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A possible mechanism for impaired joint attention in autism

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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

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- 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

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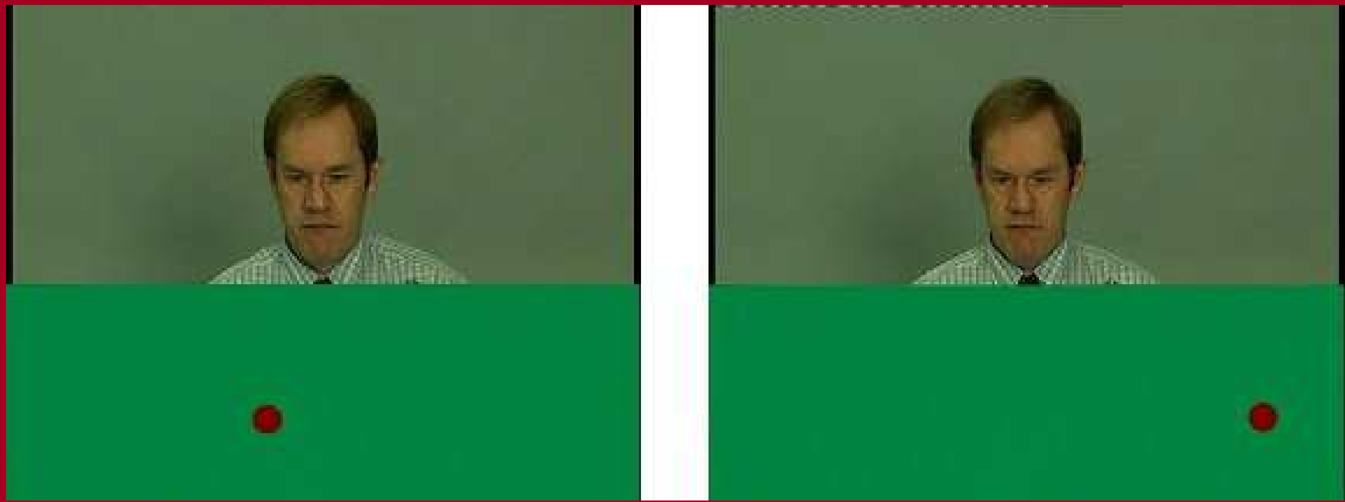
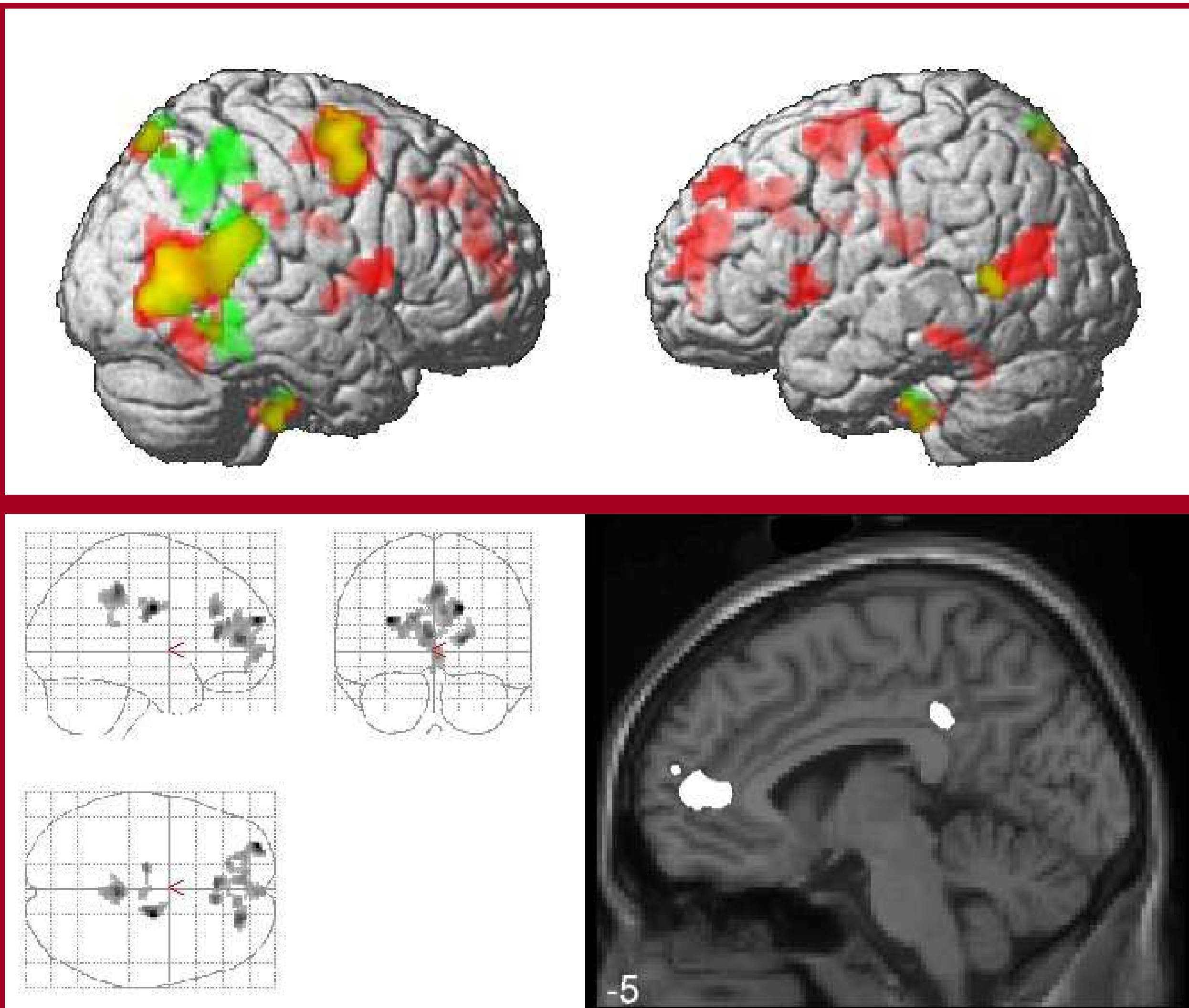


