z = 2.82$, $p = .004$) and Money Usage ($Z = 2.58$, $p = .007$) . The same set of analysis carried out in the domains of the Formal test showed significant differences between the groups in Number comprehension ($Z = 3.05$, $p = .002$), Transcoding ($Z = 3.13$, $p = .001$), Logic and Principles ($Z = 3.45$, $p = .0005$) and Written operations ($Z = 2.54$, $p = .007$). No other domain showed significant group differences (all p s > .008). Additionally, there was no correlation between age and the participants' scores on the NADL's sub-tests and domains.

3.2 Neurocognitive Modeling of Numerical Abilities in MCI

The stepwise regression in which the Informal assessment of the NADL was the dependent variable settled on a final model that comprised language and visuo-spatial abilities as predictors. Measures of long-term memory predicted Time estimation, while the model for Money usage included visuo-spatial abilities and abstract reasoning as predictors.

Patients' visuo-spatial abilities, executive functions and abstract reasoning emerged as significant predictors of performance in the Formal assessment. For Number comprehension the only predictor was visuo-spatial abilities, while language abilities predicted the patients' performance on the Transcoding tasks. Finally, abstract reasoning, visuo-spatial abilities, and executive functions and attention predicted the patients' performance on written operations. Abstract reasoning predicted also the performance on the Logic and principles tasks. All results are reported in Table 2.

3.3 Neurocognitive Modeling of Numerical Abilities in Controls

Controls' abstract reasoning ($\beta = .45$; $p = .02$), and long-term memory abilities ($\beta = .98$; $p = .008$) predicted the performance on written operations (Model $R^2 = .31$, $F(1,28) = 5.39$; $p = .01$). No neuropsychological measures predicted the controls' performance on the remaining NADL sub-tests.

3.2. VBM results

3.2.1 Voxel-based regression models

The NADL sub-tests and domains that showed significant between-group differences in the behavioral analyses were entered into separate regression models to evaluate the GM and WM volume correlations with the tests. Money-usage scores showed significant positive correlations with GM volume in the left mesial frontal cortex, right superior frontal cortex and right superior temporal areas in the MCI group. Total scores of the Formal test were significantly associated with GM volume values in the right middle occipital areas in the MCI group. Similarly, Number Comprehension and Logic and principles tasks showed significant positive correlations with GM volume in the right frontal gyrus and right occipital cuneus, respectively (see Figure 1). Logic and principles performance also correlated positively with volumetric changes of WM in the right occipital areas. Significant positive correlations between Money-usage and WM volume were also found in the sub-lobar, extra nuclear area of the corpus callosum. There were no significant correlations in other sub-tests and domains. No significant positive correlations between scores on any of the NADL measures and brain volumes (GM and WM) were found in the control group. Significant negative correlations between Money-usage and GM volume were found in the right-occipital, left-temporal and left-posterior cingulate. Similarly, Time estimation showed significant negative correlations with GM volume in the left-occipital and the proximity of the substantia nigra nuclei, in the right portion of the midbrain. Table 3 shows a summary of the findings.

3.2.2. Voxel-based factorial model

This analysis, as the previous one, was carried out onlyon the NADL sub-tests and domains that showed significant between-group differences in the behavioral analysis. Significant GM volume reduction was detected in MCI patients with respect to healthy controls for the Transcoding sub-test in the left insula and Left Superior Temporal Gyrus. This difference was conspicuous between the high-performing sub-group of patients and the high-performing sub-group of controls. Moreover, in the Money-usage subtest a number of areas including the left/right Inferior Temporal Gyrus and left superior Temporal Gyrus showed a significant interaction between performance and group (Table 4 and Figure 2): while controls differed according to the level of performance, such difference did not appear in MCI. No significant between group differences or interactions were detected in any other subtests.

