Establishing the relationship between cortical atrophy and semantic deficits in Alzheimer's disease and Mild Cognitive Impairment patients through Voxel-Based Morphometry

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Abstract

The aim of this study was to determine the brain areas responsible for the semantic impairment observed in Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) patients. Thirteen AD, 14 MCI patients, and 13 matched healthy older adults were assessed with a test battery aimed to study their semantic competence. Different subtasks were designed to study their semantic knowledge related to objects and faces in the context of semantic retrieval- and semantic association-dependent tasks. Aggregate scores obtained in the different tests were entered into voxel-based regression analyses with grey matter volume values obtained from three-dimensional brain MRI scans. Areas of significant correlation between volume loss and poor semantic scores were restricted to the temporal lobe in the AD group, while in the MCI and control groups significant associations were found with lower grey matter volume values in a widely distributed network of bilateral fronto-temporo-parietal regions. Our results suggest that degradation of partially overlapping and widely distributed neural networks, mainly including temporal regions, subserve semantic deficits related to objects and faces in AD and MCI patients.

1. Introduction

The brain atrophy that occurs in aging, and especially in pathological aging, involves loss of the cognitive functions dependent on that tissue. In Alzheimer's disease (AD), the most common and best known of the neurodegenerative dementias, the earliest symptoms concern episodic memory, particularly difficulties in new learning (Fox, Warrington, Seiffer, Agnew, & Rossor, 1998). This is unsurprising given the well established connection between anterograde amnesia and the hippocampus and entorhinal cortex which are seriously affected in AD even in its early development (Braak & Braak, 1991).

However, recent findings have shown that not only episodic memory but also semantic memory, i.e. knowledge about the world, facts, concepts and beliefs, deteriorates in the early stages of the disease (Albert, Moss, Tanzi, & Jones, 2001; Dudas, Clague, Thompson, Graham, & Hodges, 2005). Alterations in semantic memory manifest in these patients as difficulties in tasks like naming (Rodríguez-Ferreiro, Davies, González-Nosti, Barbón, & Cuetos, 2009) or semantic fluency (Cuetos, Martínez, Martínez, Izura, & Ellis, 2003; Venneri et al., 2008). These difficulties are more dramatic in the case of memory for public events or people, information that is shared by all members of a culture, as shown by the evidence of poor performance in tasks that involve famous people naming (Cuetos, Rodriguez-Ferreiro, & Menéndez, 2009; Green & Hodges, 1996). Moreover, even in the asymptomatic stage of the familiar form of Alzheimer's disease, carriers of the E280 mutation in the Presenilin-1 gene had significantly lower scores than non-carriers on tasks requiring famous people naming (Arango-Lasprilla, Cuetos, Valencia, Uribe, & Lopera, 2007).

In mild cognitive impairment (MCI), a condition that is often considered a transitional stage between normal aging and dementia, deficits in semantic memory have also been found (Cuetos, et al., 2009). Several studies have reported that the performance of MCI patients in typically semantic tasks, such as picture naming, semantic fluency or semantic association, is severely affected (Duong, Whitehead, Hanratty, & Chertkow, 2006). Similarly to what happens in AD patients, the most damaged semantic component in MCI seems to be memory for public events or people. In fact, naming of famous faces appears to be one of the tasks that best discriminates MCI patients from healthy older adults (Cuetos, et al., 2009; Dudas, et al., 2005).

From a neuro-pathological viewpoint, the finding of early alterations in semantic memory in MCI and in the early stages of AD might be unexpected since brain atrophy in these patients is said to be confined to the hippocampus and entorhinal area and it is assumed that semantic memory depends on other cortical regions, particularly on the lateral temporal gyri (Martin, Wiggs, Ungerleider, & Haxby, 1996), which, according to Braak and Braak (1991) are affected in more advanced stages of the disease. Studies carried out with neuroimaging techniques in non-demented adults have found that object naming results in activation of the inferior and middle temporal cortices (Moore & Price, 1999). For specific knowledge of people and faces, the literature indicates that the temporal pole and fusiform regions are the brain areas responsible for processing of this type of information (Gorno-Tempini et al., 1998). However, other areas like the medial frontal cortex also appear to be involved in their processing, especially in faces and names of famous persons (Gorno-Tempini, et al., 1998), and a relation between frontal lobe lesions and memory for faces has been established (Rapcsak et al., 2001).