- Williams et al. (2005)
  - FMRI
  - Adult participants “watch the moving dot”
  - Consequently, self-related gaze direction of stimulus video is either congruent or incongruent.

Results



MN areas implicated but effects of congruency were in medial frontal cortex , frontal pole and caudate

Overlap with grey mater differences in ASD vs Controls in frontal pole (BA10)

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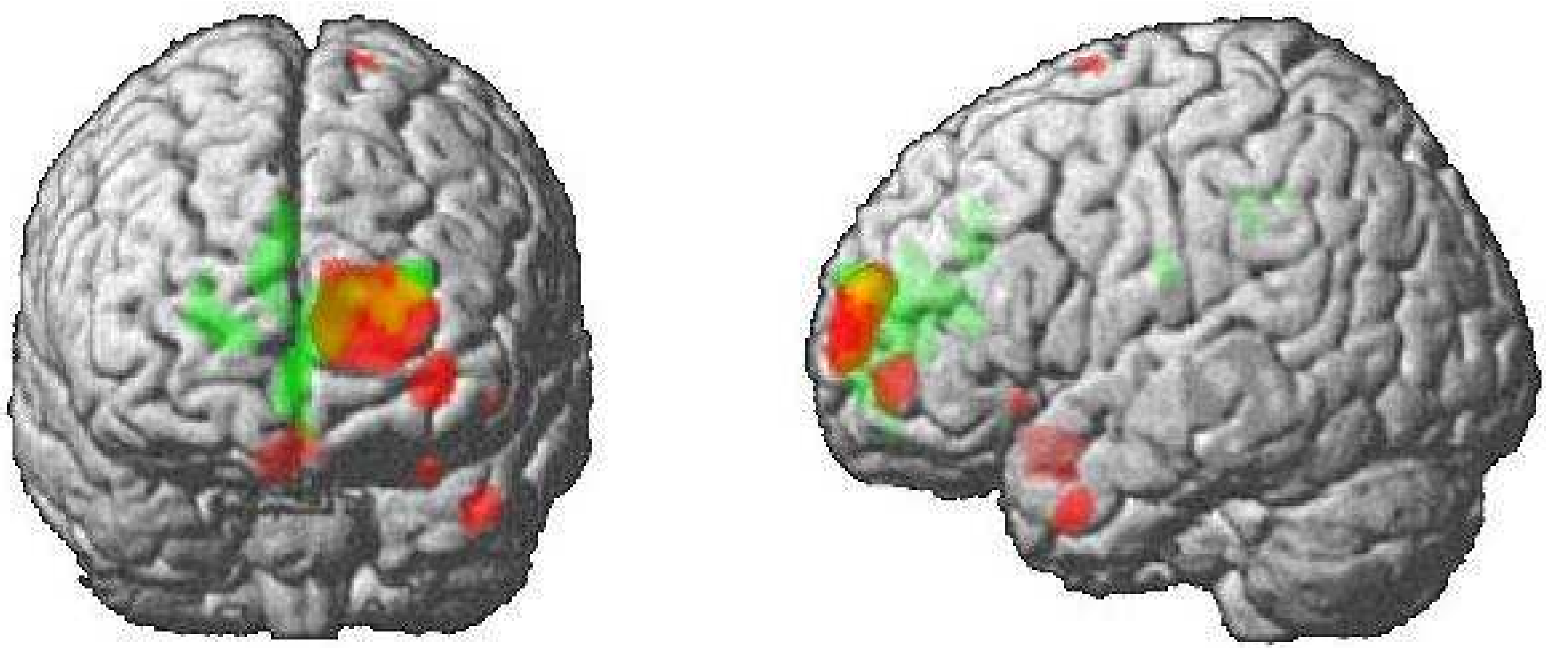
Red= grey matter differences; Green = fMRI activation in typical population



