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Increased functional connectivity in Default Mode Network in Mild Cognitive Impairment: a maladaptive compensatory mechanism associated with poor semantic memory performance

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Abstract

Semantic memory decline and changes of default mode network (DMN) connectivity have been reported in Mild Cognitive Impairment (MCI). Only a few studies, however, have investigated the role of changes of activity in the DMN in semantic memory in this clinical condition. The present study aimed to investigate more extensively the relationship between semantic memory impairment and DMN intrinsic connectivity in MCI. Twenty-one MCI patients and twenty-one healthy elderly controls matched for demographic variables took part in this study. All participants underwent a comprehensive semantic battery including tasks of category fluency, visual naming and naming from definition for objects, actions and famous people, word-association for early and late acquired words and reading. A subgroup of the original sample (sixteen MCI patients and twenty healthy elderly controls) were also scanned with resting state functional magnetic resonance imaging (fMRI) and DMN connectivity was estimated using a seed-based approach. Compared with healthy elderly, patients showed an extensive semantic memory decline in category fluency, visual naming, naming from definition, words-association and reading tasks. Patients presented increased DMN connectivity between the medial prefrontal regions and the posterior cingulate and between the posterior cingulate and the parahippocampus and anterior hippocampus. MCI patients also showed a significant negative correlation of medial prefrontal gyrus connectivity with parahippocampus and posterior hippocampus and visual naming performance. Our findings suggest that increasing of DMN connectivity may contribute to semantic memory deficits in MCI, specifically in visual naming. Increased DMN connectivity with posterior cingulate and medio-temporal regions seems to represent a maladaptive reorganization of brain functions in MCI, which detrimentally contributes to cognitive impairment in this clinical population.

Introduction

Although the main symptom of Mild Cognitive Impairment (MCI) is episodic memory impairment, semantic memory decline has also been described in this clinical condition [1,2,3 4] representing the earliest sign of Alzheimer's disease (AD) [5]. Semantic deficits may be more distinctive of MCI due to AD (prodromal AD) than disorders of episodic memory or other cognitive functions, because they do not normally appear in normal ageing [6] . Differently from episodic memory, attentional or spatial orientation disorders which, to a degree, are experienced by most normal ageing individuals, especially in the presence of some vascular brain burden or symptoms of depression, semantic memory remains fairly stable across the lifespan [4,7,8,9].

Semantic impairments are subtle, however, and may remain unnoticed unless probed with specific neuropsychological tasks. Typical semantic memory tasks include category fluency, picture naming, naming to definition, semantic categorization, semantic association or definition of words. MCI patients score significantly lower than healthy people on all these tasks [10].

Category fluency tasks are very sensitive to cognitive impairment in the early stages of neurodegeneration leading to dementia [11] and MCI patients usually produce significantly fewer items than healthy elderly controls for each semantic category [12,13]. Poorer performance has also been noted in action fluency tasks, that is, to say names of things that people do (e.g., to eat, to walk), and significant differences between MCI patients and controls have been reported [4,14]. The same results have been observed in picture naming tasks [15,16], which can detect early cognitive impairment [10]. Naming of famous people appears to most sensitive of these tasks to detect semantic memory impairment in MCI [17, 18] and the best predictor of future dementia [19, 20].

Semantic memory processes are supported by a wide network of regions in temporal and inferior parietal association cortex [21], and in medio-temporal and frontal areas [3,22] involving both modality-specific sensory, motor, and emotion systems and large brain regions which are not

modality-specific. In line with recent semantic memory neurobiological models [21], modality-specific systems project to high-level temporal and inferior parietal structures involved in the storage of abstract representations of entity and events. Prefrontal structures would control the selection of information stored in temporo-parietal regions, whereas the posterior cingulate and precuneus would mediate between the semantic network and the hippocampal memory system, encoding meaningful events into episodic memory. Many of these regions involved in semantic memory operations are also part of the Default Mode Network (DMN) of the brain. The DMN structures are interconnected and organized around two main hubs, i.e. the posterior cingulate cortex (PCC) and the ventromedial prefrontal cortex (vMPFC), regions that have the highest number of connections with the rest of the network [23].

Although DMN changes have been reported in patients with MCI [24,25,26], to our knowledge, only few studies have investigated the relationship between semantic memory performance and functional connectivity within the DMN in healthy [27] and in MCI participants [28]. Wirth and colleagues [27] examined the spatial and functional convergence of DMN connectivity with semantic, phonological and perceptual decision tasks and found less deactivation with scores on the semantic task than on the other two tasks for the entire DMN and within the DMN regions in the left hemispheric. The evidence from this study indicates that areas of the DMN are involved in semantic memory processes with an observed overlap between DMN structures and those activated during a semantic memory task. Dong et al. [28] found lower functional connectivity within the DMN in the inferior parietal lobule and left angular gyrus in MCI, in comparison with a control group. These authors speculated that this lower level of functional connectivity manifests phenotypically with semantic memory deficits in a verbal fluency task.

The DMN connectivity can support different cognitive processes and clinical studies have shown alterations of DMN connectivity in several diseases, such as schizophrenia [29], obsessive-compulsive disorder [30], autism [31], depression [32] and Alzheimer's disease [33]. Altered DMN

connectivity has also been detected in normal aging [34]. Usually structures of the DMN are deactivated during the execution of a goal-directed task in the young population, whereas in older people lack or diminished deactivation was observed during fMRI activation studies [34]. Abnormal deactivation of structures within the DMN manifests itself with increased DMN connectivity and might be associated with poorer cognitive performance, high levels of distraction by irrelevant information and an allocation of resources not adequate for the task [35,36]. In pathological aging, abnormal DMN connectivity has been reported both in MCI and in AD, resulting in a modification of the topological architecture of distributed large-scale brain networks [26] and pathological cognitive performance [26,37]. In AD the posterior areas of the DMN, i.e. posterior cingulate and precuneus, show reduced connectivity and lack of deactivation during cognitive tasks even in the early phases of the disease [25,33]. Beta amyloid deposition in these regions of the brain is particularly high in AD, and this may relate to the high metabolic consumption and functioning of these regions, which make them particularly vulnerable to the effects of AD neurodegeneration [25]. In MCI, similarly to AD, an alteration of DMN connectivity in the posterior cingulate and ventro-medial pre-frontal cortex has also been reported [25]. MCI is associated with alteration of connectivity in the posterior part of the DMN, a set of regions connected with the medial temporal lobes, which support memory processes; and this disruption increases with disease progression [24]. This latter evidence suggests that abnormality in DMN connectivity might be an early and suitable neuroimaging marker of initial neurodegeneration [25,26].