4. Discussion

Basic numerical abilities and their use in everyday life were found to be significantly poorer in MCI patients than in healthy controls. In contrast, no significant group difference was found in the score assessing awareness of numerical difficulties in everyday life. This is an important finding insofar as it shows that MCI patients, typically complaining about memory and naming difficulties (e.g. Joubert et al., 2010), do not express concerns about progressively deteriorating numerical skills. Such unawareness may exacerbate the patients' deficit, which heavily impacts on their daily life.

MCI patients do not experience difficulties in every numerical domain, however. Within basic abilities, only Number comprehension, Transcoding, applying logic and principles, and Written operations account for the difference with the control group. This finding might be possibly due to an overall higher level of difficulty of these particular tasks than other numerical tasks. Although the current data do not rule out this possibility, this interpretational avenue seems rather unlikely. In fact, if the intrinsic difficulty of the tasks were influencing the level of performance, one should expect that patients with other neurological conditions should also fail in this or in other similar tests. Rather, it is now well-established that different degenerative diseases show characteristic impairment profiles which follow particular lesional/degeneration patterns, such as in the case of Alzheimer disease (Carlomagno et al., 1999; Delazer, Karner, Proell & Benke, 2006; Helpern, McMilla, Moore, Dennis & Grossman, 2003; Martini, Domahs, Benke & Delazer, 2003; Zamarian et al., 2007b), Parkinson disease and other basal ganglia dysfunctions (Benke, Delazer, Bartha & Auer, 2003; Delazer et al., 2004; Tamura et al., 2003; Zamarian et al., 2006), semantic dementia (Cappelletti, Butterworth & Kopelman, 2001, 2012), amyothrophic lateral sclerosis (Palmieri et al., 2013), and genetic defects (e.g., Bertella et al., 2005; Semenza et al., 2008; Semenza et al., 2012). Each degenerative disease seems to affect aspects of number processing and calculation in a distinct way. Likewise, it is thus possible that the current findings also reflect a profile that specifically reflects the cognitive decline in MCI. The present study, however, is the first which has used the NADL to assess numerical competence; the specificity of this pattern can only be determined by comparing the pattern detected in this MCI sample with those of future studies with other populations tested using the same instrument.

Similarly, when numerical abilities are tested with everyday life tasks, only some tasks and not others seem to be affected in MCI. The domains that were found significantly impaired in the current study, i.e. Time estimation and Money usage, reflect activities that do not imply sophisticated financial knowledge (Griffith et al., 2003). These numerical activities seem the first to be disrupted by the mechanisms of neural deterioration usually present in cases of MCI. Since a pattern of association was found between these simple numerical abilities and composite measures of long-term memory and abstract reasoning, their early impairment in MCI seems to reflect the consequences of a decline in these fundamental cognitive abilities. In addition, the fact that Alzheimer's disease, the most likely neuropathological cause of MCI (Morris et al., 2001), is characterized by significant changes in these two cognitive domains is consistent with and corroborates this evidence. Moreover, the results obtained in the regression analyses suggest that compensatory/adaptative mechanisms may guide the performance of MCI patients on those NADL sub-tasks. In fact, the cognitive domains predicting performance in MCI were not predictive of the same ecological numerical capacities in the control group.

Data from the VBM analyses showed a pattern of significant brain structure correlation that can provide some clues about the anatomical areas supporting performance on the NADL in patients with MCI. Total scores of the Formal test, as well as those of Number Comprehension and Logic and Principles were significantly associated with GM volumes in the right occipital areas and right frontal gyrus. The evidence of a significant association emerging in frontal and occipital areas may reflect the need to recruit structures not traditionally associated with basic numerical skills such as the inferior parietal cortex (Dehaene & Cohen, 1995; 1997; Arsalidou & Taylor, 2010) to support performance on one of the most difficult tasks for MCI patients: Number comprehension. Frontal regions are normally involved in explicit reasoning; their recruitment might signify loss of automatic processing, and might reflect reversal to a more effortful (and ineffective) elaboration of this type of stimuli, while, on the other hand, the association with volumes in occipital regions might reflect a widespread recruitment of structures involved in visual processing, which support task performance through reliance on a visual strategy. It is also the case that the three tasks included in the Number comprehension domain, i.e., Number line marking, Number comparison, and Digit comprehension, all involve, to a large extent, visuospatial processing. As a consequence, when structures supporting this type of processes are subjected to a progressively volumetric loss, this is reflected by poorer performance on tasks which heavily rely on these areas.

