Cognitive therapy combined with augmentative and alternative communication approaches modulate white matter architecture in autism

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Background
Despite the current limited understanding of the neural bases of autism, different interventions have been employed to reduce symptoms severity and to enhance functioning of autistic individuals, albeit with limited effectiveness (Hammad et al., 2009).

Recently, the search of the neural basis of autism has been focused on the role of white matter altered maturation (Courchesne, 2004) and structural abnormalities (Just et al., 2004; Pardini et al., 2006) in autism psychopathology (Muller, 2007). While major correlation can be probed in vivo with Diffusion Tensor Imaging (DTI), a brain MRI technique that measures the physical constraints to the motion of water molecules in the brain (Basser and Pierpaoli, 1996). DTI can be used to extract quantitative indices of white matter structural organization, such as Fractional Anisotropy (FA), a measure that assesses fibre density, axonal diameter, and myelination. FA yields values between 0 and 1; overall, higher FA values are found in more organized white matter tracts (Pierpaoli and Basser, 1997).

Aim of the study
We employed DTI to investigate the effects on white matter architecture of long-term cognitive therapy combined with augmentative and alternative communication in subjects with autism.

Methods
Subjects
Twenty-two low-functioning, right-handed, non-verbal autistic males enrolled from those undergoing rehabilitation in our centre were included in the study. The diagnosis of autism was based on DSM-IV-TR criteria (American Psychiatric Association, 2000). Clinical and demographical data are reported in Table 1. All subjects and/or their legal guardians gave informed consent to the study.

Rehabilitation protocol
The aim of the long-term intervention was to enhance cognitive, communication, and social skills, while reducing autistic symptoms and related problematic behaviours. Communication-focused interventions were based on augmentative and alternative communication (AAC) approaches to substitute or enhance speech (Lloyd et al., 1997) combined with adapted cognitive techniques (Kendall, 2006).

Behavioural evaluation
Childhood Autism Rating Scale (CARS) scores (Schopler et al., 1980) were collected before the enrolment in the rehabilitative protocol and at the time of the MRI. IQ was assessed at the time of the enrolment using the Leiter International Performance Scale-Revised (Leiter, 1979).

Magnetic resonance imaging acquisition and statistical analysis
Scans were obtained on a 3T scanner (Intera Achieva, Philips Medical Systems, Best, the Netherlands) equipped with both 80 mT/m/ms gradient coils, and an 8-channel surface coil and an 8-channel head coil. DTI was performed using a single-shot spin-echo-planar imaging (TR=10,000 msec, TE=69 msec, FLIP angle 90°, matrix size 112x112, FOV 224 mm; slice thickness 2 mm; gap between slices≤10% NSA=4 SENSE factor=2, b=1,000 sec/mm²). Diffusion gradients were applied in 32 non-collinear directions. DTI data were processed using FDT, a software included in FSL (Smith et al., 2004).

Results
The correlation between CARS scores difference and UF mean FA values was significant (Figure 1; r=0.66; p=0.001), while there was no significant correlation between DTI and MRI data within the created two subgroups. Statistical significance was set at p<0.05 (two-tailed) Bonferroni-corrected.

Discussion
In this study, we investigated the use of DTI to explore the impact of a long-term rehabilitation program on white matter architecture in autistic individuals. We observed a direct correlation between the increase of uncinate fasciculus structural organization and the clinical improvement, the precocity and length of the intervention, independency of symptomatology severity and IQ scores.

The uncinate fasciculus is the main ventral limbic tract that connects frontal and temporal territories, i.e., areas that play a key role in autism (Muller, 2007; Walter et al., 2004). Severe socio-emotional deprivation has been shown to impact uncinate fasciculus maturation and to be correlated with reduced uncinate fasciculus mean FA values (Esveldt et al., 2008). Moreover, uncinate fasciculus maturation has been linked with the acquisition of verbal language in DTI studies (Maddalozzo et al., 2009). Early rehabilitative interventions have been recently related to a better functional outcome in a subset of autistic subjects; this observation seems to be in line with our finding of a correlation between age at therapy onset and uncinate fasciculus increased structural integrity.

Our findings need to be interpreted with caution as our study was not a randomized clinical trial, but an observational study based on a retrospective design. Even so, in this small sample of low-functioning autistic subjects, our data seem to point to an association between rehabilitative interventions and white matter structural properties of a tract, the uncinate fasciculus, thought to play a significant role in autistic symptomatology.