The present study aimed to investigate extensively the relationship between semantic memory deficits and DMN connectivity changes in MCI, suggesting that functional connectivity alterations in this network might negatively impact on semantic memory processing in this condition.

Materials and Methods

Participants

Twenty-one MCI patients [13 males, 8 females; mean age 70.62 (SD = 4.66); mean education 9.19 (SD = 4.83)], and twenty-one healthy elderly controls [7 males, 14 females; mean age 69.75 (SD = 6.45); mean education 11.74 (SD = 5.08)] took part in this study. The two groups did not differ in age ($t_{(1, 40)} = -.496$, $p = 0.622$), education ($t_{(1, 40)} = 1.623$, $p = 0.113$) or gender (χ^2 test = 3.436, $p = 0.064$).

MCI patients were diagnosed following the Petersen's criteria [38] and divided in amnestic MCI (N=14) presenting an isolated memory impairment without involvement of other cognitive functions, such as language, attention, praxis, visuo-spatial and executive functions; multi-domain MCI (N=4) presenting memory decline plus impairment in some other cognitive functions and non-amnestic MCI (N=3) who had spared memory and pathological performance in some other cognitive domains. All MCI patients had a Mini-Mental State Examination (MMSE) [39] score higher than 24/30, full preservation of daily living functional activities, and no other neurological or psychiatric pathologies, nor any vascular or other clinical condition that could account for their memory decline.

The healthy elderly controls were recruited amongst the relatives of Staff at the Memory Clinic and amongst caregivers and patients' relatives. Healthy elderly controls had to meet the following criteria: no history of past or current psychiatric or neurological disorders; MMSE score higher than 27; absence of neuropsychological, functional, neurological or brain alterations; good general health.

The present study received ethical approval from the University and Health Board joint Ethics Committee of Parma, Italy. All participants were provided with details of the study, all understood its aims and gave their written informed consent before taking part in the study.

Procedure

All participants were administered an extensive multi-task semantic memory battery including category fluency, picture naming, naming from definition, word-association and word reading of three different types of item, i.e. objects, actions and famous people. A subgroup of sixteen MCI patients and twenty healthy elderly controls also participated in a scanning session during which resting state functional MRI scans were acquired.

Semantic memory battery.

Further details on the administration and scoring of the semantic memory tests are also available in Gardini et al. [4]. Five types of task were used: semantic fluency and word-association tasks, followed by confrontation naming tasks, naming from definition tasks and reading tasks.

The semantic fluency task included seven trials and required participants to retrieve exemplars from seven semantic categories, namely animals, fruits, tools, furniture, singers, politicians and actions. Once the experimenter named the semantic category, participants had sixty seconds to recall as many exemplars as they could remember from that category within the given time. The word-association tasks required participants to produce as many word-association as possible for either early or late acquired target words. Twelve words with an early Age of Acquisition (AoA) and twelve words with a late AoA were presented, one at a time, and participants had thirty seconds to produce, in two separate sessions, all verbs and nouns they could remember associated with the target word. The early and late AoA words were selected randomly from the database of Burani et al. [40]. The order of administration of the semantic fluency and word-association tasks, semantic categories for the semantic fluency task, types of words to be produced (nouns or verbs) and stimuli (with late or early AoA) in the word-association tasks were counterbalanced across participants.

A computerized paradigm was devised to administer the confrontation naming, naming from definition and reading tasks using Sun Java Swing (http://marchi.ricerca.di.unimi.it/elprimo/).

The confrontation naming task required participants to name objects, actions and famous people presented as colour images displayed on a computer screen. Objects included tools, animals, vegetables and items of daily use. Famous people stimuli were selected from the database provided by Rizzo et al. [41]. All famous people had high familiarity rates. Verbs consisted of frequent every-day life actions, such as running, cooking and dancing. In the experimental paradigm, as soon as the image appeared on screen, participants had to say aloud the name of the stimulus. If he/she failed, a screen containing four written alternatives (the target and three distractors) was presented and the participant had to select their answer amongst the alternatives. The same examiner recorded the participant's individual responses using a dedicated external keyboard. This mode of recording responses was chosen to minimize the number of errors made by patients due to incorrect key selection rather than inappropriate choice. Two stimuli were administered as examples and then thirty stimuli were presented as experimental stimuli. The scoring system assigned a score of 2 to each correct immediate recall when participants reported the correct answer after stimulus onset promptly; a score of 1 was given to a correct response following a cue and 0 for errors. A global naming score and a total score for each category was calculated.

The naming from definition task provided participants with a verbal definition for each object, action and famous person. Participants had to say the appropriate common or proper name matching the definition. Similarly to the confrontation naming task, in case of wrong response, a further screen providing four alternatives was presented and the participant had to choose amongst these. The same stimuli and scoring system of the confrontation naming tasks were used. A total naming from definition score as well as individual scores for each category were calculated. The order of administration of the confrontation naming and naming from definition tasks, and the order of the semantic categories in each task was counterbalanced across participants.

The final task was a test of reading including the same stimuli presented in the confrontation naming and naming from definition tasks. Each stimulus appeared sequentially on screen one at a time. Using the external keyboard the experimenter inputted the participants' responses. A score of 1 was given to correct readings and 0 to those items read incorrectly. A total reading score and individual scores for each category were calculated.