No significant correlations between GM volume and arithmetical tasks were found in the group of control participants. Lack of sufficient variance in the scores of controls might explain this negative result. There is, however, some recently published evidence of significant associations between GM volume and measures of performance on number/arithmetic in the right interparietal sulcus, cuneus, and temporoparietal junction (Cappelletti et al., 2012). Based on this evidence it seems that numerical abilities in MCI patients are associated with regions that are not typically associated with numerical representations. It is therefore possible that, as shown for other cognitive abilities (Gardini et al., 2013; Rodriguez-Ferreiro et al., 2012), the anatomical associations detected with the VBM correlation models reflect progressive reliance over brain structures that are less affected by AD pathology which would take over in supporting performance over time. This spreading of associations may occur over several years as a compensatory and adaptive strategy to counteract the effects of AD neurodegeneration and sustain performance. This strategy, however, might be successful only for a while, but as pathology spreads, the cognitive system becomes progressively less and less effective. Regional associations become more loosely able to sustain behavioral performance, reflecting maladaptive rather than compensatory processes. The approach used in this study, however, cannot distinguish between compensatory and maladaptive spreading of significant associations. This kind of distinction can be achieved only by examining functional and structural connections between crucial regions normally associated with numerical and arithmetic processing. Future studies should focus on these parameters in this population of patients.

The association between volumetric variance and variability of performance on complex numerical tasks used in everyday life activities are harder to interpret. Money usage in the MCI group seems to rely on the temporal lobes bilaterally. Such tasks may rely on semantic information and, possibly, imagery. Moreover, Money-usage scores positively correlate with GM volume in the left mesial frontal cortex, right superior frontal cortex and right superior temporal areas in this same group. Interestingly, significant positive correlations between Money-usage and WM volume were also found in the sub-lobar, extra nuclear area of the corpus callosum. Significant negative correlations were found between GM volume and the performance of control participants in ecological tasks. These negative correlations are likely to reflect the presence of more efficient structural networks that support performance (Grady, 2012). Thus, presumably, healthy participants who show lower levels of performance recruit larger and possibly less efficient networks, while high-performing controls recruit less widespread regions but have higher levels of computational optimization.

On the whole, these findings may reflect a deficit in processing that, in addition to other areas, involves the frontal lobes bilaterally in a task that requires coordination of disparate sources and an overload of attention where computational capacities begin to fail. This observation is in agreement with evidence found in several other studies. For instance, more intense reliance on frontal lobe activity is required in learning tasks that are unfamiliar, and when additional resources are needed to sustain the best possible level of performance in such challenging circumstances (for the anatomical correlates of math learning, see Delazer et al., 2003). However, MCI adults cannot rely on this compensatory mechanism endlessly, as their frontal lobes will ultimately end up being called into action and, then, fail.

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FIGURE CAPTIONS

Figure 1. Representative regions significantly correlated with the MCI group performance on specific NADL subtests. The image is superimposed on a standard high definition T1 template. LH=left hemisphere; R= rostral view; RH= right hemisphere; V= ventral view, C= caudal view; D=dorsal view