- 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

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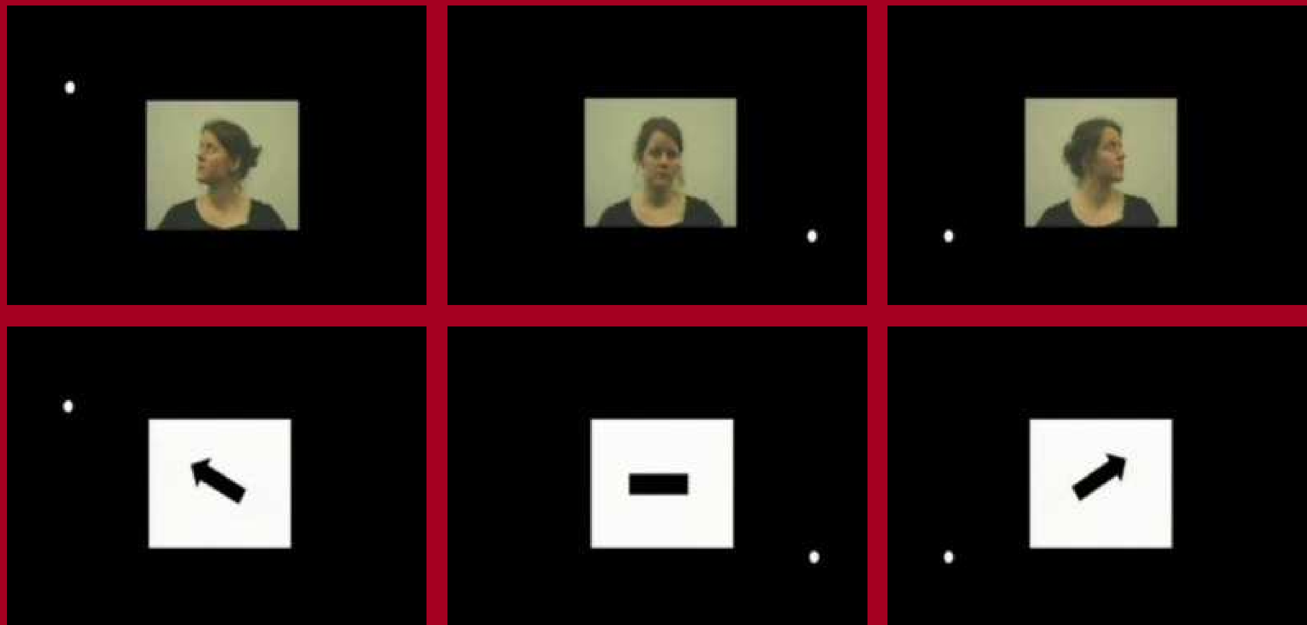
Self-related cue-direction