Semantic memory analyses.

Multivariate ANOVAs were carried out to identify significant differences between MCI patients and healthy elderly controls: semantic scores were entered as within-subjects factors and group (MCI and healthy controls) as between-subjects factor. Analyses were carried out using the SPSS software (version 20).

Functional Imaging Acquisition.

MRI data were acquired on a General Electric 3T MR 750 scanner with an 8-channel phased array receiver head coil at the University of Parma, Italy. Two hundred and fifty BOLD T2*-weighted images were acquired using echo-planar imaging. Each functional image consisted of 38 2.9mm thick axial slices with 0.5 mm interslice gap acquired sequentially and covering the entire brain (TR=2000 ms; TE=30 ms; field-of-view=205 mm; flip-angle=90°; matrix=64x64; acceleration factor 2). For resting state imaging, scanning was carried out in darkness, and the participants were instructed to relax without falling asleep, to keep their eyes closed, not to think about anything special and to move as little as possible. The scanning procedure did not involve any experimental tasks prior or after the resting-state scan, nor were participants asked to perform any cognitive tasks offline before the scan. A high-resolution three dimensional T1-weighted structural scan was also acquired after the BOLD data using a three-dimensional inversion recovery prepared

fast spoiled gradient recalled sequence (IR-prepared FSPGR) (TE=4 ms; TR=9700 ms; resolution=0.9×0.9×0.9 mm; number of slices=192).

Image Processing. All the imaging data were preprocessed using AFNI (Cox, 1996) and FSL (www.fmrib.ox.ac.uk) with the 1000 Functional Connectomes Project scripts (www.nitrc.org/projects/fcon_1000). Briefly, after discarding the first 15 volumes of the time series to account for MRI equilibration effects, all functional volumes were realigned to the mean volume using Fourier interpolation. Realigned data were skull-stripped, intensity normalized, smoothed with a 6-mm FWHM isotropic 3D Gaussian kernel, mean-intensity normalized, band-pass filtered ($0.007<f<0.1$ Hz) and linear detrended. Eventually, residuals from a multiple regression analysis on this data using 6 motion parameters, white matter, CSF, and global signal were used to estimate functional connectivity. Motion (three translations and three rotations) parameters were estimated from the realignment procedure. White matter (WM), grey matter (GM) and cerebro-spinal fluid (CSF) signals were calculated averaging the time series from voxels within each individual's segmented threshold ($p>0.80$). Each individual's high-resolution structural image was registered to the Montreal Neurological Institute 152-brain (MNI-152) template using a linear affine transformation with 12 degrees of freedom. This transformation was then applied to each individual's residual functional data with a 3-mm isotropic voxel size.

In this study, two 7.5-mm spherical seeds were centred on the coordinates of the midline hubs of the DMN as detailed in Fox et al. [42]: medial prefrontal cortex (mPFC; x=-1, y=47, z=-4), and posterior cingulate (PCC; x=-5, y=-49, z=40). The time series was extracted and averaged across all the voxels within a seed, and then correlated with the signal from each voxel of the brain, thus producing a whole-brain connectivity map for each individual and for each seed. Each connectivity map was then Z-scaled using Fisher's r-to-z transformation.

Each participant's Z-scaled connectivity maps for each seed were entered into SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk) and analysed separately using second level random-effects analyses. For each diagnostic group, the spatial extent of each seed connectivity was determined using a one sample t-tests. Eventually two sample t-tests were used to compare connectivity across diagnostic groups for each seed. Brain-behaviour relationship with the semantic battery indexes was assessed using simple correlations. Significant clusters were identified using an uncorrected voxel-wise threshold of $p<0.005$ and small volume corrected for multiple comparisons with alpha=0.05 (family wise error correction at the voxel level) for the PCC, mPFC and the hippocampus as identified using WFU pick atlas (http://fmri.wfubmc.edu/software/PickAtlas). All coordinates are reported (following appropriate conversion) in Talairach space.

Results

Semantic memory results

Compared with healthy elderly, MCI patients showed significantly lower scores in several semantic memory tasks with some different effects across semantic tasks and conceptual categories of actions, objects and famous people (see Table 1). Bonferroni correction for multiple comparisons was applied to all statistical analyses.

- Insert Table 1 about here -

Semantic fluency was impaired in the MCI group: the total semantic fluency score of the patients and the individual scores for each semantic category, except for the tools category, were statistically lower than those of controls.

The MCI group produced fewer word associations (nouns and verbs) both in reference to early and late acquired words. Patients obtained lower scores in the total word-association tasks, verbs and nouns associated with early and late acquired words, when considered separately or collectively.

The total confrontation naming score and the confrontation naming score for each conceptual category of objects, actions and famous people were significantly lower in MCI patients than controls, but the difference was greater for famous people. Patients achieved fewer correct free and immediate recalls for all categories. They had a higher number of correct responses with cue for objects and famous people. Finally, MCIs made more errors than controls, giving more wrong responses with cues, but only in the famous people naming test.

In the naming from definition task, the MCI group had a lower total score and again performed worse in the naming from definition of famous people. Patients made more errors for the objects and famous people categories than controls.

Analysis of the scores obtained on the reading task indicated that the MCI group had a significantly worse performance in the total reading score and in the score achieved in the subtest requiring the reading of names of famous people.

Functional Imaging results.

Group comparison showed that patients had increased functional connectivity between the medial prefrontal cortex (mPFC) and the bilateral posterior cingulate (PCC) (BA 29/30), and between the PCC and the right parahippocampus and anterior hippocampus (BA 36), than healthy elderly (see Figure 1, Figure 2 and Table 2).