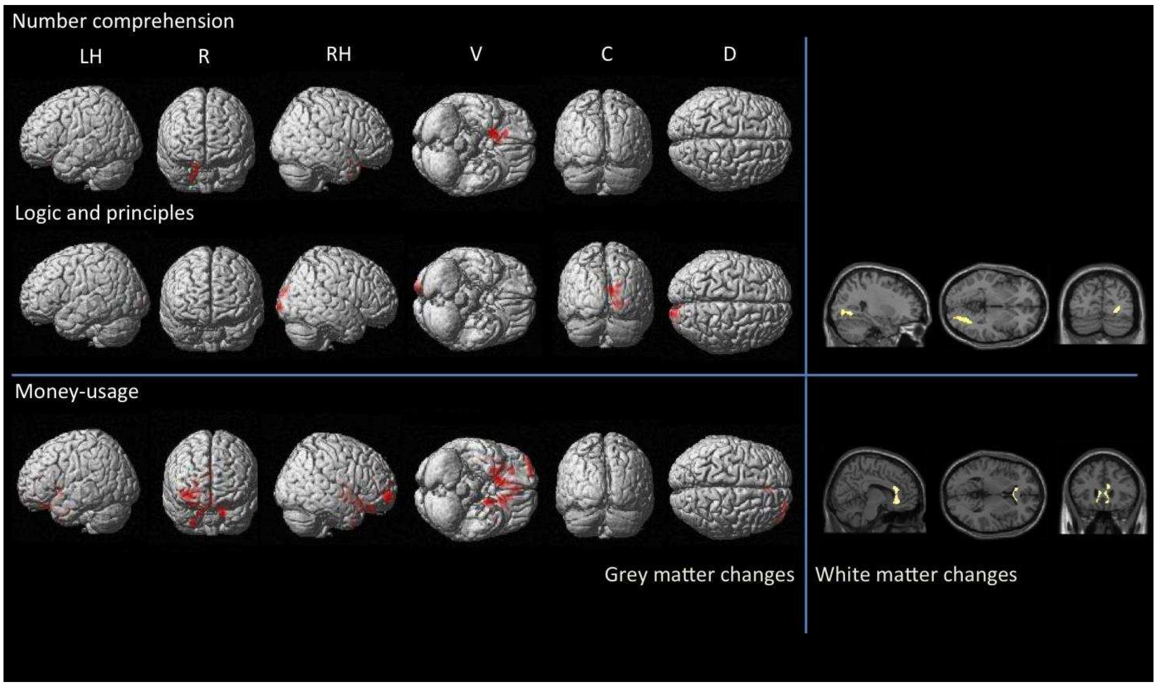
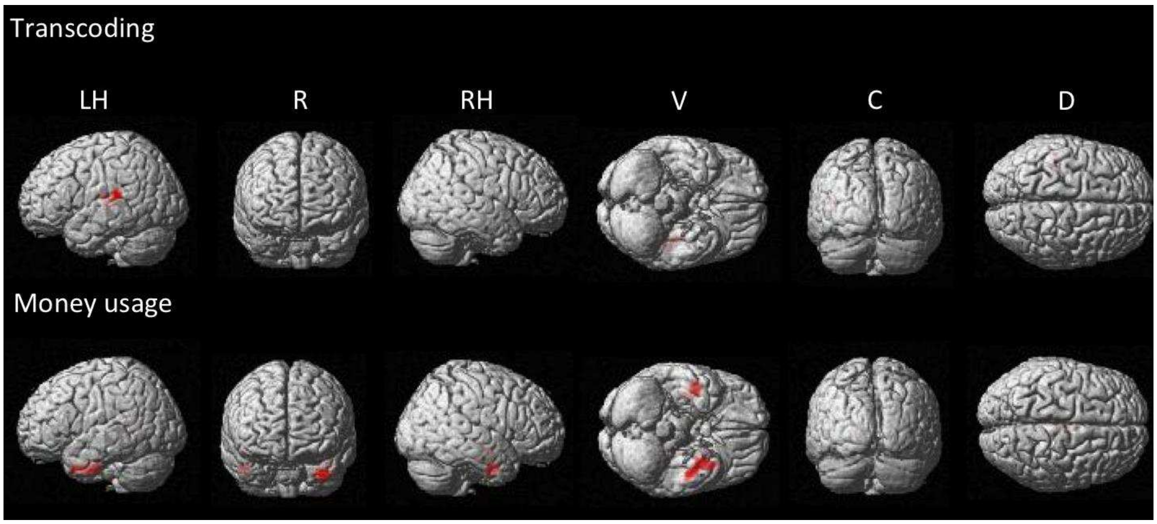