Congruent | Baseline | Incongruent

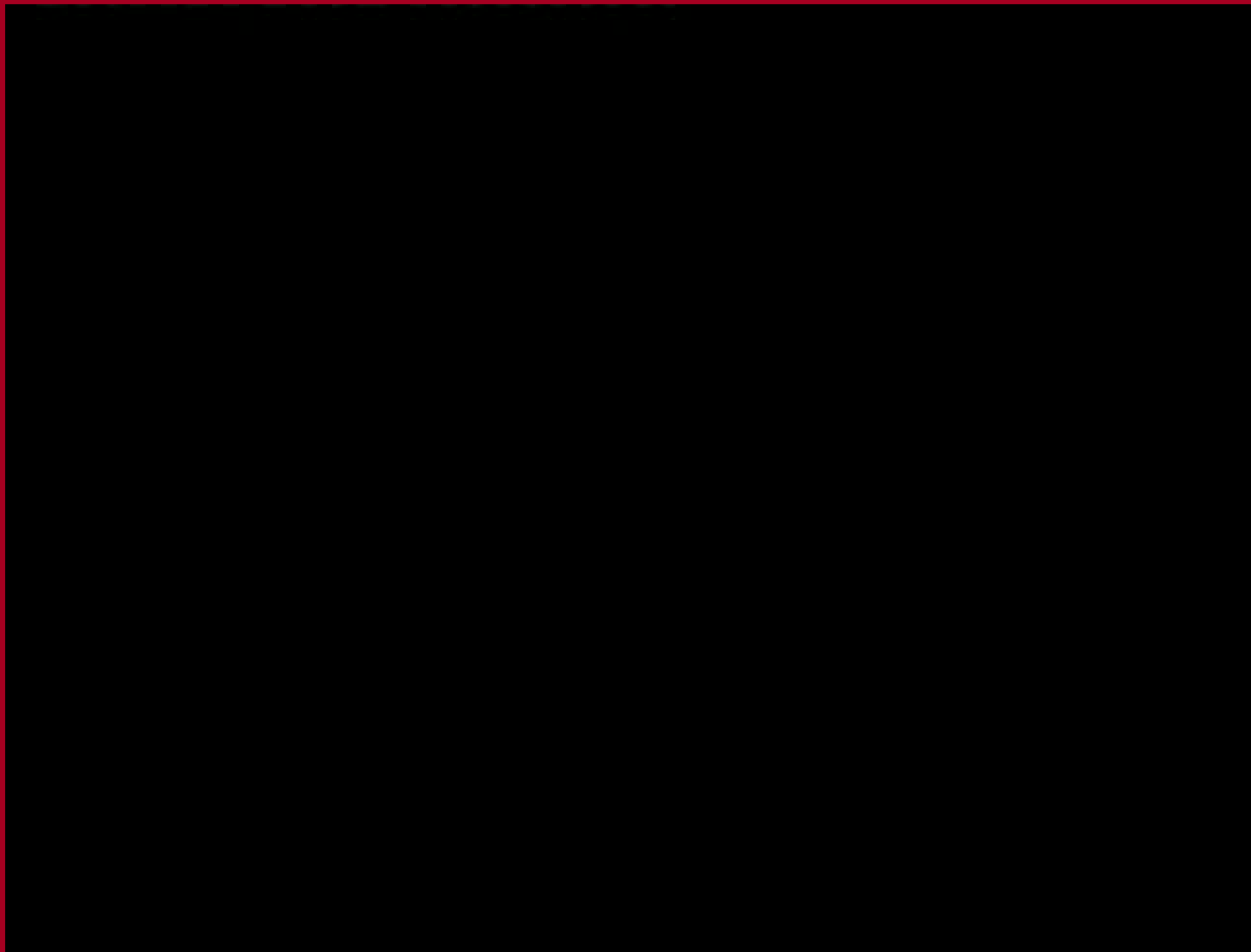
Faces

Social or symbolic

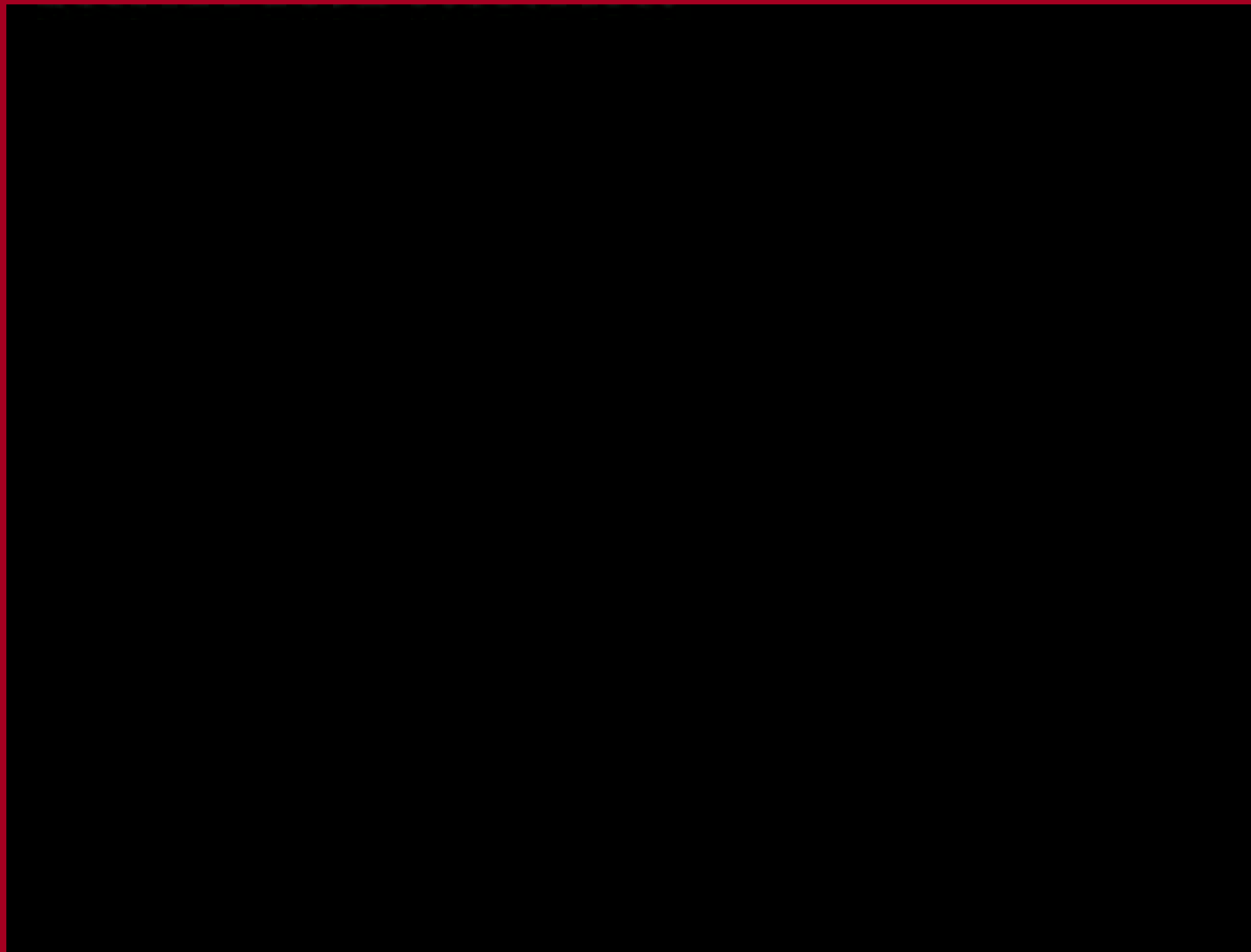
Arrows



Methods – Stimuli 1



Methods – Stimuli 2



Methods – Stimuli 3

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Methods - Participants

Recruitment:

Autism – Clinical services

Controls – Local schools

ADOS/ADI

Group	Total N	Age Y.M	SRS	Handedness L:R	IQ
ASD	13	13.7	107.8	10:3	112
Controls	13	13.5	19.9	11:2	112

Methods – MRI