- Insert Figures 1 and 2 and Table 2 about here -

The correlations between functional connectivity and semantic battery indexes showed that patients presented a significant negative correlation of mPFC connectivity with left parahippocampus and posterior hippocampus (BA 27) and total scores on the visual naming task (see Figure 3 and Table 3).

- Insert Figure 3 and Table 3 about here -

General Discussion

MCI patients showed a significant extensive failure in semantic memory performance compared with healthy elderly controls, suggesting a general degeneration of semantic memory processing. In some tasks, such as semantic fluency and visual naming, there was poorer performance, and a differential effect related to the type of semantic category of objects, actions and famous people. Patients performed worse in semantic fluency in all categories except tools, and produced fewer word-associations of nouns and verbs, both for early and late acquired words. In the confrontation naming task, the MCI patients obtained lower total scores and correct immediate recalls for all categories of objects, actions and famous people. Moreover, patients had a higher number of correct responses with cue for objects and famous people and they made more errors, i.e. wrong answers with cues, than healthy controls only in the famous people naming test. In the naming from definition task, the MCI group had a lower total score and performed worse than controls in the naming from definition of famous people. Patients made more errors than controls for the objects and famous people categories. The MCI patients also performed worse than controls in the total reading task and when reading famous people's names. The fMRI results showed increased functional connectivity between the medial prefrontal cortex (mPFC) and the posterior cingulate (PCC) (BA 29/30), and between the PCC and the parahippocampus and anterior hippocampus (BA 36) in MCI patients. Patients also showed a significant negative correlation of

mPFC connectivity with parahippocampus and posterior hippocampus (BA 27) and total scores on the visual naming task.

Our data are in line with previous studies [11-14] and confirm the decline of semantic memory in MCI using an extensive multi-task semantic memory battery [3,4,10,43]. Semantic fluency is largely impaired in MCI patients who produced significantly fewer items than healthy elderly controls in different semantic categories, including animals, fruits, singers, politicians, furniture and actions, except tools. This result highlights a reduction of semantic memory fluency that is observed across categories and might indicate a wide-spread brain degeneration causing erosion of conceptual knowledge [44].

The word-associations test revealed that MCI patients produced fewer nouns and verbs in association with both early and late acquired words. This outcome might reflect a general impoverishment of semantic memory retrieval or a degradation of semantic chunks between conceptual knowledge due to initial neurodegeneration. In line with Hodges et al. [18], semantic memory failure might be interpreted as reflecting degradation of conceptual knowledge storage which becomes manifest with limitation in word retrieval.

Confrontation naming was largely impaired in MCI patients [15], indicating an extensive impairment in the retrieval of a specific name following presentation of a visual image, both when it was an object, a representation of an action or a face of a famous person. This evidence might indicate a degradation of semantic and visuo-perceptive knowledge of these concepts or a disconnection between the buffer of storage of this semantic knowledge and the language systems, reflecting either a problem in access to this knowledge or a language deficit. Our data indicate that for actions and objects, once the cue was provided, the patients answered correctly, whereas for famous people, even when the cue was presented after a missing or wrong answer, patients' performance showed no improvement. These results suggest a different semantic pathway for retrieval of names for actions and objects and proper name retrieval for famous people in MCI. For

actions and objects, failure of visual naming seems to be related to a problem of access to this information, which is readily accessible once a cue (the name) is provided. Differently, for the famous people category, breakdown of visual naming appears to reflect loss of knowledge about the identity of the famous people, because patients failed to retrieve the correct identity even when the name was provided in a multiple choice setting. Impairment of visual naming for famous people seems to be related both to the different encoding and peculiarity of this type of information and to damage of selective neural regions deputed to storage of visual and semantic information related to famous people. There is evidence that common and proper names have independent representations, and that these two types of name are handled by the cognitive system as completely different entities. Semenza and Zettin [45] described a patient with a selective anomia for proper names who had spared retrieval of common names. There are of course countless numbers of cases of anomia for common names with sparing of proper name retrieval. Taken together, the evidence of a double dissociation in common/proper name retrieval suggests that these name categories are independently represented in segregated neural regions and as such can be differentially eroded by neurodegeneration as well. Name-face associations are arbitrary, as pure referring expressions and unique entities, whereas the association between common names and objects/actions is mediated by several visual cues, which can help name retrieval. From a cognitive perspective, the Bruce and Young model [46] of face recognition suggests that face recognition consists of a number of separate processing stages, starting from structural encoding to the retrieval of information stored in memory. MCI patients might experience a deficit in the final stages of the recognition process, when the incoming visual information should be compared with information stored in memory and the personal identity node retrieved. Also other clinical data have confirmed that faces are a special category of object [47] and prosopagnosia is a selective and unique, face specific problem. In a review, Gainotti [48] concluded that the loss of feeling of familiarity and of retrieval abilities for person specific information from face stimuli occurs when the right temporal lobe is damaged and

that a prevalent impairment in finding proper names is associated with selective damage to the anterior parts of the left temporal lobe. Differently, memories related to actions and objects would encompass both modal and amodal representations, which are more widely distributed in the brain [49]. Altogether, these data confirm that naming of famous people is a selective mental process and a valuable task to detect MCI [17,18].

The naming from definition task presents as a cognitive tool tapping the ability to name the correct target, such as an action, an object or a famous person, starting from its verbal definition. It includes a verbal comprehension component, which will allow access to semantic information. The present results showed that the total naming from definition score and the naming from definition of famous people were tasks more impaired in MCI than in controls, indicating a decline in the retrieval of semantic memory prompted by verbal access, and the presence of a selective impairment for famous people. Moreover, MCI made more errors, such as wrong responses when the cue was provided, for both objects and famous people, which might indicate an impoverishment of semantic memory for both categories and/or difficulty in the comprehension of verbal definitions, a problem already previously described in MCI [50].

