

Anatomical connectivity to assess brain tissue modifications in Alzheimer's disease

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Introduction

Recent neuroimaging studies suggest that the clinical manifestations of Alzheimer's disease (AD) are not only associated with regional grey matter damage (1,2), but also with abnormal functional integration between different brain regions by disconnection mechanism (3). Recently, a measure of anatomical connectivity derived from diffusion MRI tractography has been proposed (4). Anatomical connectivity mapping (ACM) is obtained by initiating streamlines from all parenchymal voxels, and then counting the number of streamlines passing through each voxel of the brain. A recent paper (5) demonstrates that patients with AD have reduced ACM compared to elderly healthy subjects (HS) in the supramarginal gyrus, but also areas of increased ACM (which was not found in patients with mild cognitive impairment, MCI), mainly located in regions nearby the putamen. This finding was interpreted as a possible consequence of processes of brain plasticity driven by cholinesterase inhibitors (ChEIs). Here, we extend previous findings by assessing ACM in a larger group of patients with AD. Moreover, we investigate the relationship between this quantity and exposition (duration \times dosage) to ChEIs treatment.

Methods

Thirty-eight patients with moderate AD (mean age 73.4, SD=7.5; mean MMSE=18.4, SD=6.0) were recruited. Nineteen of them were under treatment with ChEIs (8 Rivastigmine, 11 Donepezil), and there were no differences between the two subgroups with respect to mean age, mini mental state examination (MMSE) score, or years of education. Eleven healthy subjects (mean age 68.4, SD=7.5) served as controls. All patients and controls were tested with an extensive neuropsychological battery. Diffusion MRI data were obtained at 3T using a twice-refocused spin echo EPI (TR=7 s, TE=85 ms, 61 diffusion directions, maximum b factor=1000 mm^{-2} , isotropic resolution 2.3mm 3). All subjects had also a T1-weighted 3D MDEFT (TR=1338 ms, TE=2.4 ms, Matrix = 256x224, n. slices = 176, thick. 1 mm), which was coregistered with diffusion data and segmented into white and grey matter and CSF using SPM8 (www.fil.ion.ucl.ac.uk/spm/). A binary parenchymal mask was obtained by combining grey and white matter segments and retaining only voxels with intensity greater than 0.8 on the resulting image. Diffusion data were first corrected for eddy current induced distortion using a tool from FSL (www.fmrib.ox.ac.uk/fsl/). All the remaining processing was done using Camino (www.camino.org.uk/), if not otherwise specified. The intra-voxel fibre orientation distribution functions (ODFs) and the principal directions of diffusion (with a maximum of 3 per voxel) were reconstructed in every voxel using Q-ball (6). Probabilistic tractography using the probabilistic index of connectivity (PICO, 7) with 10 Monte Carlo iterations was initiated from all voxels in the parenchymal mask. ACMs were obtained by counting the total number of streamlines passing through each voxel, and normalising it by the total number of streamlines initiated. ACM images were normalised into MNI space using the transformation obtained during the segmentation step, and smoothed with a 8 mm 3 FWHM Gaussian filter. Voxel-wise statistics was carried out using SPM8 to assess: 1) the presence of between-group differences comparing all AD patients with HS (adjusting for age, gender, years of education and number of voxels in the parenchymal mask); 2) the presence of between-group differences when comparing patients under ChEIs treatment and drug-free patients (adjusting for the same variables as above, and for MMSE scores); 3) the correlation between ACM and the dosage \times duration of therapy product (only in the 19 AD patients under ChEIs treatment)

Results

When comparing all patients with AD to HS, ACM was found to be reduced in the fornix, in the supramarginal gyrus (bilaterally) and in the cingulum bundle (Fig 1, red areas), and increased in the cortico-spinal tract (Fig 1, blue areas). When comparing the 2 subgroups of patients (those drug free and those under treatment with ChEIs), no significant group difference was found. Conversely, a strong direct association was observed between ACM in the left anterior limb of the internal capsule and the dose \times duration product of ChEIs (Fig 2A). Finally, a significant MMSE \times therapy interaction was observed in the same subcortical area (Fig 2B), indicating that drug free patients show a direct correlation between their MMSE score and ACM in that area, which is lost in patients under medication with ChEIs.

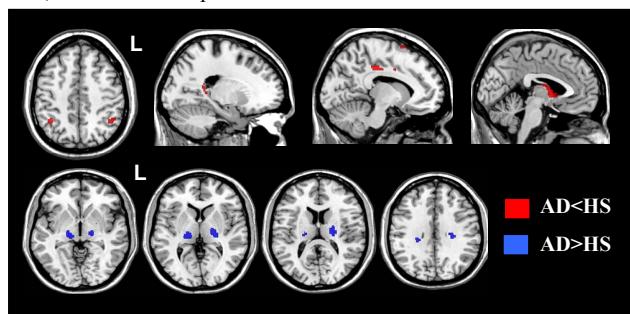


Fig. 1. Voxel-wise comparison of ACM between AD patients and HS. Reductions of structural connectivity in patients are shown in red, while increases are shown in blue. See text for further details

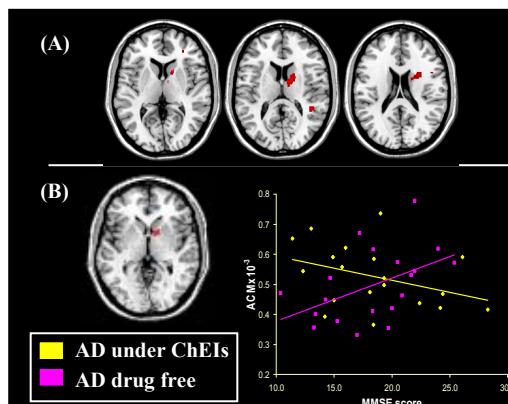


Fig. 2. Areas of direct correlation between ACM and dose \times duration product in AD patients under treatment with ChEIs (A). Area whose ACM values show a MMSE \times therapy interaction (B). Correlation between ACM values and MMSE scores are present in drug free patients (yellow circles), and is completely lost in those under treatment with ChEIs (purple squares).

Discussion

Regional reductions of ACM in the supramarginal gyrus, cingulum, and fornix, confirm and extend our preliminary findings (4), and provide, for the first time *in vivo*, evidence for structural brain disconnection in AD pathophysiology, as previously shown by functional imaging data (3). Moreover, the ACM reduction in the fornix is consistent with previous findings suggesting a critical involvement of this structure in the conversion from MCI to AD (8). The interpretation of ACM increase in the cortico-spinal tracts of AD patients, is more challenging. We hypothesize that, due to the normalisation of ACM maps by the total number of streamlines initiated, the overall reduction in connectivity translates into an artificial increase of connectivity of those tracts which are relatively spared by AD pathology. The positive impact of medication with ChEIs (dosage \times time) in AD brains, seems to be localized in the same subcortical regions found in our preliminary investigation (5), which involved a smaller but independent group of AD patients. This finding might reflect the putative neurotrophic and neurorestorative role that ChEIs may exert on cholinergic neurons (9), as also suggested by the positive effect of medication in modulating the relationship between MMSE score (a measure of global cognitive impairment) and structural connectivity in the same subcortical region. If this was the case, an increased number of regenerating axons and sprouting of collateral fibres might explain the observed modulation of ACM in AD brains.

References

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