Neural correlates of constructional apraxia in patients with Alzheimer's Disease.

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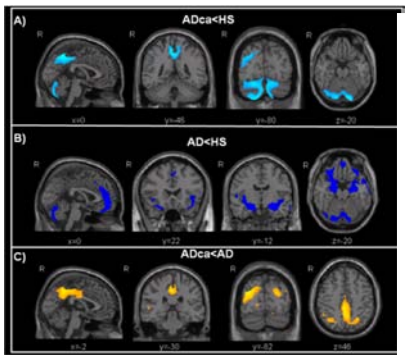
Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder which is typically characterized by early memory deficits, followed by a progressive increase of cognitive disabilities until conversion to dementia [1]. Impairment of constructional skills has been recognized as a rather common feature of AD since the early clinical stages [2]. Constructional apraxia (CA) is defined as an acquired impairment of the ability to reproduce spatial relationships between objects, in the absence of any motor impairment [3]. Patients with CA perform poorly on drawing tasks or when required to arrange blocks or objects. Previous literature suggests that CA is a complex neuropsychological disorder involving basic abilities, such as visuo-spatial perception and analysis, visuo-motor integration [4], as well as executive functions, such as planning and response monitoring [5]. CA is generally due to parietal [4] and frontal lobe dysfunction [6], although its precise anatomical-functional substrate still remains largely unclear. First aim of this study was to assess whether, in AD patients, CA is due to a specific deficit of planning of drawings or it is due to a less specific visuo-spatial dysfunction. Second aim was to investigate, using a voxel-based morphometry (VBM), whether there is any peculiar pattern of regional gray matter (GM) atrophy that characterizes AD patients with CA as an independent subgroup. **Methods:** Participants: a cohort of forty-eight patients, with a diagnosis of probable AD, and 20 healthy subjects (HS) were enrolled for this study. Classification criteria to define the level of constructional apraxia**:** In order to evaluate the impact of constructional apraxia on the clinical manifestation of AD, we divided our patients' cohort on the basis of the scores they obtained at the Freehand copying of drawing task (see below) [7]. Twenty-four out of 48 patients could be classified as suffering from constructional apraxia (ADca), while the remaining ones were classified as suffering from typical AD (AD). Test for evaluation of constructional apraxia: the presence of constructional apraxia was ascertained based on the performance at the Freehand copying of drawings task (CD)[7]. In this task, subjects are given 3 A4 paper sheets, each one showing a linear drawing on the upper half (a star, a cube and a house), which they are requested to copy in the lower half of the sheet. No time constraint is given for the copying task. The performance score for each drawing ranges from 0 to 4. A score of 0 is given in the presence of a closing-in phenomenon; 1 is given in the case the reproduction shows some inaccuracies with respect to symmetry, orientation, or perspective; 4 is given when the model is adequately reproduced. Following normalization of the raw score according to age and education, the normality cut-off score for this test is set at 7.18, corresponding to the lower limit of the 95% tolerance interval in the Italian normal population distribution [7]. All patients and HS underwent an extensive neuropsychological assessment and an MRI examination at 3T, including the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); 2) fast-FLAIR (TR=8170 ms, TE=96 ms, TI=2100ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2,4 ms, Matrix=256x224, n. slices=176, thickness=1 mm). TSE and FLAIR scans were reviewed to exclude the presence of remarkable macroscopic brain abnormalities. VBM analysis and statistics: All T1 images were segmented and normalized into GM, WM, and CSF, using the VBM protocol [8] implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Statistical analysis was performed on smoothed (12 mm FWHM kernel) GM maps within the framework of the general linear model. We used an ANOVA full factorial design, with a 3 level factor to model the groups (ADca, AD and HS), and with intracranial volume (ICV) (obtained by adding up WM volume +GM volume + CSF volume), years of formal education, gender and MMSE scores as nuisance covariates to adjust for potential confounds. P values were considered significant if survived after False Discovery Rate (FDR) correction for multiple comparisons ($p<0.05$). **Results:** Neuropsychological assessment: there were no differences between patients with ADca and with AD in terms of level of dementia. As expected both AD groups performed worse than HS in all cognitive domains. Conversely patients with ADca showed lower performances than patients with AD only at tests requiring the processing of visuo-spatial data. No differences were detected between the two groups of AD patients in the verbal tests. VBM analysis: when comparing distinctly the two AD groups with HS, different patterns of GM loss were found (Figure 1). More specifically, patients with ADca compared to HS (Fig.1 Panel A) showed GM atrophy in a large area involving the bilateral precuneus (BA7), the bilateral posterior cingulate cortex (BA23/31), the lateral occipital cortex, and the right cerebellum. Conversely, patients with AD compared to HS (Fig.1 Panel B) showed a more prominent GM loss in medial temporal lobe structures (in the amygdala and hippocampus bilaterally, and in the left parahippocampal gyrus), in the left orbito-frontal cortex (BA11), in the right dorsolateral prefrontal cortex (BA47), in the paracingulate (BA32) and cingulate cortex (BA24) bilaterally. The direct comparison between ADca and AD patients (Fig.1 Panel C) revealed, in the former group, the presence of GM atrophy confined to the right hemisphere involving the fusiform gyrus (BA37), the middle temporal gyrus (BA21), the angular gyrus (BA39), the precuneus (BA7), the posterior part of the cingulum (BA23/31) and the lateral occipital cortex (BA18). No area of GM loss were found in AD compared to ADca patients.

Figure 1



Discussion: This study supports the idea that the occurrence of CA in patients with AD requires the specific involvement of a widespread visuo-spatial network. Indeed, neuropsychological findings fit well with the peculiar pattern of regional GM atrophy observed in ADca, but not in AD patients, which includes regions traditionally implicated in visuo-spatial processing. Overall, this study suggests that impairment of both, spatial logical and working memory functions is needed to produce CA in AD patients. Future studies are needed to clarify whether patients with ADca have a different prognosis when compared to those with AD.

References:
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