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- 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

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- 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

fMRI data → Realign → Smooth Temporal → Co-register → Normalise → Smooth Spatial → Subject GLM

Figure 1: Single Subject Pipeline

Results

1. Overall Group Differences

Controls > ASD

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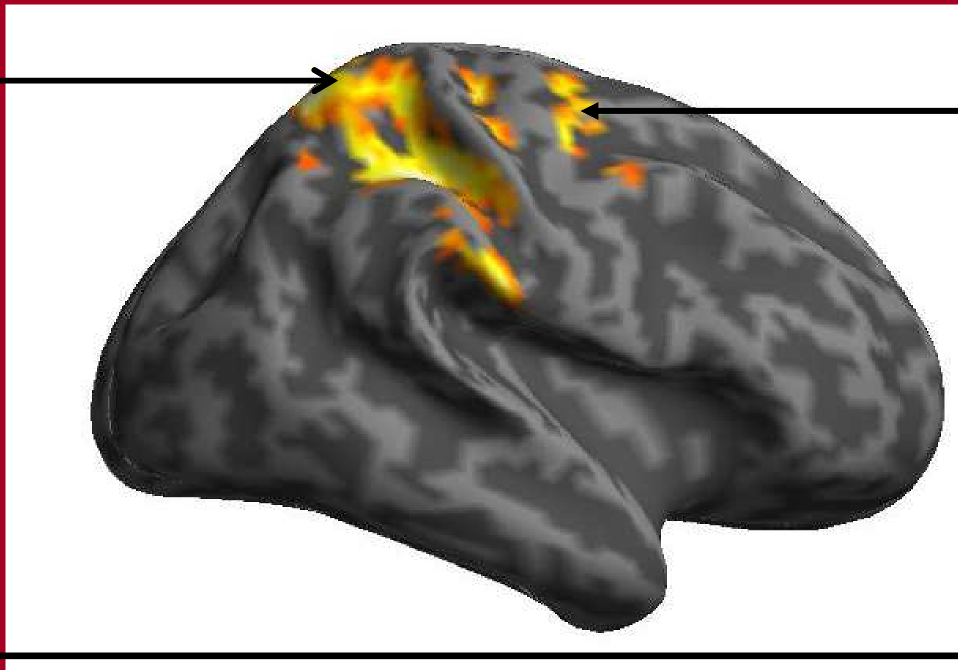
Right I.P.S.

