



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 (Howlin 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., 2009) in autism physiopathology (Muller, 2007). White matter organization can be probed in vivo with Diffusion Tensor Imaging (DTI), a brain MRI technique that measures the physical restraints to the motion of water molecules (Pierpaoli and Basser, 1997). 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

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 sensitivity encoding (SENSE) coil. DTI was performed using single-shot spin-echo echo-planar imaging (TR=10,000 msec; TE=59 msec; FLIP angle 90°; matrix size 112x112; FOV 224 mm; slice thickness 2 mm; gap between slices=0; NSA=3; SENSE factor=2; b=1,000 sec/mm²). Diffusion gradients were applied in 33 non-collinear directions. DTI data were processed by using FDT, a software included in FSL (Smith et al 2004). Associations between variables were assessed using Spearman's correlations and partial correlations. U Mann-Whitney tests were used to compare clinical and MRI data between the created two subgroups. Statistical significance was set at p=0.05 (two-tailed) Bonferroni-corrected.

Results

Table 1. Demographic, clinical and MRI characteristic of the whole autistic sample and of the high and low CARS difference subgroups.

	All subjects	High CARS difference subgroup	Low CARS difference subgroup
Age at MRI (years)	21.9 ± 0.5	21.4 ± 0.7	22.5 ± 0.7
Age therapy onset (years)	15.5 ± 0.8	13.2 ± 0.9	17.2 ± 0.8
Therapy Length (months)	72.5 ± 6.7	91.5 ± 7.6	53.4 ± 7.6
CARS score at therapy onset	40.5 ± 0.8	41.6 ± 1.4	39.5 ± 0.9
CARS score at MRI	34.0 ± 1.0	32.6 ± 1.7	35.4 ± 1.0
CARS difference	6.5 ± 0.6	9.0 ± 0.4	4.0 ± 0.5
ADOS (in 2006)	16.2 ± 0.9	-----	-----
Non verbal IQ at therapy onset	48.9 ± 1.6	47.8 ± 2.7	49.9 ± 1.7
CST mean FA	0.61 ± 0.01	0.62 ± 0.02	0.59 ± 0.02
UF mean FA	0.58 ± 0.01	0.60 ± 0.01	0.55 ± 0.01

Behavioural evaluation

CARS scores are reported in Table 1. There was a significant correlation between CARS scores difference and therapy length (p=0.001; r=0.57) and age of therapy onset (p=0.001; r=-0.70). There was no significant correlation between therapy length or age of therapy onset and CARS scores at the beginning of the therapy or at the time of the MRI scanning.

DTI metrics and cognitive therapy

MRI data are reported in Table 1. A significant correlation was found between uncinate fasciculi mean FA and therapy duration (Figure 1; r=0.65, p<0.001) and age of therapy onset (Figure 1; r=-0.85, p<0.001). The correlations between UF mean FA values and therapy duration (r=0.8; p=0.001) and age of therapy onset (r=-0.80; p=0.001) remained significant controlling for CARS scores and IQ using a partial correlation approach. There was no significant correlation between CST mean FA values and therapy length and age of onset.

DTI metrics and behavioural data

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 CARS scores difference and CST mean FA values. The correlation between UF mean FA values and CARS scores remained significant controlling for CARS scores and IQ (r=0.70; p=0.001) using a partial correlation approach.

High vs. low CARS difference subgroups.

Clinical and MRI data for the two subgroups are reported in Table 1. Between the two subgroups, the difference of UF mean FA values was significant (Figure 2; z= -3.3; p=0.001), as well as the difference of therapy duration (z=-2.96; p=0.002) and age of therapy onset (z= -2.9; p=0.002). There was no significant difference in IQ scores, mean FA values or mean CARS scores at the time of therapy enrollment nor at the time of MRI scanning between the two groups.

Figure 1: Scatterplots of autistic subjects uncinate fasciculi mean FA values and CARS scores difference (panel A), therapy length (panel B), and age of therapy onset (panel C).

