

## Brain differences in toddlers at risk of ASD

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**Introduction:** Autism spectrum disorder (ASD) is marked by significant behavioural, social and cognitive deficits<sup>1</sup>. Early intervention is key in allowing children with ASD to reach their full potential. However, early intervention is challenged by difficulties in early diagnosis (i.e. before 3 years of age). Thus, there is a clear need for a better understanding of the origin and progression of ASD prior to full presentation. A number of imaging studies are targeting children at genetic risk of ASD (i.e. siblings with an existing ASD diagnosis) in an attempt to answer this need. However, a more naturalistic sampling of the population can provide additional insights, as the disorder may not be identical in multiplex ASD families compared to isolated ASD cases. In this work a small cohort of at-risk children were identified from a longitudinal imaging study of typical brain development<sup>2</sup>. Brain myelin content was compared between this group of at-risk children and an age and gender-matched group of typically developing peers from the same study.

**Methods: Image Acquisition:** A surrogate measure of myelin content, termed the myelin volume fraction ( $VF_m$ ), was measured using a multi-component relaxometry technique (mcDESPOT)<sup>3</sup>, which derives the  $VF_m$  using a three-pool model fit to a combination of  $T_1$ -weighted SPRG and  $T_2/T_1$ -weighted bSSFP imaging data, with additional correction for  $B_0$  and  $B_1$  magnetic field inhomogeneities<sup>4</sup>. Data were acquired on a 3T Siemens scanner with a 12-channel head coil. All imaging was performed on toddlers during natural sleep.

**Subjects:** 11 children (average age  $20 \pm 8$  months, 9 male) were identified as being at-risk of ASD (screen positive) using either the Modified Checklist for Autism in Toddlers (M-CHAT)<sup>5</sup> or the Communication and Symbolic Behavior Scale Developmental Profile – Infant Toddler Checklist (CSBS-DP ITC)<sup>6</sup>. Because these children were enrolled in a longitudinal study, scans  $\sim 6$  months prior to screen positive were available for a subset of 9 children ( $11 \pm 5$  months, 7 male), and scans  $\sim 6$  months post screen positive were available for 4 children ( $23 \pm 3$  months, 4 male). Each screening timepoint was compared to a cohort of age and gender-matched typically developing children: at screen positive, 33 typical children (27 male), prior to screen positive 23 typical children (17 male), and post screen positive 11 children (11 male), with no statistical difference in age between groups at each time point ( $p>0.9$ ).

**Image analysis:** Following acquisition and processing, voxel-wise  $VF_m$  maps were non-linearly aligned to a study specific  $T_1$ -weighted template in approximate MNI space<sup>2,4</sup> and smoothed using a 3mm Gaussian kernel. Group analyses (unpaired t-tests) were performed using randomise<sup>7</sup> with age as a covariate of no interest, ( $p<0.05$ , uncorrected) to test the hypothesis that myelin content is significantly altered in children showing early signs of developmental delays consistent with ASD.

**Results:** At screen positive (20 months), myelin content was found to be *lower* in children with ASD in a number of regions, including occipital, temporal, cerebellum and motor areas. At  $\sim 6$  months prior to screen positive (11 months), myelin content was *higher* in children with ASD in regions including frontal and motor areas. At  $\sim 6$  months post screen (23 months), myelin content was *lower* in children with ASD in regions including cerebellum and motor areas, and *higher* in regions including left occipital, temporal, and internal capsule.

**Discussion & Conclusion:** We have identified differences in brain myelin content in 11 children at-risk of ASD, at an age younger than typical diagnosis and prior to onset of the full set of symptoms of the disorder. Differences were also found both 6 months prior, and 6 months post screening positive, suggesting that brain differences significantly precede ASD diagnosis. Interestingly, these findings complement the results of a recent study<sup>8</sup> using diffusion tensor imaging that showed atypical developmental trajectories of fractional anisotropy (FA) in children with ASD compared to typically developing, where children with ASD tended to *higher* FA at younger ages and crossing over the typical trajectory to *lower* FA values at between 6 and 16 months of age (depending on the brain structure). Our results at 6 months post screening are less consistent, with regions of both *higher* and *lower* myelin content in children with ASD; however, this timepoint was particularly limited by a small sample size ( $N=4$ ). This work is limited by small sample sizes overall – a result of the naturalistic selection of subjects, and as such should be repeated with a larger cohort of at-risk children. Additionally, these results will prove most interesting once this cohort is old enough to be accurately assessed for ASD.

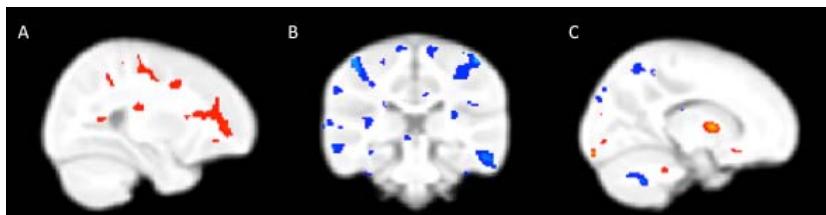


Fig 1: Regions of difference in myelin content between ASD and typically developing children. Red = myelin content *higher* in ASD, blue = myelin content *lower* in ASD. A) 6 months prior to screen positive (11 months), B) at screen positive (20 months), and C) 6 months post screen positive (23 months) (C).

References: [1] Akshoomoff A et al, Dev. Psychopathology 2002; 14:613-634, [2] Deoni SCL, et al, NeuroImage 2012; 63(3):1038–1053, [3] Deoni SCL et al, MRM 2008; 60:1372–1387, [4] Deoni SCL, Proc. Advanced White Matter Imaging, Iceland, 2011 (2012); p. A10, [5] Robins DL, et al, J Dev & Behavioral Pediatrics 2006; 27:S111-119, [6] Wetherby AM et al, Autism 2008; 12: 487-511, [7] <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>, [8] Wolff JJ, et al, Am J Psychiatry 2012;169(6):589-600