The aim of this study was to examine the relationship between atrophied brain areas and alterations in semantic knowledge through volumetric analysis of the brains of older adults with cognitive decline, more specifically, patients suffering from MCI or AD. Some studies have shown that MCI and AD patients follow a different cognitive deterioration course. It is a well known fact that the MCI label is applied to a very heterogeneous group of patients, with some being diagnosed AD in a short period of time (Petersen et al., 2001) whereas others will never develop the disease. The question, therefore, remains to be addressed of which patterns of cortical atrophy are responsible for the performance in semantic tasks of these two populations. In order to respond to this question, a group of patients diagnosed with probable AD, a group of patients with MCI, and a matched control group were assessed. They were presented with several cognitive tasks aimed to assess the degree of semantic impairment, and to clarify whether variance in their scores on these tasks correlated with regional atrophy in areas associated with the processing of semantic information obtained from grey matter volumes extracted from three dimensional brain MRI scans.

Two versions of a test battery, including four tasks each, were designed. The two tasks that have been more discriminative in previous studies, namely picture naming and semantic fluency, were included in the battery. Furthermore, two additional semantic tasks, picture-word and word-picture matching, were also included in the study. Whereas naming and fluency tasks depend on lexical-semantic retrieval abilities,

matching tasks rely on semantic association capacities. Thus, the inclusion of these four tasks was expected to reveal a more comprehensive profile of the patients' semantic memory abilities. Moreover, given the well known dissociation between object- and face-related semantic knowledge, each of the two batteries focused on one of these two semantic domains. While one of the batteries used noun stimuli related to conceptual knowledge pertaining to objects, the other one consisted of proper noun stimuli related to public knowledge associated with famous faces. The scores obtained by each patient in these two batteries were entered into multiple regression models along with their grey matter volume segments extracted from three-dimensional high resolution brain MRI scans. Compared with healthy controls, AD patients were expected to produce significantly poorer scores in the two batteries, and their performance was presumed to be correlated with grey matter thinning in the lateral temporal cortex in the case of object-related knowledge, and probably more anterior areas in the case of knowledge related to famous people. MCI patients, on the other hand, were expected to produce scores intermediate between those obtained by AD patients and healthy older adults in the two batteries due to the early stage of their pathological condition. Given the more heterogeneous profile of grey matter degradation present in this sample, a more distributed network of cortical regions was predicted to be associated to the performance of this group.

2. Method

2.1 Participants

Thirteen probable AD patients (five males) scoring 4 in the Global Deterioration Scale (GDS: Reisberg, Ferris, de Leon, & Crook, 1982), 14 patients (twelve males) diagnosed with the amnestic variant of MCI (GDS 3) and a control group comprising 13 healthy older adults (seven males) took part in the experiment. They all were right-handed, and they came from a similar socioeconomic background. Planned t-tests ruled out significant differences (ps>.05) between the three groups on age and years of education. A summary of their demographic characteristics is presented in Table 1. All the patients were diagnosed a priori by the neurology group of the Cabueñes Hospital according to the NINCDS-ADRDA criteria (McKhann et al., 1984; Tierney et al., 1988) in the case of AD and the Petersen et al. (2001) criteria in the case of MCI. None of the participants had a history of psychiatric disorder or alcohol abuse. Other sources of cognitive

impairment such as focal lesions were ruled out by neuroimaging tests. Planned t-tests showed significant differences between the MMSE scores of the three groups (ps<.001). All participants or their relatives gave informed consent prior to their inclusion in the study and ethical approval was obtained from the hospital board where data collection was undertaken.

[INSERT TABLE 1 HERE]

2.2 Tasks

Two variants of a test battery were designed. Each of them consisted of two subtests comprising either semantic retrieval-based tasks: fluency and naming, or semantic association-dependent tasks: picture-word and word-picture matching tasks. Different lists of words and pictures corresponding to different categories of objects and famous people were selected for use in the two versions of the battery. Object stimuli consisted of 24 household items (12 kitchen tools and 12 bathroom utensils) and 24 animals (12 wild animals and 12 domestic animals). Famous face stimuli included 12 politicians, 12 singers, 12 TV presenters and 12 sportsmen. The retrieval subtest was presented first, starting with the fluency task. Then the participants were presented with the association test starting with the word-picture matching task. The order of presentation of the four tasks remained constant, while the order of presentation of the objects and people versions of the batteries, and of the stimuli within each task was counterbalanced across participants.

Retrieval subtest - Fluency. Participants were asked to produce orally as many names of members of a category as they could in one minute. For the object variant of the battery they were asked to produce names of animals and household items. In the faces variant of the battery they had to produce the proper names of politicians and sportsmen.

Retrieval subtest - Picture Naming. Participants were asked to name 48 coloured drawings of objects and 48 pictures of famous people for the object and face versions of the battery respectively.

Association subtest - Picture-Word Matching. Again, participants were presented with two separate versions of the task, one including 48 objects and the other 48 famous

people. In these tasks, a picture of the object or person was presented with the names of two semantic categories or professions written under it. Participants were asked to select the semantic category or profession to which the picture corresponded.