Overall, MCI patients seem to be more impaired in retrieval of semantic memory information via visual encoding than via verbal encoding. One cognitive explanation of this effect might be that in the naming from definition task, the verbal channel used for providing the answer is already activated by the verbal definition, differently from the visual confrontation naming test in which encoding is via images and the answer is verbal. As described by Kasai et al. [51] non-verbal learning is impaired in very mild Alzheimer's disease, suggesting a degradation of visual memory. Even if Testa et al. [52], using the Boston Naming Test (BNT), found that confrontation naming does not add incremental diagnostic utility in MCI and Alzheimer's disease after delayed recall impairments were included in the model, our results suggest that confrontation naming, when assessed using multi-categorical stimuli, seems to be severely impaired in MCI. From a

neuroanatomical perspective, a more severe impairment in visual naming than in naming from verbal definition in MCI might reflect selective damage caused by early stage neurodegeneration in visual associative posterior parietal areas specifically deputed to retrieval of visual images of different conceptual entities, such as faces and objects [53,54]. An alternative explanation might be found in the down regulation of activity in posterior regions of the DMN found in AD and aging [55,56], which are involved in retrieval of visual information. The smaller impairment observed in the naming from definition task might be due to sparing of areas of the brain that support sentence comprehension. Within this framework, visual shapes of words would be recognized in left temporal visual areas, namely the *Visual Word Form* (*VWF*) area [57,58], which would trigger the retrieval of meaning, via verbal working memory processes that involve the cortex in inferior frontal regions and in the supramarginal gyrus. These anterior temporal and frontal circuits are relatively spared in the initial phase of AD neurodegeneration [59].

Finally, reading abilities were poorer in MCI patients than in controls and a decline of total score and a selective impairment of reading of famous people's names was observed. These results are in agreement with studies that have previously shown impairment of reading abilities in Mild Cognitive Impairment and Alzheimer's Disease [60].

Overall, the present neuropsychological findings confirmed that semantic memory is impaired in MCI and tasks tapping this cognitive function, especially confrontation naming and semantic fluency, represent valid and sensitive cognitive assessment tools for the early detection of subtle pathological cognitive decline.

The neuroimaging results showed increased functional connectivity between the medial prefrontal cortex (mPFC) and the posterior cingulate (PCC) (BA 29/30), and between the PCC and the parahippocampus and anterior hippocampus (BA 36) in MCI patients. Moreover, patients also showed a significant negative correlation of mPFC connectivity with parahippocampus and posterior hippocampus (BA 27) and the total score on the visual naming task.

These results suggest an aberrant function of the DMN in MCI, which might be the response to neuronal loss in this initial phase of neurodegeneration. Increased functional connectivity between the posterior cingulate, and the parahippocampus and anterior hippocampus in MCI patients may reflect a maladaptive mechanism. This mechanism would represent the damaged brain's attempt to cope with regional atrophy/amyloid deposition in the hippocampal complex, in the transition from healthy neuroplastic compensatory mechanisms (as observed in ageing) to maladaptive processes (as those seen in this prodromal mild cognitive impairment stage of AD). Hippocampal activation increases in MCI and subsequently decreases with disease progression [61], would reflect the transition from maladaptive processes to sustain residual function to loss of function in established AD. Derangement of medio-temporal function is the first neuroanatomical correlates of initial AD neurodegeneration in MCI, which can start a cascade of aberrant neuro-functional alterations in posterior cingulate and medial prefrontal cortex [62].

Age-related changes in DMN manifest as linear increases of activity with age in areas normally deactivated during task performance in medial frontal and parietal regions, and a lower level of activation in dorsolateral prefrontal cortex in response to a task [34,35]. This mechanism has been defined as an alteration in the balance between default-mode and task-related activity, and it has been interpreted as a compensatory process or a deficit in cognitive control with deficient resource allocation [36]. Deactivation of these brain regions at rest is even more severely reduced in MCI patients and AD [33]. The increased connectivity between the frontal, medio-temporal and posterior cingulate regions, found in this study in MCI might reflect lower levels of deactivation in these areas at rest. Increased DMN connectivity in the anterior hub and between the posterior cingulate and medio-temporal lobe might be interpreted as a way by which the brain reacts to and potentially adapt, in a detrimental way, to damage generated by neurodegeneration [62]. These areas may lose functional specificity as a result of neurodegeneration and therefore be functionally active even when they should be off, eventually causing disadvantageous and damaging effects on

brain function. A loss of deactivation might have a detrimental effect on cortical connections and on neuronal systems, representing a pathological threshold of cerebral activity.

Different studies have revealed that there are both consistencies and discrepancies in DMN changes in MCI, possibly due to methodological differences and/or clinical heterogeneity among MCI patients [63]. In agreement with Jin et al. [64] and Qi et al. [62] who found increased connectivity in the anterior mPFC hub of the DMN.

Brain-function correlation showed a negative relationship between medial prefrontal cortex connectivity and parahippocampus, posterior hippocampus and total scores on the visual naming task. This finding might indicate an alteration of functional synchronicity between concept centres in frontal cortex and retrieval mechanisms in mediotemporal cortex which interferes with behavioural performance. This malfunctioning in DMN connectivity, therefore, manifests phenotypically as decreased performance in visual naming, indicating that alteration in brain DMN activity is a maladaptive process resulting in cognitive impoverishment. Previous studies have shown that lack of deactivation/increased connectivity of the DMN is associated with poorer cognitive performance [34], higher distraction by irrelevant information and an allocation of resources not adequate for the task [35,36].

The diverse neurofunctional pattern observed between normal aging and MCI in this study might reflect the differentiation previously suggested between neuroplastic compensatory mechanisms which happen in normal aging and maladaptive neuroplastic changes that take place in prodromal AD [65,66]. Furthermore, the absence of an association between posterior cingulate connectivity and semantic memory might be due to functional connectivity variations of this region in MCI [67] (Han et al., 2012).

