A possible mechanism for impaired joint attention in autism

Justin H G Williams
Morven McWhirr
Gordon D Waiter
Joint attention in autism

- Declarative and receptive aspects – initiating and following
- Involves shared goal
- High diagnostic value e.g. ADOS
- Important prognostically e.g. predicts development of language
- Any ‘theory’ of autism must explain joint-attention.
Self-other mapping ‘theory’ of autism

- Rogers and Pennington, 1991:
  - At the root of autism is “impaired formation/co-ordination of specific self-other representations”.
  - Manifest first in impaired imitation, followed by a cascade of impairments in emotion-sharing, joint attention and pretend play.
Action-based hypotheses for joint-attention in autism

- Joint-attention concerns shared representation of 2 goal-directed actions (pointing, looking, head turning).
- Direction of other’s action is understood in relation to direction of own action.
- Shared-representation of goal-directed actions is served by ‘mirror neurons’.
- Dysfunction of ‘mirror neurons’ disrupts joint attention processes (Williams et al, 2001)
Neural Correlates of Joint Attention

• Williams et al. (2005)
  - FMRI
  - Adult participants “watch the moving dot”
  - Consequently, self-related gaze direction of stimulus video is either congruent or incongruent.
Results

MN areas implicated but effects of congruency were in medial frontal cortex, frontal pole and caudate.
Overlap with grey matter differences in ASD vs Controls in frontal pole (BA10)

Red = grey matter differences; Green = fMRI activation in typical population
• Self-other mapping is more distributed function, utilizing frontal cortex
• BUT frontal processes are not-specific to action-processing and are ‘domain-general’ executive function processes, not part of self-other mapping.
• What happens in autism?
• If there are deficits, will they be driven by problems specific to processing social stimuli or by more general problems?
Experimental Design

Self-related cue-direction

<table>
<thead>
<tr>
<th>Congruent</th>
<th>Baseline</th>
<th>Incongruent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faces</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social or symbolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrows</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Faces
- Social or symbolic
- Arrows
Methods – Stimuli 1
Methods – Stimuli 2
Methods – Stimuli 3
## Methods - Participants

### Recruitment:
- Autism – Clinical services
- Controls – Local schools

<table>
<thead>
<tr>
<th>Group</th>
<th>Total N</th>
<th>Age Y.M</th>
<th>SRS</th>
<th>Handedness L:R</th>
<th>IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>13</td>
<td>13.7</td>
<td>107.8</td>
<td>10:3</td>
<td>112</td>
</tr>
<tr>
<td>Controls</td>
<td>13</td>
<td>13.5</td>
<td>19.9</td>
<td>11:2</td>
<td>112</td>
</tr>
</tbody>
</table>

ADOS/ADI
Methods – MRI

- Philips 3T MRI Scanner
- Stimuli presented via eye tracking goggles

- fMRI total scan time: 15 minutes
- Structural scan times: 40 minutes

- Scanning parameters
  - 2500/40 (TR/TE)
  - Slices 23
  - Slice thickness 5mm
  - Matrix 128 * 128
Analysis

- Created a study specific template
- Median temporal filter
- Normalised to template
- Spatially smoothed 8mm Gaussian smoothing kernel at fwhm

Full Factorial Model
- all conditions
- movement parameters
- filter 600

Figure 1: Single Subject Pipeline
Results

1. Overall Group Differences
Controls > ASD

Right I.P.S. 16, -54, 56
Z = 4.79
FWE-corrected at voxel level: p<0.023

Post’r MFC 4,0,62
Z = 4.35
FWE-corrected at cluster level = 0.023
ASD > Control

<table>
<thead>
<tr>
<th>Region</th>
<th>x,y,z</th>
<th>Z (peak voxel)</th>
<th>P (voxel: FWE-corrected)</th>
<th>P(cluster: FWE corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Caudate</td>
<td>4,14, 8</td>
<td>5.58</td>
<td>0.001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>12,-36,4</td>
<td>4.37</td>
<td>0.123</td>
<td>0.003</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>10,-40,4</td>
<td>4.10</td>
<td>0.421</td>
<td>0.065</td>
</tr>
</tbody>
</table>
Interpretation

- Right IPS and Posterior MFC are associated with regulation of attention.
- Right IPS widely implicated in regulation of visual attention when competing demands are present.
- Posterior MFC associated with managing response conflict e.g. the Stroop.
- Task causes attentional conflict between central and peripheral stimuli.
- Therefore seems Controls are showing greater utility of IPS and MFC in managing attentional conflict than group with autism.
- Caudate nucleus implicated in reward-based attention and hippocampus is associated with spatial memory. Suggests group with autism are putting more effort into remembering spatial locations.
  - Learning position of dot in the sequence?
Are people with ASD just ignoring the central cue?

2nd level: Effects of self-related cue-direction and cue-type, and interaction with group.
Social vs. Non-Social

Greater activation to faces
- Fusiform Gyrus
- STS
- Precentral Gyrus
- Precuneus