Figure 2. Representative regions evidencing significant differences and interactions between MCI patients and healthy controls. The image is superimposed on a standard render of the brain. LH=left hemisphere; R= rostral view; RH= right hemisphere; V= ventral view, C= caudal view; D=dorsal view



TABLES

Table 1. Summary of behavioral results

	Interview with patient
	Mean (SD)
	Total Score (max 10)
MCI	8.7 (1.6)
Healthy Controls	9.4 (1.0)

Informal Test of Numerical Competence in everyday contexts						
Mean (SD)						
Time estimation (max. 5)	Measure (max. 1)	Transportation (max. 1)	Communication (max. 1)	Semantic knowledge of numerical information (max. 7)	Money usage (max. 8)	Total score (max. 23)

MCI	4.0 (0.9)	0.8 (0.4)	0.6 (0.5)	0.8 (0.4)	5.6 (0.8)	6.5 (1.7)	18.4 (3.0)	
Healthy Controls	4.5 (0.7)	1.0 (0.0)	0.8 (0.4)	0.9 (0.2)	6.0 (0.8)	7.3 (0.8)	20.8 (1.5)	

	Formal Test of Numerical Abilities							
	Mean (SD)							
	Number comprehension (max. 19)	Reading Arabic Numerals (max. 5)	Writing Arabic Numeral (max. 5)	Mental Calculation (max. 18)	Knowledge of Calculation rules (max.7)	Logic and Principles (max. 8)	Written operations (max. 17)	Total score (max. 79)
MCI	16.8 (1.6)	4.4 (0.6)	4.6 (0.5)	16.2 (2.1)	5.5 (1.2)	4.7 (2.1)	12.6 (4.0)	64.9 (9.3)
Healthy Controls	17.8 (1.1)	4.8 (0.4)	4.9 (0.3)	17.2 (1.0)	6.1 (1.1)	6.5 (1.4)	14.8 (2.1)	72.2 (4.8)

Table 2. Predictors of Performance on NADL domains of Participants with Mild Cognitive Impairment

NADL tests	Predictor	Coefficient of determination	p-value
Informal Assessment General Score	Language	1.361	0.013
	Visuo-spatial abilities	0.767	< 0.001
Time estimation	Long-term memory	0.466	< 0.001
		0.377	0.002
Money usage	Visuo-spatial abilities		
	Abstract reasoning	0.732	0.012
Formal Assessment General Score	Executive functions	5.638	0.020
	Visuo-spatial abilities	1.563	0.007
	Abstract reasoning	4.528	< 0.001
		0.597	< 0.001
Number comprehension	Visuo-spatial abilities		
Transcoding	Language	0.557	< 0.001
Logic and principles	Abstract reasoning	2.519	< 0.001

Written operations	Executive functions and attention	3.304	0.007
	Visuo-spatial abilities	0.551	0.049
	Abstract reasoning	1.362	0.033