Altogether the present cognitive and neurofunctional results support different main points: 1. Semantic memory processes are impaired in the early phase of MCI, representing valid neuropsychological markers; 2. Within the DMN there is an aberrant increase in connectivity in

medial prefrontal (mPFC), posterior cingulate and medio-temporal regions in MCI patients; 3. Increased mPFC connectivity with the hippocampal complex is associated negatively with performance in visual naming, suggesting a detrimental role of increased DMN connectivity in MCI.

The present study found a significant alteration of the intrinsic architecture of a large-scale brain system, i.e. the DMN, in MCI. In line with previous data [62], we suggest that amnestic MCI might recruit alternative networks and develop novel cortical connections to compensate for the loss of cognitive functions and memory deficits generated by medio-temporal derangement.

The limited number of participants involved in this study and the lack of longitudinal data, however, weaken the generalizability of these findings. Studies with bigger numbers of participants would be necessary to establish the role of the DMN changes in AD neurodegeneration, in the prediction of evolution to dementia in MCI, and to clarify the relationship between DMN connectivity alterations and performance in other cognitive domains in MCI due to AD.

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Table 1. Mean (and SD) scores obtained by MCI patients and healthy elderly controls on the semantic tasks (* significant between group differences)

	Means (SD)		
Cognitive Tests	***Controls***	***MCI***	***p values***
Semantic Fluency			
Total score	84.62 (13.65)	63.29 (17.21)	0.0001 *
Animals fluency	17.52 (3.86)	13.38 (3.76)	0.001 *
Fruits fluency	13.86 (3.78)	10.95 (2.99)	0.009 *
Singers fluency	9.10 (3.76)	5.81 (3.90)	0.008 *
Politicians fluency	8.10 (2.96)	5.10 (3.78)	0.007 *
Tools fluency	10.05 (2.87)	8.33 (2.97)	0.065
Furniture fluency	11.52 (1.86)	9.19 (1.91)	0.0001 *
Actions fluency	14.48 (4.50)	10.52 (4.57)	0.007 *
Words Associations			
Total score	122.57 (43.34)	82.86 (39.89)	0.004 *
Verbs associated with early AoA words	23.48 (12.29)	13.76 (9.20)	0.006 *
Verbs associated with late AoA words	25.19 (10.55)	16.19 (12.14)	0.014 *
Nouns associated with early AoA words	33.81 (11.82)	23.48 (10.65)	0.005 *
Nouns associated with late AoA words	40.10 (12.45)	29.43 (10.84)	0.005 *
Total associations to early AoA words	57.29 (23.09)	37.24 (19.17)	0.004 *
Total associations to late AoA words	65.29 (21.29)	45.62 (21.65)	0.005 *
Confrontation Naming			
Total correct responses	164.19 (11.23)	147.86 (13.429)	0.0001 *
Actions - Total correct responses	57.43 (3.15)	55.43 (3.12)	0.046 *
Actions - Correct immediate recall	27.81 (2.42)	26.29 (2.30)	0.043 *
Actions - Correct responses with cue	1.81 (1.91)	2.86 (2.08)	0.097
Actions - Wrong responses with cue	0.38 (0.97)	0.86 (1.31)	0.190
Objects - Total correct responses	58.33 (2.11)	55.57 (4.01)	0.008 *
Objects - Correct immediate recall	28.62 (1.69)	26.19 (3.26)	0.004 *
Objects - Correct responses with cue	1.10 (1.45)	3.19 (2.89)	0.005 *
Objects - Wrong responses with cue	0.29 (0.64)	0.62 (1.24)	0.282
Famous People - Total correct responses	48.43 (8.63)	36.86 (10.12)	0.0001 *
Famous People - Correct immediate recall	19.86 (7.40)	11.62 (5.45)	0.0001 *
Famous People - Correct responses with cue	8.71 (6.51)	13.62 (5.12)	0.010 *
Famous People - Wrong responses with cue	1.43 (1.91)	4.76 (5.88)	0.018 *
Naming from definition task			
Total correct responses	150.67 (16.39)	136.52 (22.48)	0.025 *
Actions - Total correct responses	55.86 (3.86)	53.52 (4.73)	0.088
Actions - Correct immediate recall	26.10 (3.63)	24.10 (4.26)	0.110
Actions - Correct responses with cue	3.67 (3.46)	5.33 (3.94)	0.154
Actions - Wrong responses with cue	0.24 (0.54)	0.57 (0.87)	0.143
Objects - Total correct responses	50.71 (5.71)	46.52 (7.78)	0.054
Objects - Correct immediate recall	22.14 (4.33)	19.19 (5.96)	0.074
Objects - Correct responses with cue	6.43 (3.25)	8.14 (4.47)	0.163
Objects - Wrong responses with cue	1.43 (1.69)	2.67 (2.17)	0.046 *
Famous People - Total correct responses	44.10 (9.41)	36.48 (13.54)	0.040 *
Famous People - Correct immediate recall	16.29 (7.76)	12.10 (8.57)	0.105
Famous People - Correct responses with cue	11.52 (6.33)	12.29 (5.85)	0.668
Famous People - Wrong responses with cue	2.19 (2.01)	5.62 (5.94)	0.017 *
Reading			
Total correct answers	89.00 (1.26)	86.00 (4.84)	0.009 *
Actions - Total correct answers	29.76 (0.44)	29.19 (1.33)	0.068
Objects - Total correct answers	29.86 (0.48)	29.38 (1.02)	0.061
Famous People - Total correct answers	29.38 (0.74)	27.43 (3.20)	0.010 *

Table 2. Brain areas that showed significant increased DMN connectivity in MCI versus healthy elderly controls with a) the medial prefrontal cortex; b) the posterior cingulate.

Brain area	Left/Right	Brodmann area (BA)	Z value at local maximum	Talairach coordinates		
				x	y	z
a)						
Posterior Cingulate	L	29	3.83	-3	-39	6
	R	30	3.31	3	-42	6
b)						
Parahippocampal gyrus/anterior hippocampus	R	36	3.85	39	-18	-24

Table 3. Brain areas that showed a significant negative correlation between the Medial Prefrontal Cortex connectivity and visual naming total scores.