No greater activation to arrows

No Group Differences
### Congruous > Incongruous Faces, Controls > Autism

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Region</th>
<th>BA</th>
<th>p</th>
<th>z</th>
<th>extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>-14</td>
<td>21</td>
<td>Insula</td>
<td>13</td>
<td>0.0011</td>
<td>3.06</td>
<td>311</td>
</tr>
<tr>
<td>22</td>
<td>-11</td>
<td>21</td>
<td>Caudate</td>
<td></td>
<td>0.0017</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>-17</td>
<td>52</td>
<td>Medial Frontal Gyrus</td>
<td>6</td>
<td>0.0016</td>
<td>2.95</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>-18</td>
<td>25</td>
<td>Cingulate Gyrus</td>
<td>23</td>
<td>0.0023</td>
<td>2.83</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>-5</td>
<td>Anterior Cingulate</td>
<td>24</td>
<td>0.0024</td>
<td>2.82</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0011</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10</td>
<td>-46</td>
<td>6</td>
<td>Parahippocampal Gyrus</td>
<td>30</td>
<td>0.0013</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>-30</td>
<td>-63</td>
<td>22</td>
<td>Middle Temporal Gyrus</td>
<td>39</td>
<td>0.0019</td>
<td>2.9</td>
<td>29</td>
</tr>
<tr>
<td>-36</td>
<td>-29</td>
<td>0</td>
<td>Caudate</td>
<td></td>
<td>0.0038</td>
<td>2.67</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0038</td>
<td>2.67</td>
<td>21</td>
</tr>
<tr>
<td>-14</td>
<td>38</td>
<td>4</td>
<td>Medial Frontal Gyrus</td>
<td>10</td>
<td>0.0038</td>
<td>2.66</td>
<td>29</td>
</tr>
<tr>
<td>-22</td>
<td>36</td>
<td>15</td>
<td>Anterior Cingulate</td>
<td>32</td>
<td>0.0039</td>
<td>2.66</td>
<td>29</td>
</tr>
</tbody>
</table>
• Lack of group interaction between cue-type and group suggests that both groups are looking equally at the faces compared to the arrows. Therefore, not simply a matter of people with autism ignoring central cue.
• Effect of self-related gaze-direction shows more activity for congruity in controls in insula.
• Supports ‘mirror neuron’ hypothesis (Gallese, TICS, 2005, argues for MN function of Insula).
• BUT Group difference is weak and in posterior insula.
So far....

- Group differences are largely non-specific to condition.
- No group differences to social vs non-social cue
- No group differences for condition as a whole but weak group differences to self-related gaze-direction.

So

- Does response to social-cue depend upon direction relative to self, and is that affected by group?
• In what areas does the brain's response to a directional cue depend BOTH on its direction relative to the self AND according to whether it is social or non-social?
Do groups respond differently to cue-type depending on direction?

- 3rd level analyses:
  - Interactions between condition and cue-type
  - Both groups and separate for each group. Threshold $p<0.01$ uncorrected
Both groups interaction between self-related cue-direction (to or away)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Region</th>
<th>pFWE-corr</th>
<th>Z (peak voxel)</th>
<th>extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>-46</td>
<td>-10</td>
<td>Right fusiform gyrus</td>
<td>0.008</td>
<td>5.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right temporo-parietal junction</td>
<td>0.017</td>
<td>4.86</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>-44</td>
<td>4</td>
<td>Right medial frontal cortex</td>
<td>0.021</td>
<td>4.81</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>56</td>
<td>Left medial</td>
<td>0.012</td>
<td>4.94</td>
<td></td>
</tr>
<tr>
<td>-14</td>
<td>-44</td>
<td>-30</td>
<td>Cerebellum</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of congruency for face > arrow

Controls only – same post’r insula activation as before.

\[ x, y, z = 30, -16, 22; \ Z (\text{peak voxel}) = 3.48, \]

\[ p(\text{peak voxel, uncorrected}) = 0.0005; \ p(\text{cluster, FDR-corrected}) = 0.043 \]
Effect of Incongruity (>Congruous) for face>arrows

Controls

ASD
Effect of Baseline (>Congruous) for faces > arrows
<table>
<thead>
<tr>
<th>Location</th>
<th>x,y,z</th>
<th>Cluster size</th>
<th>P(cluster) FWE-corr</th>
<th>Z (peak voxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Sup’r Frontal Gyrus</td>
<td>-12,22,54</td>
<td>2639</td>
<td>0.000</td>
<td>4.37</td>
</tr>
<tr>
<td>R.IPS</td>
<td>40,-46,-48</td>
<td>3055</td>
<td>0.000</td>
<td>3.91</td>
</tr>
<tr>
<td>Ant’r right MFC</td>
<td>16,48,16</td>
<td>955</td>
<td>0.035</td>
<td>3.60</td>
</tr>
<tr>
<td>Ant’r left Insula</td>
<td>-34,0,0</td>
<td>1073</td>
<td>0.021</td>
<td>3.44</td>
</tr>
</tbody>
</table>
Symbol-arrow interactions in medial frontal cortex

Incongruous

baseline
Medial prefrontal cortex locations in relation to Amodio & Frith (2006)
In controls, interaction between self-related cue-direction and cue-type indicated that BOTH conditions modulated activity in aMFC, AI, R.IPS and L.FG.

Both populations showed equally differential responses in face-processing areas to social vs non-social stimuli

BUT Participants with ASD did not show evidence of modulating response to social stimuli according to self-related cue-direction.
Conclusions

• In a goal-directed attention task controls showed areas of brain where activity depended upon a directional cue, that was both social and its relationship to the observer’s gaze direction.
• This is evidence of “self-other mapping” of observed actions to actions executed by the self.
• This mapping may involve insula and IPS (human mirror neuron sites) but also involves MFC.
• Menatalizing and self-other mapping utilise common substrate in arMFC.
• No cue-type, cue-direction interaction in people with autism indicative of an absence of self-other mapping in autism.
Further work

1. Post-hoc parameter estimates still required.
2. Eye-tracking analyses
3. Larger numbers
Acknowledgements

Children and families who participated

Funding by Northwood Charitable Trust, Enders Analysis and Aberdeen Oil Golfer’s Association.