Association subtest - Word-Picture Matching. In these tasks, participants were asked to select which of four alternative pictures corresponded to 48 written object names or proper names of a famous person. Again, the objects and famous people were presented in two different tasks.

2.3 MRI acquisition processing and analysis

Whole-brain T1-weighted MR images were acquired using a 1.5T Signa EchoSpeed scanner (GE medical systems). A heavily T1-weighted structural 3D sequence was used to obtain high resolution images (SPGR; TR 15ms, TE 6ms, flip angle 15°, 3 NEX) with 120 sagittal sections. Matrix size was 256 x 256 x 232 with a 280mm field of view. Voxel dimensions were 1.09mm x 1.09mm x 0.80mm. In addition to this structural imaging protocol, the patients were also scanned with a FSE spin echo T2 weighted diffusion sequence and with gradient echo imaging to exclude significant vascular pathology or microbleeds, which might either interfere with the diagnosis of MCI or make the segmentation of the T1-weighted images suboptimal. The image preprocessing steps and statistical analyses were carried out using the image analysis software SPM5 (The Wellcome Trust Centre for Neuroimaging, London). Grey matter segments were obtained using unified tissue-segmentation and spatial normalization procedures (Ashburner & Friston, 2005). Then, modulated normalized grey matter images were smoothed with an 8mm FWHM Gaussian kernel in order to reduce the variability between participants. Separate regression analyses were conducted with the smoothed modulated normalised grey matter segments of each participant in the MCI and AD groups and their accuracy scores in each of the experimental batteries. Height threshold was set at $p<.001$ (uncorrected) for all analyses. Ages, gender, years of education, MMSE scores, and total intracranial volume values were included in the analyses as covariates. Significant clusters were identified by means of the non-stationarity cluster extent correction toolbox (http://fmri.wfubmc.edu/cms/NS-General) to avoid problems due to non-stationarity. Only significant clusters comprising a minimum of 5 consecutive voxels are reported. Anatomical regions were identified using the Talairach Daemon Client (http://www.talairach.org/); following conversion of

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the Montreal Neurological Institute coordinates extracted from the SPM analyses into Talairach coordinates using the GingerAle application (http://www.brainmap.org/ale/).

[INSERT TABLE 2 HERE]

3 Results

3.1 Behavioural results

A summary of the results of the three groups in the retrieval and association sbtests is presented in Table 2. Probability values of planned t-test analyses comparing the two patient groups with the control participants are also reported. The three groups of participants obtained significantly better scores in response to objects than to faces (ps<.001). Previous studies have pointed out that comparisons between tests assessing various semantic categories should take into account differences in task difficulty between items of the two categories as a possible cause of differences between the scores of the participants (Joubert et al., 2010; Lyons, Kay, Hanley, & Haslam, 2006). In order to explore this possibility, we compared the scores obtained in response to selected groups of ten items for which the control group obtained matched results in the naming task (76.4% correct responses for both objects and faces). Percentages of correct responses produced by the MCI group were 73.6% and 55.7% for objects and faces respectively, whereas AD patients produced 52.1% of correct responses in the case of objects and 22.9% in the case of faces. A repeated measures ANOVA showed significant effects of participant group (F(2,36)=77.179, p<.001), semantic domain (F(1,18)=7.311, p=.015) and the interaction of the two variables (F(2,36)=10.548, p<.0001). Planned t tests showed that significant differences appeared between faces and objects scores of the MCI (t(14.1)=-2.264, p=.04) and AD (t(18)=-17.394, p<.001) groups, but not between the scores of the control group.

[INSERT TABLE 3 HERE]

3.2 VBM Results

Areas in the cerebral cortex where grey matter volume values significantly correlated with participants' scores in the different subtests are presented in Table 3. No significant correlations were obtained in the analyses of the face retrieval scores of the control participants, nor in the object retrieval scores of the AD group. In the control participants behavioural scores were significantly correlated with grey matter volume

values in an extensive cortical system including regions in the temporal, frontal and parietal lobes bilaterally. Similarly, scores obtained by the MCI group in the objects battery were significantly associated to grey matter volume values in a widely distributed network of bilateral regions. Conversely, their scores in the faces battery correlated with regions in the fronto-temporal cortex only. Significant correlations in the AD group, on the other hand, were restricted to the temporal lobe in both the objects and faces versions of the test battery. Figure 1 shows some of the significant regions corresponding to the objects and faces versions of the association subtest for the AD and MCI groups. Figure 2 presents a graphical representation of individual correlations in the cluster of higher significance for the same subtest.