16, -54, 56

Z = 4.79

FWE-corrected at voxel level: $p<0.023$

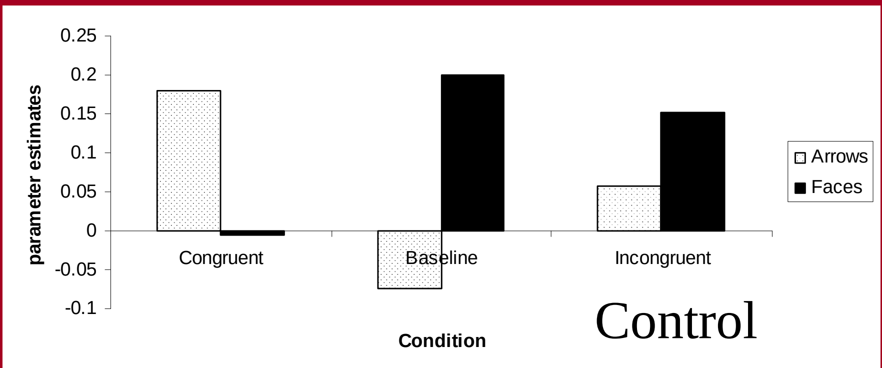


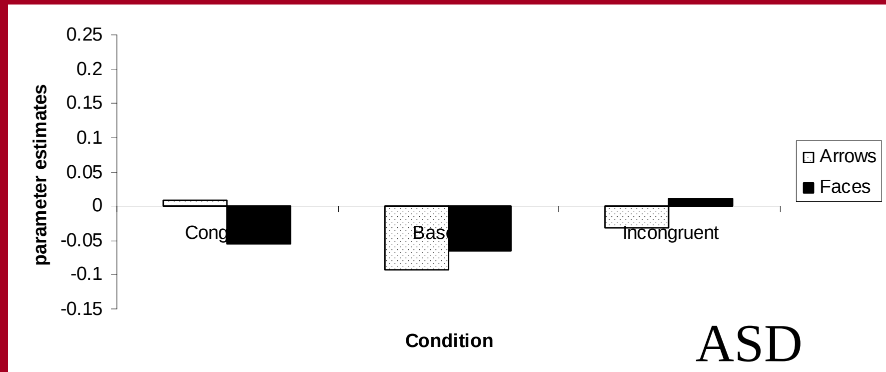
Post'r MFC

4,0,62

Z = 4.35

FWE-corrected at cluster level = 0.023





ASD > Control

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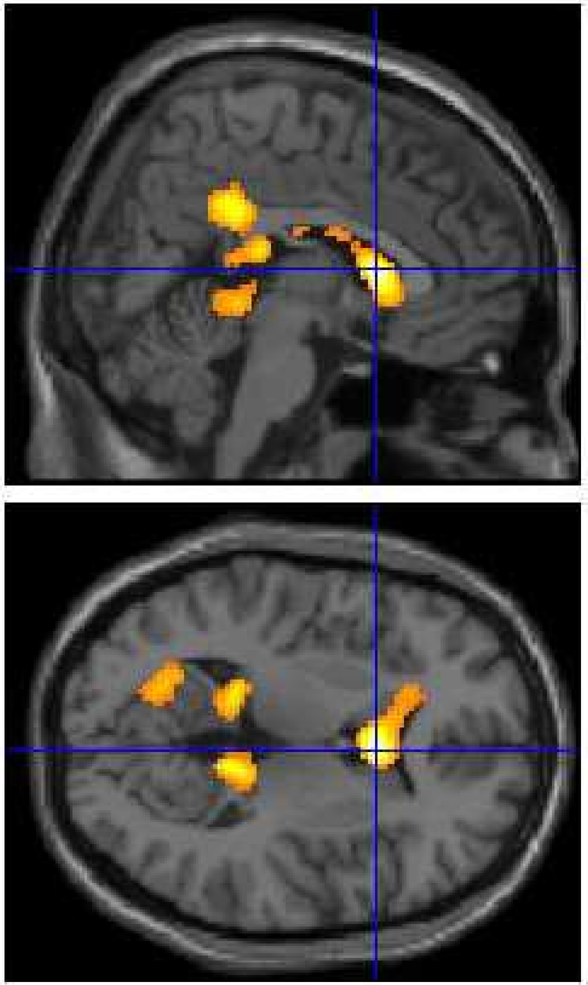

	x,y,z	Z (peak voxel)	P (voxel: FWE-corrected)	P(cluster: FWE corrected)
Right Caudate	4,14, 8	5.58	0.001	<0.0001
Right hippocampus	12,-36,4	4.37	0.123	0.003
Left hippocampus	10,-40,4	4.10	0.421	0.065

Interpretation

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- 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?