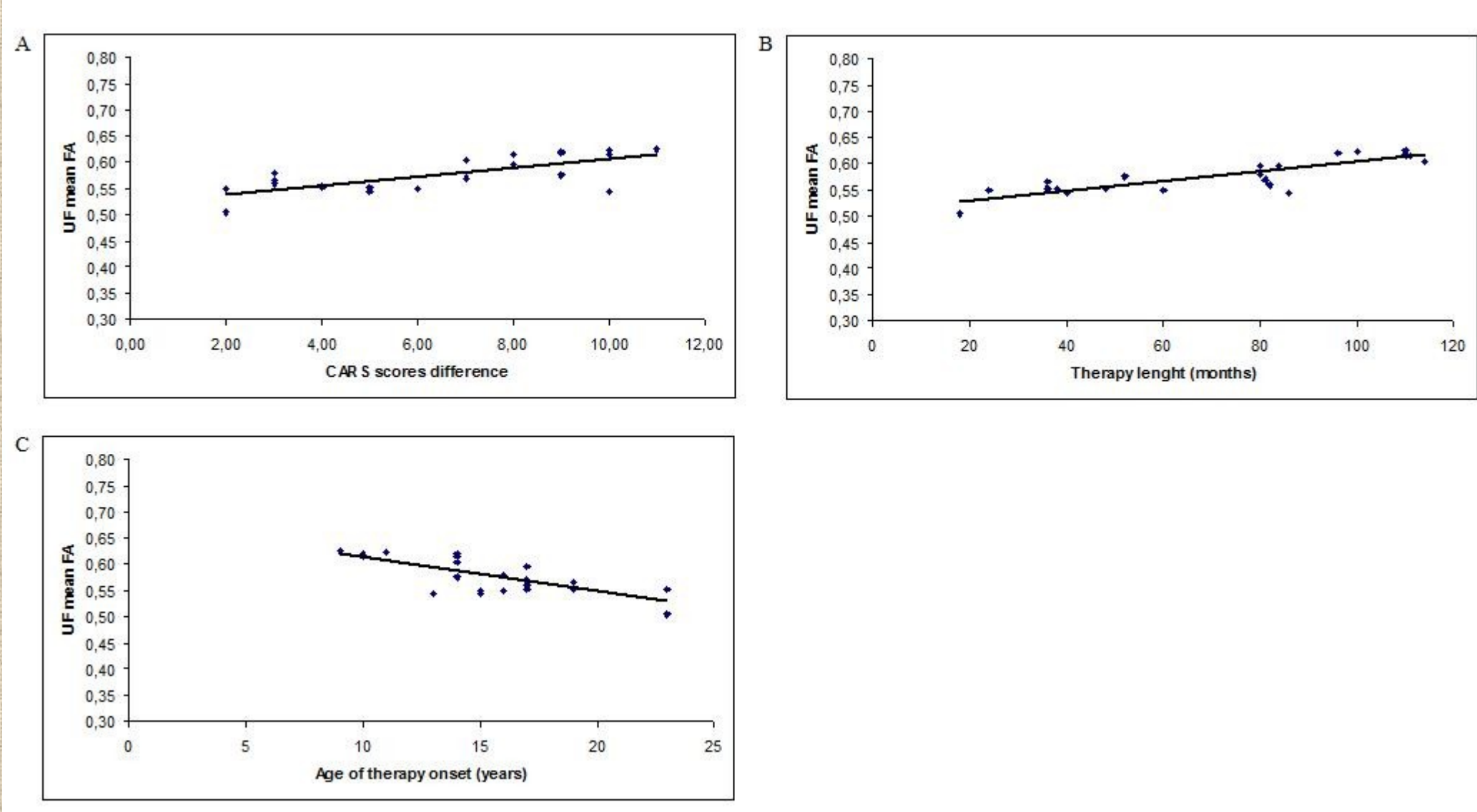
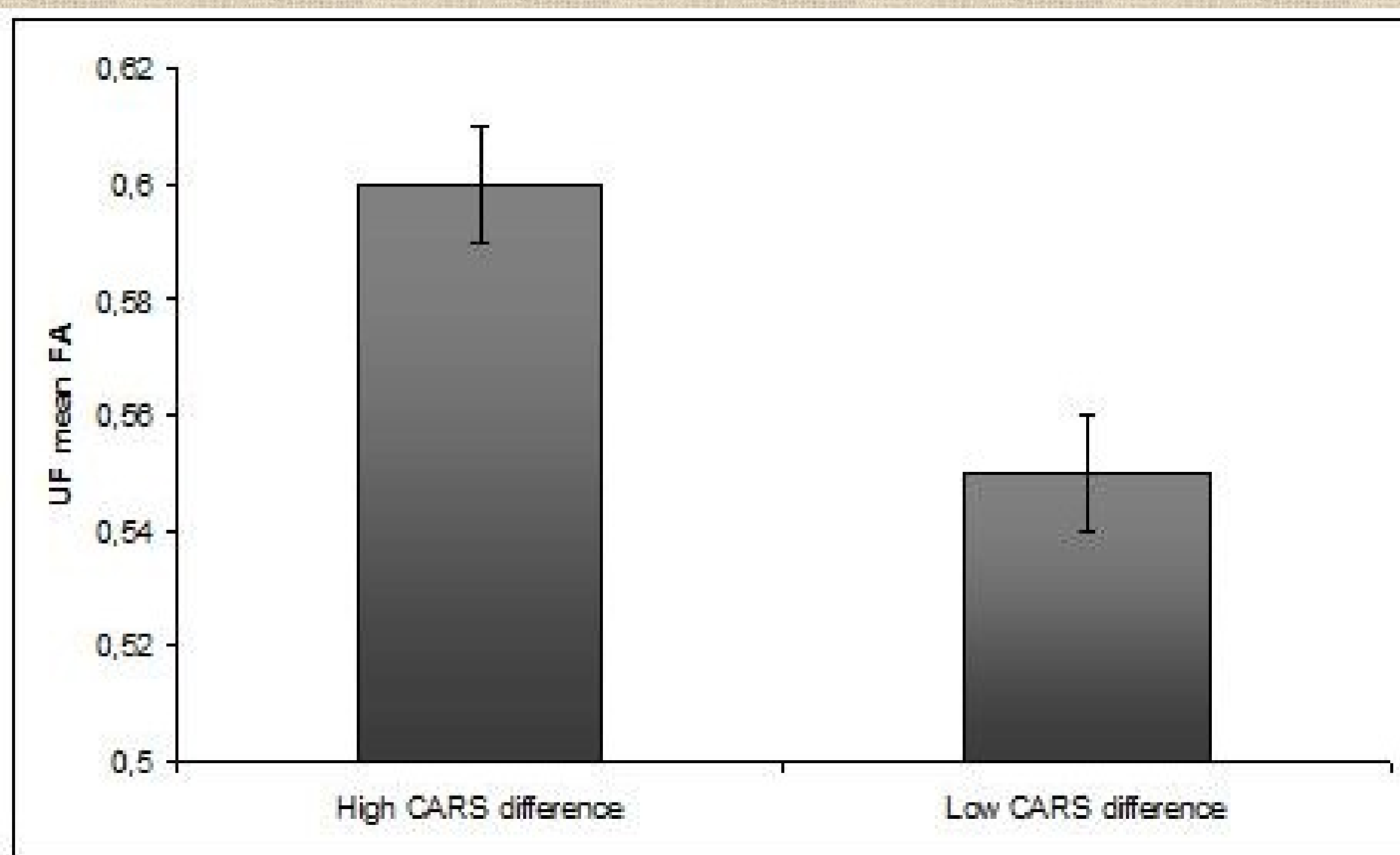


Figure 2: UF mean FA values for the high and low CARS difference subgroups. Error bars represent standard errors.



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, independently of symptoms 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; Waiter 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 (Eluvathingal et al., 2006). Moreover, uncinate fasciculus maturation has been linked with the acquisition of verbal language in DTI studies (Mabbott 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.

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