[INSERT FIGURES 1 & 2 AROUND HERE]

4. Discussion

The aim of this study was to determine the relationship between grey matter loss and semantic competence in stages of dementia and incipient cognitive deterioration. The scores of two groups of patients diagnosed with AD and MCI, and a group of matched healthy older adults obtained from two test batteries comprising objects- and faces-related semantic tasks were entered into multiple voxel-based regression analyses with cortical volume values extracted from high resolution three-dimensional brain MRI scans.

A pattern of semantic impairment similar to that shown in previous studies of AD (Albert, et al., 2001; Cuetos, et al., 2003; Dudas, et al., 2005; Venneri, et al., 2008) was also seen in our AD patients and was clearly detectable in their performance in the two batteries. The analyses showed that, compared with control participants, AD patients obtained significantly poorer scores in either the retrieval or in the association subtests. The semantic deficit of the MCI participants was evidenced by their scores in the retrieval subtest of the objects battery. Contrasting with the results of previous studies which had pointed out tasks assessing face-related knowledge as useful indicators of MCI (Cuetos, et al., 2009; Dudas, et al., 2005), no significant differences appeared between the scores of the MCI and control groups neither in the retrieval nor in the association face-based batteries. Nevertheless, it should be taken into account that issues related to excessive difficulty of the items might have been responsible for the lack of power of these specific tasks to discriminate between impaired and unimpaired

participants. In order to explore this possibility, another analysis was conducted including only a set of objects and faces stimuli in response to which control participants had obtained comparable results in the naming task. This analysis revealed that, item difficulty being equal, both AD and MCI groups obtained worse scores in response to faces compared to objects. Moreover, whereas MCI and control participants obtained similar scores in the object domain, the scores of MCI participants in the face domain were clearly impaired.

Correlations between cortical thinning and scores obtained by the AD group both in response to tasks requiring association of objects- and faces-related knowledge were restricted to the right middle temporal region. In contrast, grey matter volumes of control and MCI groups were associated to a widely distributed cortical network comprising areas situated mostly in the temporal, parietal and frontal lobes bilaterally in the case of the object-related tasks, and in the right frontal and temporal areas in the case of the face-related tests.

As for subtests depending on retrieval processes, scores obtained by the AD group were again correlated with cortical thinning in the temporal regions, although this was the case only for face related-tasks, as no regions appeared to be significantly related to object-related behavioural scores at the .001 threshold chosen for this analysis. Once more, scores obtained in the objects battery by control and MCI participants were associated to grey matter volume in a variety of bilateral temporal, frontal and parietal regions. On the other hand, although no region appeared to be significantly correlated with scores obtained by healthy controls in the face-related retrieval subtest, areas of the right middle temporal and frontal gyri were associated with scores obtained by the MCI group in this battery.

In line with previous findings (Martin, et al., 1996), our results reveal that lateral regions of the temporal lobe have a crucial role in the representation of semantic knowledge. Indeed, analyses in the AD group showed a significant correlation between their scores in the object and face variants of the batteries and grey matter thinning in various gyri in the lateral region of the temporal lobe in both the retrieval and association subtests. This finding suggests that a reduction of grey matter in that area underlies the semantic memory impairment detected in these patients.

The findings in the MCI group, on the other hand, give us a different perspective. Differential patterns of cortical distribution can be observed in the analyses corresponding to the patients' performance in the objects and faces versions of the test

battery. While the analyses including the battery variant that involved the processing of object semantics, both in the retrieval and association subtests, yielded significant correlations in a widely distributed network of fronto-temporo-parietal areas, significant correlations were mostly restricted to more specific regions of the right frontal and temporal lobes when scores corresponding to the face-related subtests were entered into the analyses. The patterns of cortical regions significantly related to behavioural performance in the MCI group were similar to those yielded by the analyses in the control group, with great resemblance of findings between healthy older adults and these non-demented patients who are still at the very early stages of cognitive impairment. These results might indicate that public semantic knowledge related to face processing, and, alternatively, conceptual memory associated to objects, depend on different, although partially overlapping, neural mechanisms. However, the lack of significant correlations between grey matter volumes of the control participants and their scores in the retrieval subtest of the faces battery limits the extension of this speculative conclusion to the results of this specific subtest.

In summary, our results highlight the contribution of a distributed neural system, including frontal and temporal regions, to semantic memory. This cortical network appears to decrease in extent during the course of cognitive decline associated with the MCI and AD conditions. The essential role played by lateral regions of the temporal lobe in the processing of semantic knowledge became dramatically apparent in the analyses of the scores obtained by the AD group. On the other hand, the analyses of the data from the MCI participants revealed a strong involvement of a more extensive cortical network including also frontal structures in the retrieval of semantic information, especially in the case of knowledge related to objects.

5. Acknowledgements

6. References

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