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

Social vs. Non-Social

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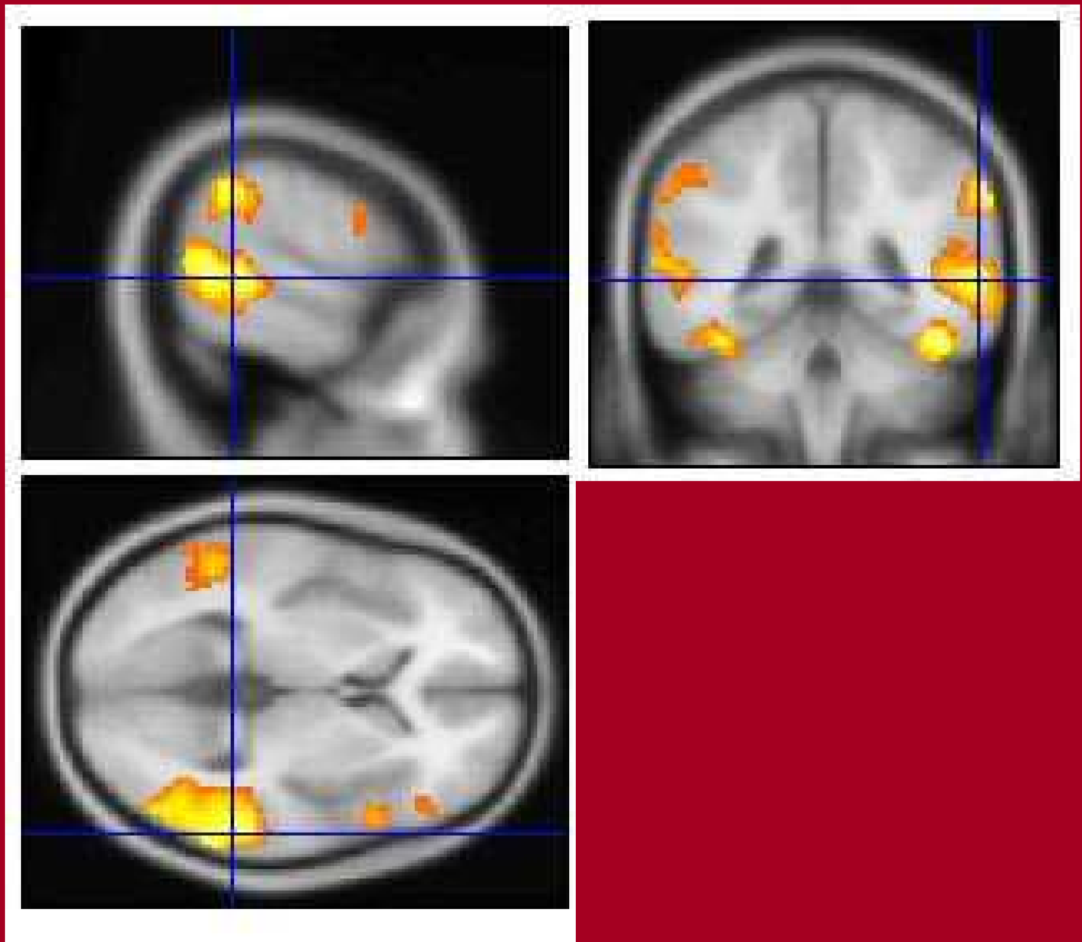

Greater activation to faces

- -Fusiform Gyrus
- -STS
- -Precentral Gyrus
- -Precuneus

No greater activation to arrows

No Group Differences

Congruous > Incongruous Faces, Controls>Autism

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X	Y	Z	Region	BA	p	z	extent
Right							
30	-14	21	Insula	13	0.0011	3.06	311
22	-11	21	Caudate	Caudate Body	0.0017	2.94	
14	-17	52	Medial Frontal Gyrus	6	0.0016	2.95	17
6	-18	25	Cingulate Gyrus	23	0.0023	2.83	24
4	31	-5	Anterior Cingulate	24	0.0024	2.82	27
Left							
-10	-46	6	Parahippocampal Gyrus	30	0.0013	3	49
-30	-63	22	Middle Temporal Gyrus	39	0.0019	2.9	29
-36	-29	0	Caudate	Caudate Tail	0.0038	2.67	18
-14	38	-14	Medial Frontal Gyrus	10	0.0038	2.67	21
-22	36	15	Anterior Cingulate	32	0.0039	2.66	29

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- 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.