Brain area	Left/Right	Brodmann area (BA)	Z value at local maximum	Talairach coordinates		
				x	y	z
Parahippocampal gyrus/posterior hippocampus	L	27	4.02	-15	-30	-3

Figure 1. Areas of significant increased DMN connectivity between the mPFC and the PCC (BA 29/30) in MCI patients when compared with healthy elderly.

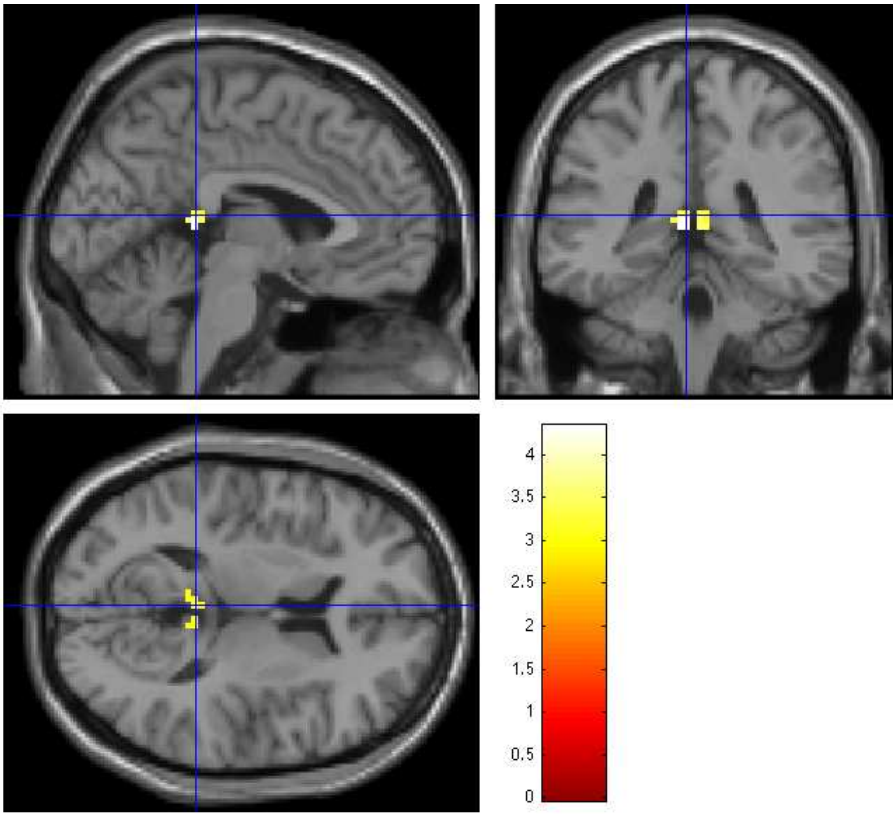


Figure 2. Areas of significant increased DMN connectivity between the PCC and the parahippocampus (BA 36) in MCI patients when compared with healthy elderly.

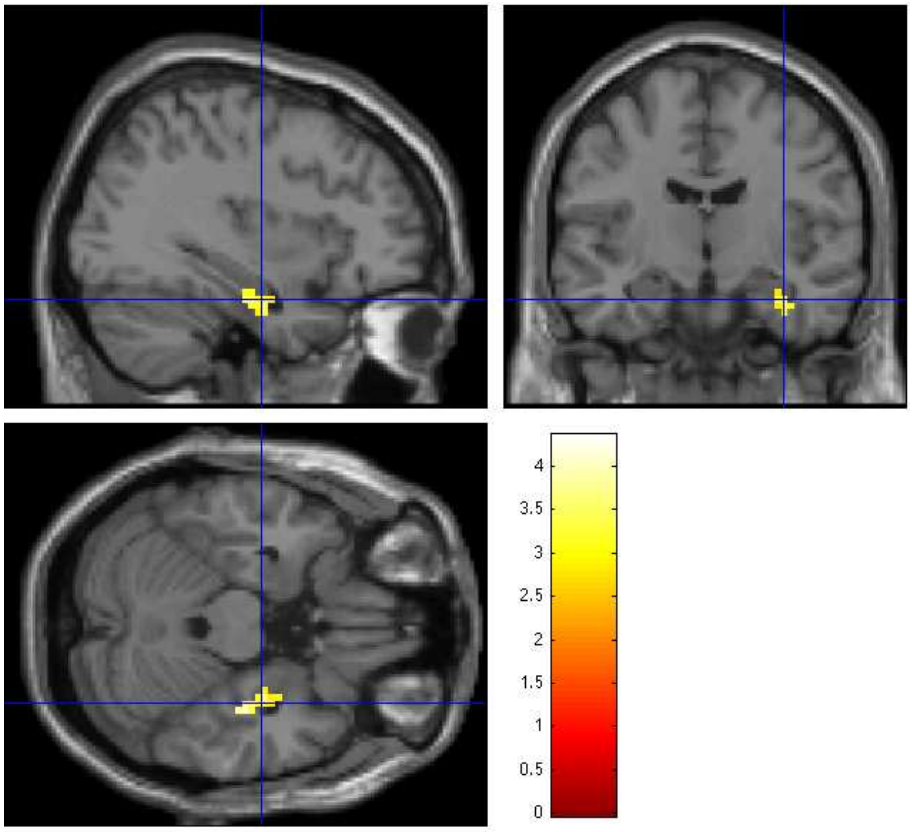


Figure 3. a) Areas of significant negative correlation of mPFC connectivity with parahippocampus and posterior hippocampus (BA 27) and total scores on the visual naming task; **b)** The negative correlation between the hippocampal formation (HF) and medial prefrontal cortex connectivity and the total visual naming score.

