

## Intra-orbital distance as a record of social brain dysmorphology in autism.

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### Introduction

MPAs (minor physical anomalies) occur more frequently in neurodevelopmental disorders because face and brain are derived from neuroectoderm in the first trimester [1]. Conventionally, MPAs are measured by direct evaluation of external appearance but it is possible to quantify MPA using MRI. MRI circumvents potential observer bias; facilitates multi-centre data analysis and allows for simultaneous comparisons between intracranial (brain) anatomy and MPAs. Optical indices have a tightly synchronized developmental trajectory. For example, as head size increases with age, inter-orbital distance increases. This expansion is generally complete before 3 years and remains relatively fixed throughout the remainder of life [2]. Thus optical MPAs might provide a retrospective 'window' to early neurodevelopment. In autism, head size has been reported to expand dramatically up to the age of 2 years [3]. Thereafter growth is at a much slower rate than typically developing children and by mid childhood there is generally no discernible difference in overall brain size. We hypothesized that there would be increased inter-orbital distance in children with autism spectrum disorders. We also predicted that intra-orbital distance would be related to intra-regional brain anatomy in autism.

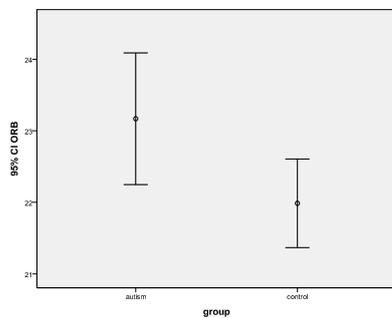
### Methods

The groups comprised  $n = 36$  children with autism spectrum and  $n = 55$  age (6-16 years) and gender matched typically developing controls. All children had a normal IQ. Inter-orbital distance was measured on T1-weighted images acquired on a GE Signa 1.5 Tesla system (General Electric, Milwaukee, WI, USA). Images were aligned along the ac-pc line, and the axial slice that displayed the largest diameter for both eyes was used for measurement. The inter-orbital distance was defined as the most medial point of the orbits located at the point of intersection between nasal bone and eyeball [4]. All measurements were 'blind' to diagnosis and inter and intra-rater reliability was measured on 10 scans at 1 week interval, inter class coefficient = 0.95. Following methods previously described [5], we also acquired a T2/PD dataset from each child to conduct a voxel-wise linear regression of grey matter volume and inter-orbital distance in each group separately. We used Cambridge Brain Activation software (CAMBA) to assess the significance of three-dimensional cluster statistics by non-parametric permutation testing [6]. The statistical thresholds were corrected for multiple comparisons by controlling the 'family wise error rate' and results accepted when the number of false positive clusters expected under the null-hypothesis was  $< 1$ ,  $p < 0.01$ . Total brain volume and age were entered as covariates.

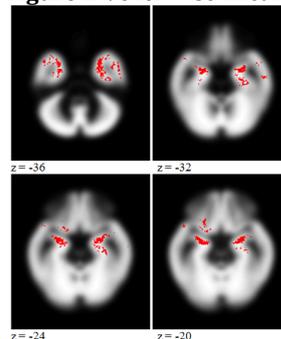
### Results

Intra-orbital distance in the autism group was significantly greater than typically developing controls ( $t = 2.16$ ,  $p = 0.03$ ; Figure A). In the autism group only, there was a significant positive correlation between inter-orbital distance and the grey matter volume of the bilateral amygdala, extending to unci and inferio-medial poles of the temporal lobes bilaterally (with peak co-ordinates  $x -26, y -7, z -30$ ;  $r > 0.7$  and  $x 28, y -23, z -32$ ;  $r > 0.7$ ). There was no significant group difference in total grey matter or volume of the amygdala based region-of-interest highlighted in red in Figure B.

**Figure A** Intra-orbital distance in autism and controls



**Figure B** Voxel-wise linear regression



In Figure B regions with significant positive volumetric correlation with intra-orbital distance were concentrated in bilateral medial temporal lobe regions including the bilateral amygdala.

### Discussion

Greater inter-orbital distance in the autism group relative to typically developing control children fits with a history of head size expansion during infancy in the autism group only. Inter-orbital distance was positively correlated with volumes in the interio-medial temporal lobe, including the amygdalae. This perhaps indicates that MPAs in autism may go hand-in-hand with "social brain" dysmorphology. Thus optical MPAs may provide a "fossil record" of early brain dysmaturation in autism.

**References:** 1. Tripi et al. 2008 *Early Hum Dev*, 84, 217-23; 2. Cohen 2002 *Am J Med Genet*, 115, 245-68; 3. Courchesne et al. 2001 *Neurology*, 57, 245-54. 4. Boyes et al. 2001 *Schizophr Res*, 50, 1-2; 5. McAlonan et al. 2009 *Br J Psychiatry*, 194, 123-9; Bullmore et al. 1999 *IEEE Transactions on medical imaging* 18.