Table 3. Correlations between GM and WM volume, and NADL scores

	Group	Matter	Correlation	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at Cluster level	*Z* value at local maximum	Talairach coordinates			Brain region (Brodmann's area)
								x	*y*	*z*	
Informal test of Numerical Competence											
Money usage	MCI	GM	Positive	1031	< 0.001	< 0.001	4.38	28	6	-37	Right superior temporal gyrus (BA 32)
	MCI	GM	Positive	306	0.001	0.013	4.05	30	58	-10	Right superior frontal gyrus (BA 10)
	MCI	GM	Positive	446	< 0.001	0.002	3.98	-12	18	-19	Left medial frontal gyrus (BA 25)
	MCI	GM	Positive	199	0.006	0.067	3.58	0	38	-17	Left medial frontal gyrus (BA 11)
	MCI	WM	Positive	243	0.008	0.029	3.6	-8	25	2	Corpus Callosum
	Control	GM	Negative	3722	< 0.001	< 0.001	4.73	14	-79	9	Right occipital cuneus (BA 17)
	Control	GM	Negative	1213	< 0.001	< 0.001	4.14	-44	-14	-9	Left-temporal sub-gyral (BA21)
	Control	GM	Negative	334	0.005	0.037	4.08	-18	-48	13	Left-posterior cingulate (BA30)
Time estimation	Control	GM	Negative	507	0.001	0.008	4.14	-20	-76	30	Left-occipital precuneus (BA 31)
	Control	GM	Negative	900	< 0.001	< 0.001	4.05	8	-12	-9	Right substantia Nigra
Formal test of Numerical Abilities											
General score	MCI	GM	Positive	504	< 0.001	0.001	4.22	14	-89	15	Right middle occipital gyrus (BA 18)
Number comprehension	MCI	GM	Positive	348	0.001	0.008	4.18	18	5	-15	Right frontal-subcallosal gyrus (BA 34)

Table 4. Significant effects at the voxel-based comparison between groups

	Effect	Number of voxels per cluster	Cluster level p value (uncorrected)	FEW corrected p value at Cluster level	Z value at local maximum	Talairach coordinates			Closest GM region (Brodmann's area)
						x	y	z	
Transcoding	Greater volume in Controls than in MCI patients	335	0.007	0.044	3.94	-36	-23	10	Left insula (BA13)
					3.74	-38	-30	16	Left Superior Temporal Gyrus (BA 41)
Money Usage	Interaction:	294	0.005	0.037	3.93	6	-10	24	Right Cingulate Gyrus (BA23)
	Controls				3.67	-4	-24	33	Left Cingulate Gyrus (BA23)
	differed as a				3.17	-10	-10	28	Left Caudate Body
	function of	403	0.001	0.018	3.92	-46	-13	-30	Left Inferior Temporal Gyrus (BA20)
	their				3.82	-32	4	-30	Left Superior Temporal Gyrus (BA38)
	performance.				3.26	-40	14	-24	Left Superior Temporal Gyrus (BA38)
	MCI did not.	407	0.001	0.018	3.90	44	-9	-30	Left Inferior Temporal Gyrus (BA20)
					3.67	38	-10	-15	Right Temporal Lobe (BA20)

			3.60	40	-21	-2	Right insula (BA13)
393	0.001	0.018	3.79	-16	-45	1	Left parahippocampal Gyrus (BA30)
			3.52	-20	-37	-8	Left parahippocampal Gyrus (BA30)
			3.45	-18	-48	12	Left Posterior Cingulate (BA30)

Supplementary table

TableS1. Composite measures of the neuropsychological tests

Executive Function and Attention
Phonemic fluency (Novelli *et al.,* 1986)
Stroop (Caffarra *et al.,* 2002b)
Attentive Matrices (Spinnler & Tognoni, 1987)
Digit span backwards (Orsini *et al.,* 1987)
Language
Semantic fluency (Novelli *et al.,* 1986)
Token test (Spinnler & Tognoni 1987)
Confrontation Naming
Short-term Memory
Digit span forward (Orsini et al., 1987)
Immediate story recall (De Renzi *et al.,* 1977)
Spatial span (Orsini et al., 1987)
Long-term Memory
Delayed recall Rey Figure (Caffarra et al., 2002a)
Delayed story recall (De Renzi *et al.,* 1977)
Supraspan (Spinnler & Tognoni, 1987)
Paired associate (Novelli *et al.,* 1986)
Visuo-spatial abilities
Immediate copy Rey Figure (Caffarra *et al.,* 2002a)
Abstract reasoning
Raven Progressive Matrices (Carlesimo *et al.,* 1996)
Similarities (from Wechsler Adult Intelligence Scale)

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