Regional assessment of white matter damage at different stages of Alzheimer's disease using TBSS

L. Serra[1], M. Cercignani[1], D. Lenzi[1,2], R. Perri[3], F. Fasano[1,4], C. Caltagirone[3,5], E. Macaluso[1], and M. Bozzali[1]

[1]Neuroimaging Laboratory, IRCCS Fondazione S. Lucia, Roma, Italy, [2]Dept of Neurological Sciences, Sapienza Università di Roma, Roma, Italy, [3]Clinical and Behavioural Neurology Laboratory, IRCCS Fondazione S. Lucia, Roma, Italy, [4]Siemens Medical, Italy, [5]Università di Roma Tor Vergata, Roma, Italy

Background and Objective. Amnesic Mild Cognitive Impairment (a-MCI) (1) is considered as a frequent prodromal state of Alzheimer's disease (AD). The annual incidence of conversion from a-MCI to AD is 10-15 %. From a neuropsychological perspective, patients with a-MCI show a relative preservation in most of the cognitive domains (2). Nevertheless, a relevant percentage of them is likely to develop a multi-domain cognitive impairment in a short time, and to eventually convert to fully developed dementia. Gross pathology (3) and neuroimaging studies (4) have shown that the neurodegeneration processes occurring in AD eventually result in a diffuse brain atrophy, with a preferential and earlier involvement of medial temporal lobe structures. It is also known that AD involves both white and grey matter, and that abnormalities of both tissues correlate with measures of cognitive decline (5,6). This study aims at localizing white matter abnormalities in patients with MCI using tract based spatial statistics (TBSS, http://www.fmrib.ox.ac.uk/fsl/), a novel approach to perform whole-brain analysis of diffusion tensor (DT) MRI (7).

Subjects and Methods. The study is designed to compare subjects with a-MCI with two different controls group: a group of patients with probable AD (8) and a group of elderly healthy subjects. So far, we studied 15 patients with a-MCI (7 females, mean age 72.8, SD: 7.9 yrs), 4 patients with AD (2 females, mean age 76.7, SD 4.3 yrs), and 10 healhty subjects (4 females, mean age 68.9, SD 7.8 yrs). Subject inclusion criteria were the following*:* right handed subjects; absence of any alternative diagnosis (neurological/psychiatric disorders or major medical illness) that might account for the observed cognitive impairment; absence of any macroscopic brain abnormalities on conventional MRI scans suggestive of an alternative or concomitant diagnosis (cerebrovascular disease) and no history of recent assumption of psycoactive drugs. According to diagnosis of a-MCI, patients obtained pathological scores exclusively in memory tests. All subjects underwent an MRI scan (Siemens Allegra 3 Tesla head-only scanner) including the following sequences: dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); fast-FLAIR (TR = 8170 ms, TE = 96 ms); 3D MDEFT (TR = 1338 ms, TE = 2,4 ms, Matrix = 256 x 224, n. slices = 176, thick. 1 mm); Diffusion weighted SE EPI (TR= 7 s, TE=85 ms, 61 diffusion directions, maximum b factor=1000 smm^{-2}, isotropic resolution $2.3mm^3$). FLAIR and TSE scans were reviewed to exclude the presence of any macroscopic brain abnormality. Fractional anisotropy (FA) maps were created for all subjects using *dtifit* (http://www.fmrib.ox.ac.uk/fsl/), and they were fed into TBSS to obtain a projection of all subjects' FA data onto a mean FA tract skeleton. Voxel-wise statistics was carried out to identify 1) areas of reduced FA in AD patients compared to healthy controls, 2) areas of reduced FA in AD compared to MCI patients, and 3) areas of reduced FA in MCI patients compared to healthy controls.

Results. Preliminary results indicate the presence of widespread white matter abnormalities in AD compared to healthy controls in the corpus callosum, cingulum, fimbria, fronto-temporal junction, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus. The areas of reduced FA in patients with AD compared to patients with a-MCI were less widespread and smaller. When comparing subjects with a-MCI to healthy controls, an area of reduced FA was found in the left frontal lobe. These findings are summarised in Fig 1.

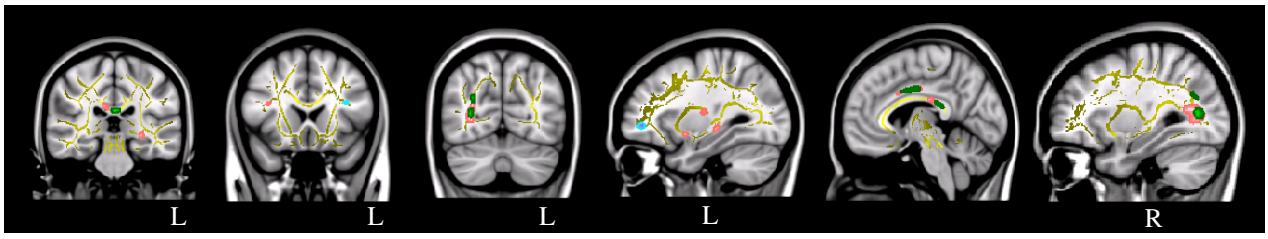

Fig 1. Areas of significantly reduced FA in AD compared to healthy subjects (pink), significantly reduced FA in AD compared to MCI (green), and significantly reduced FA in MCI compared to healthy subjects (ciano). The TBSS skeleton (yellow) is also shown, overlaid onto a T1-weighted template.

Conclusions. The FA reductions seen in the AD patient group relative to the controls are in areas that have been previously implicated in the pathology of dementia and also associated with clinical manifestations of the illness. An early involvement of frontal white matter appears to be present in a-MCI, although there is a relative preservation of other brain areas. These results further support the hypothesis that WM changes are present prior to the onset of AD, also confirming that subjects diagnosed with a-MCI represent a transitional stage between ageing to fully developed AD-type dementia.

References

1. Petersen RC et al. (2001) *Arch Neurol* **58,** 1985-92.
2. Petersen RC & Morris JC (2005) *Arch Neurol* **62,** 1160-3..
3. Braak et al. (1999) Eur Arch Psychiatry Clin Neurosci; 249:14-22.
4. Fox NC, et al. (1996) Lancet; 348:94-97.
5. Bozzali M et al. (2001) Neurology; 57:1135-7.
6. Bozzali M et al. (2002) J Neurol Neurosurg Psychiatry;72:742-6
7. Smith S et al. (2006) Neuroimage; 31: 1487-505..
8. McKhann G et al. (1984) Neurology; 34:939-944