ARE BEHAVIOURAL SYMPTOMS OF ALZHEIMER'S DISEASE DIRECTLY ASSOCIATED TO NEURODEGENERATION?

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Background and Objective.
Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive cognitive impairment. Behavioural disorders and psychological symptoms (BPSD) (1) are also frequently observed in the clinical course of AD (2), with an estimated prevalence that ranges from 25% to 80% (3, 4). BPSD are commonly observed also in patients with amnesic mild cognitive impairment (a-MCI) (5,6) a clinical condition which is widely considered as a prodromal stage of AD (5). However, in the literature, it is still a matter of a debate whether the presence of BPSD reflects specific neuro-pathological changes occurring in AD brains, or it is the expression of a personal psychological reaction to the occurrence of cognitive disabilities. In this study, we used voxel-based morphometry (VBM) (7) to identify, in a large cohort patients with AD at different clinical stages, those BPSD which are more significantly associated with regional gray matter (GM) degeneration. In this view, these BPSD would represent specific clinical features of AD, which have been poorly considered so far.

Subjects and Methods. A large cohort of patients was enrolled in this study, including 19 patients with a-MCI (5) and 27 patients with probable AD (8), of whom 12 were at an early (ADe) and 25 at a moderate stage (ADm) of cognitive decline. Twenty-seven healthy subjects (HS) were also recruited and served as controls. All subjects had to be right handed. The absence of any alternative neurological/psychiatric diagnosis was excluded in each patient. Moreover, major medical illnesses and the presence of macroscopic brain abnormalities on conventional MRI were carefully excluded in all subjects. All subjects underwent an extensive neuropsychological assessment. Moreover, a-MCI, ADe and ADm patients were assessed for the presence and severity of BPSD using the Neuropsychiatric Inventory-12 (NPI-12) (9), an instrument which is specifically devoted to assess 12 different BPSD in patients with cognitive decline. The presence of psychiatric symptoms was excluded in all HS on a clinical interview basis. All subjects underwent MRI at 3 Tesla, by collecting the following scans: (i) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); (ii) fast-FLAIR (TR=8170 ms, TE=96ms); 3D MDEFT (TR=1338 ms, TE=2,4 ms, Matrix=256x224, n. slices=176, thick.=1 mm). 3D MDEFTs were processed for VBM analysis (9) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). An ANOVA model was first employed to assess regional GM changes across groups, by testing the following contrasts: HC>a-MCI; a-MCI>ADe; ADe>ADm. Then, using a multiple regression analyses including GM maps from all patients (a-MCI; ADe and ADm) we investigated correlations between regional GM volumes and subscores obtained at NPI-12. Each subscore reflects the presence and severity of each BPSD in each patient. Results were considered as statistically significant only when surviving after FWE correction for multiple comparisons ($p<0.05$).

Results. Mood disorders, but also anxiety and agitation were already present in patients with a-MCI, while psychotic symptoms were more common in patients with probable AD (ADe and ADm). Disinhibition and motor aberrant behaviours were the only two symptoms showing a significant worsening when moving from a-MCI to ADm patients. VBM group analysis confirmed that regional GM atrophy is well confined to the entorhinal cortex, cingulate gyrus, precuneus, and insula at the stage of a-MCI (Fig. 1A). Then, it becomes progressively more widespread in patients with ADe and ADm (Fig. 1 B,C). Correlation analyses showed that presence and severity of disinhibition (Fig. 2 A) were inversely associated with GM volumes in the cingulate gyrus bilaterally, and in the right middle frontal gyrus. Occurrence and severity of delusions (Fig. 2 B) were inversely correlated with GM volume of the right hippocampus and parahippocampal gyrus, and of the right middle frontal gyrus. several associations between BPSD and prefrontal regions were also found but only at uncorrected level..
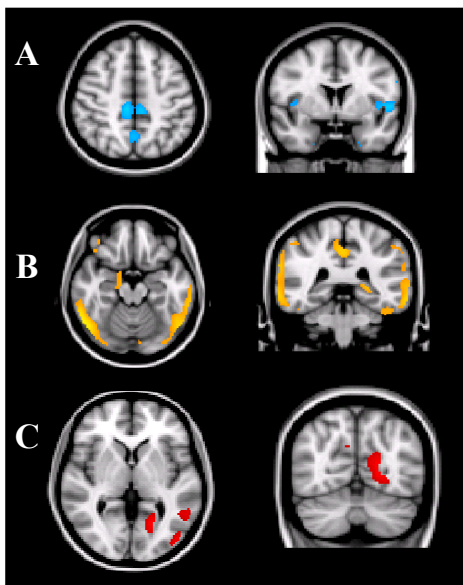

Fig 1. Regions of reduced (FWE p<0.05) GM volume in a-MCI compared to HS (A); in ADm compared to HS (B); in ADm compared to ADe (C).
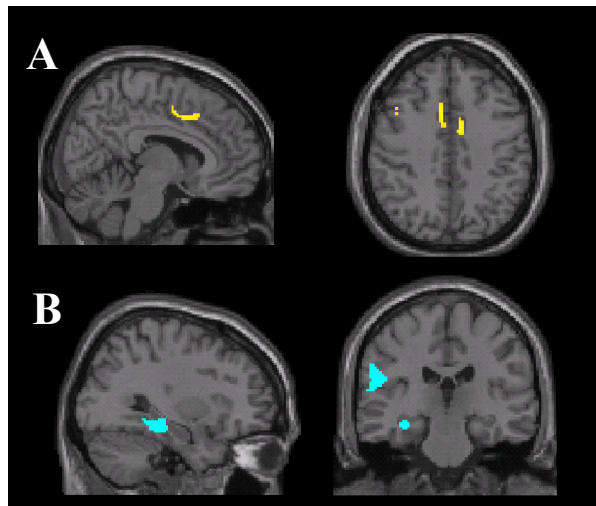

Fig 2. Association between reduced GM volume and disinhibition (A) and delusions (B) in patients with a-MCI, ADe and ADm.

Conclusions. This study confirms that BPSD are present in AD patients since the earliest clinical stages, and tend to get worse with the progression of the disease. As expected, VBM analysis demonstrated a progressive accumulation of GM atrophy across AD evolution. Moreover, VBM revealed strict associations between specific BPSD and well-defined brain structures. In particular, disinhibition and delusions were significantly associated with GM volumes in regions which are traditionally implicated in the neuropathology of AD. These findings indicate that specific BPSD are likely to be part of the clinical features of AD. This might be relevant for the development of new diagnostic and prognostic criteria for Alzheimer's disease.

References
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