Figure 3a

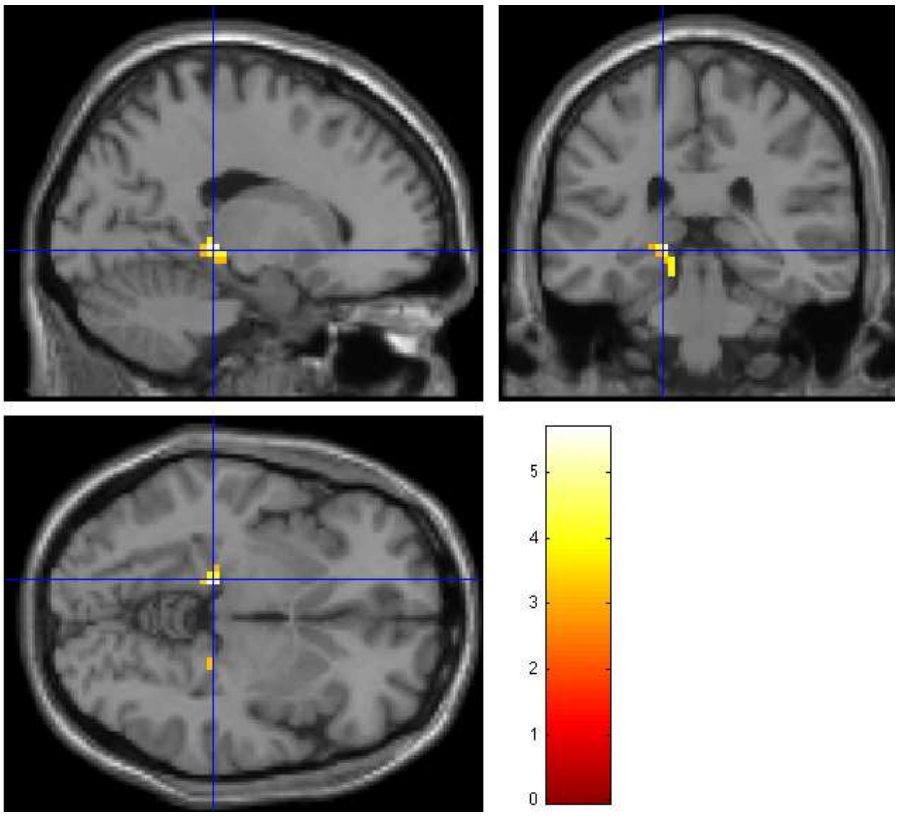
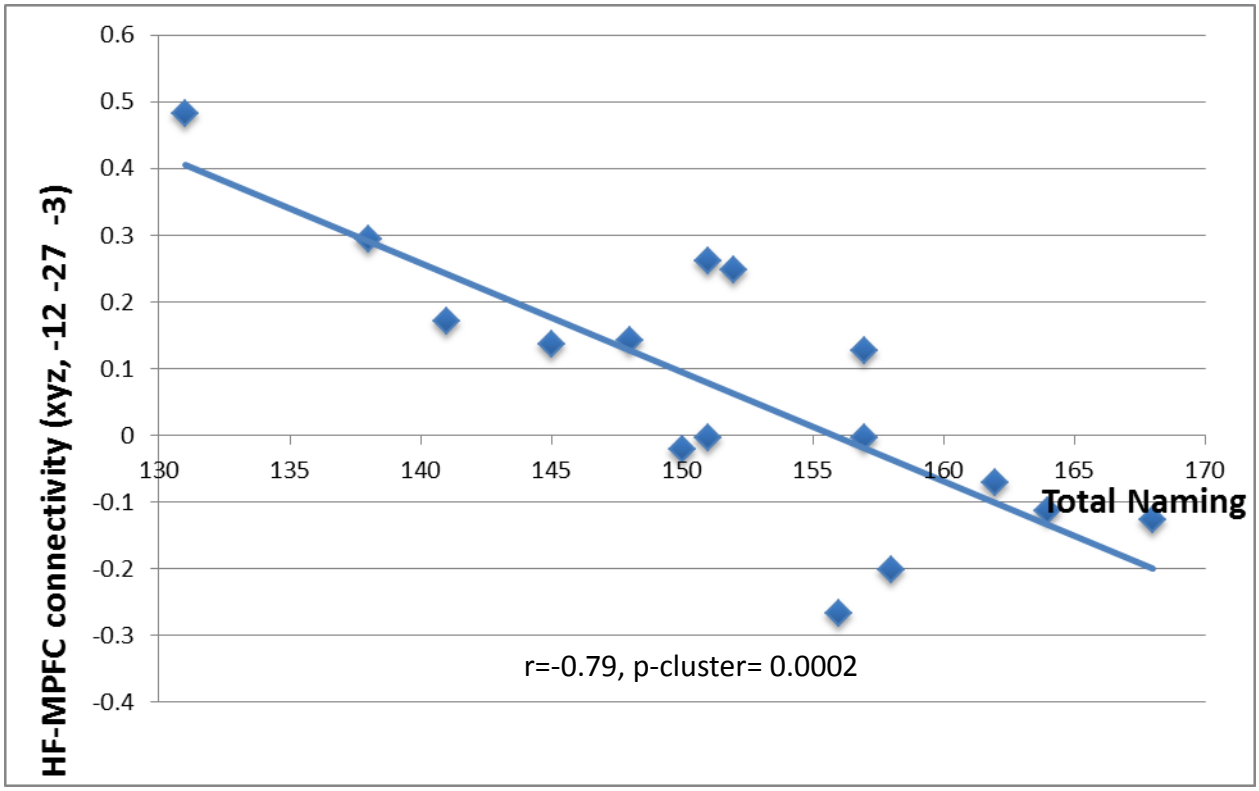


Figure 3b.


0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
130
135
140
145
150
155
160
165
170
HF-MPFC connectivity (xyz, -12 -27 -3)
Total Naming
r=-0.79, p-cluster= 0.0002