STRUCTURAL AND FUNCTIONAL UNDERCONNECTIVITY AS A NEGATIVE PROGNOSTIC MARKER FOR LANGUAGE IN AUTISM SPECTRUM DISORDER.

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Introduction

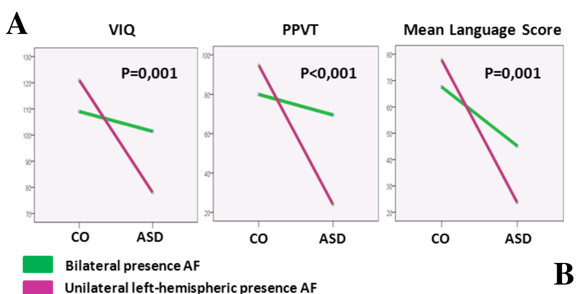
In a sub-group of children with autism spectrum disorder (ASD) the failure in spoken language is not only restricted to the domain of pragmatics but encompasses semantic, syntactic and phonological domains. Functional and structural neuroimaging are promising techniques for unraveling the neural correlates underlying the linguistic deficits of autism. However, the interplay between structural and functional connectivity and language performance in autism is largely unstudied. In this study, we examined the neurostructural and neurofunctional basis of language impairment in ASD using diffusion tensor imaging and resting state magnetic resonance imaging.

Materials & Methods

DTI imaging and rsfMRI was carried out in 17 subjects with ASD (mean age 13.95 ± 15.89 y) and 25 age-matched controls (mean age 14.48 ± 16.18 y) on a 3T Philips scanner. Patients and controls were screened for the presence of ASD symptoms using standardized parental questionnaires. All patients and controls underwent extensive language testing (Peabody Picture Vocabulary Test (PPVT), Clinical Evaluation of Language Fundamentals, Dutch version, 4th ed. (CELF-4NL)) as well as a short intelligence test (short form of WISC-III). To assess structural connectivity, DTI data were acquired using a spin-echo echo-planar-imaging pulse sequence with 45 diffusion directions (b=800 s/mm²) and with an isotropic resolution of 2 mm. This sequence was repeated twice and data were concatenated to improve the reliability of the estimated diffusion measures. Pre- and post-processing analyses were performed using ExploreDTI (1). Subsequently, deterministic fiber tractography of the arcuate fascicle (AF) was performed, using the robust ROI definition protocol of Catani (2) on a whole brain fiber tractography data set. After reconstruction of the AF, all subjects (N=42) were divided in 4 groups, according to the bilateral presence (+) or unilateral left sided presence (-) of the AF. Those groups were labeled as: ASD+ (N=7), ASD- (N=10), CO+ (N=18), CO- (N=7). The language scores were compared amongst these groups using a series of ANOVA's for normally distributed data. Because of the small sample size, the Kolmogorov-Smirnov Z test was used. The significance threshold was set at $p<0.05$. A series of MANOVA's was performed to characterize possible main or interaction effects of GROUP (ASD vs CO) and AF (+ vs -). In addition, rsfMRI data were acquired to elucidate the temporal dynamics of brain activity in neuronal circuits and assess functional connectivity. A T2* weighted GE-EPI sequence was used with the following parameters: TR=1700ms; TE=33ms; matrix size=64x64, FOV=230mm; flip angle 90°, slice thickness=4mm, no gap; axial slices=32. Two hundred and fifty functional volumes were obtained in seven minutes. On the basis of a verb generation task-related fMRI paradigm Broca and Wernicke areas were identified, which were subsequently used as seed regions for the resting state connectivity analysis. Using in-house developed software, we evaluated the functional connectivity in the language network by correlating the mean signal intensity time courses for each ROI pair combination in the 2 language network components described above. A correlation matrix was made to represent functional connectivity links among the language network.

Results

We found a unilateral presence of the AF in 28% (7/25) of the healthy control children and in 59% (10/17) of the children with ASD. A unilateral presence of the AF was associated with lower language scores in the ASD- group. An interaction effect was found for VIQ ($p=0.001$), scores on the PPVT ($p<0.001$) and Mean Language Score of the CELF-4NL ($p=0.001$) indicating that the difference in language performance between healthy control children and children with ASD is driven by the presence of the right-hemispheric AF. Resting state analyses showed a difference in connectivity between the ASD+ and ASD- group in the language network, notably less functional connectivity between Left Broca and Left Wernicke, and between Right Broca and Right Wernicke.



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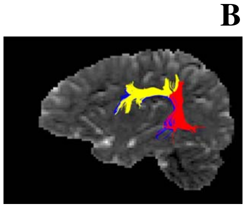

Figure 1: Figure A visualizes the interaction effect of Group (ASD/CO) and AF (Bilateral/ Unilateral) for VIQ, PPVT and Mean Language Score. Figure B visualizes the left hemispheric language network according to the reconstruction protocol of Catani.

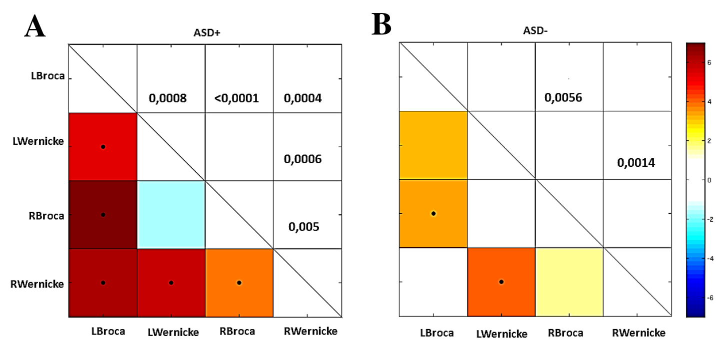

Figure 2: Figure A, B show the correlation matrices representing the functional connectivity in the language network for ASD+ and ASD- children. The color represents the T value of connectivity between 2 connected brain regions. Significant correlations at $p<0.05$ FDR corrected, are indicated with a dot at the centre of the matrix square. One-tailed P values were given for the significant correlations.

Conclusion

DTI tractography and rsfMRI have revealed a pattern of structural and functional underconnectivity in a subgroup of children with ASD. In this subgroup underconnectivity of the language network was associated with co-occurring language impairment.

References

1.Leemans et al (2009), 17th Annual Meeting of Proc. Intl Soc.Mag.Reson.Med., Hawaii, USA, (www.ExploreDTI.com), 2.Catani et al (2007), Neuroimage 17, 77-94