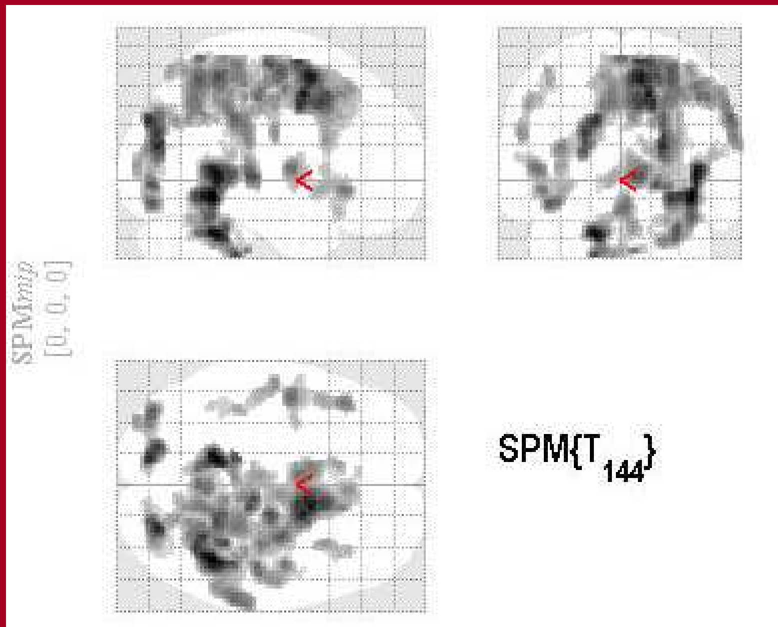
So

- Does response to social-cue depend upon direction relative to self, and is that affected by group?

- In what areas does the brains 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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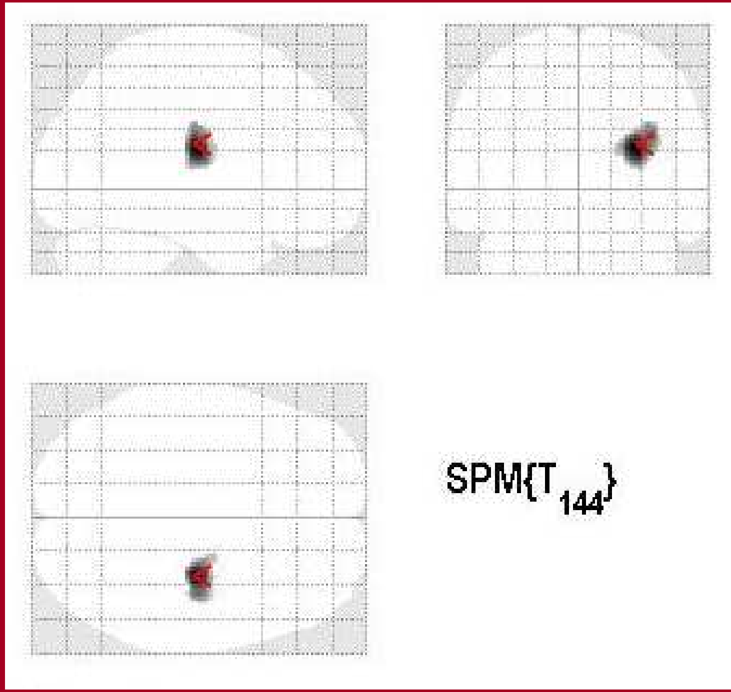
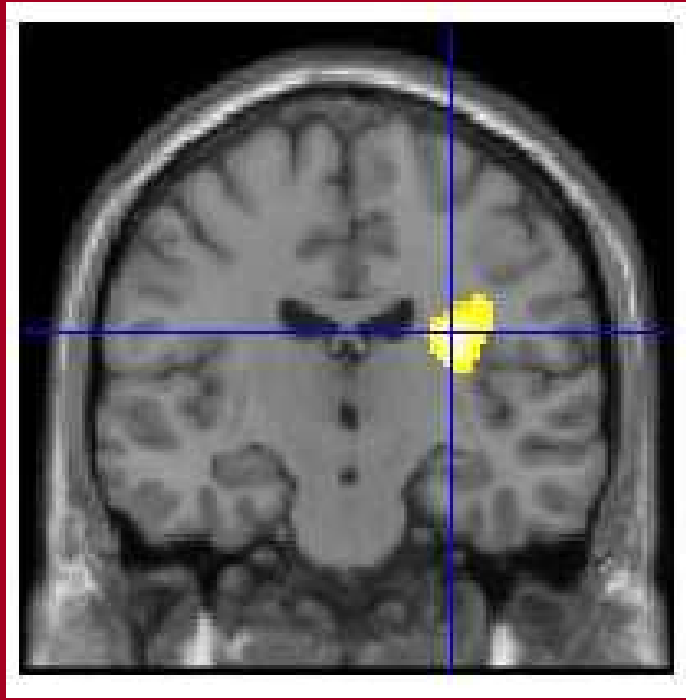
Both groups interaction between self-related cue-direction (to or away

X	Y	Z	Region	pFWE-corr	Z (peak voxel)	extent
40	-46	-10	Right fusiform gyrus	0.008	5.03	
42	-44	4	Right temporo-parietal junction	0.017	4.86	
12	8	56	Right medial frontal cortex	0.021	4.81	
-14	-44	-30	Left medial Cerebellum	0.012	4.94	

Effect of congruency for face > arrow

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





x,y,z = 30,-16,22; Z (peak voxel) =3.48,

p(peak voxel, uncorrected) =0.0005; p(cluster, FDR-corrected) = 0.043

Effect of Incongruity (>Congruous) for face>arrows

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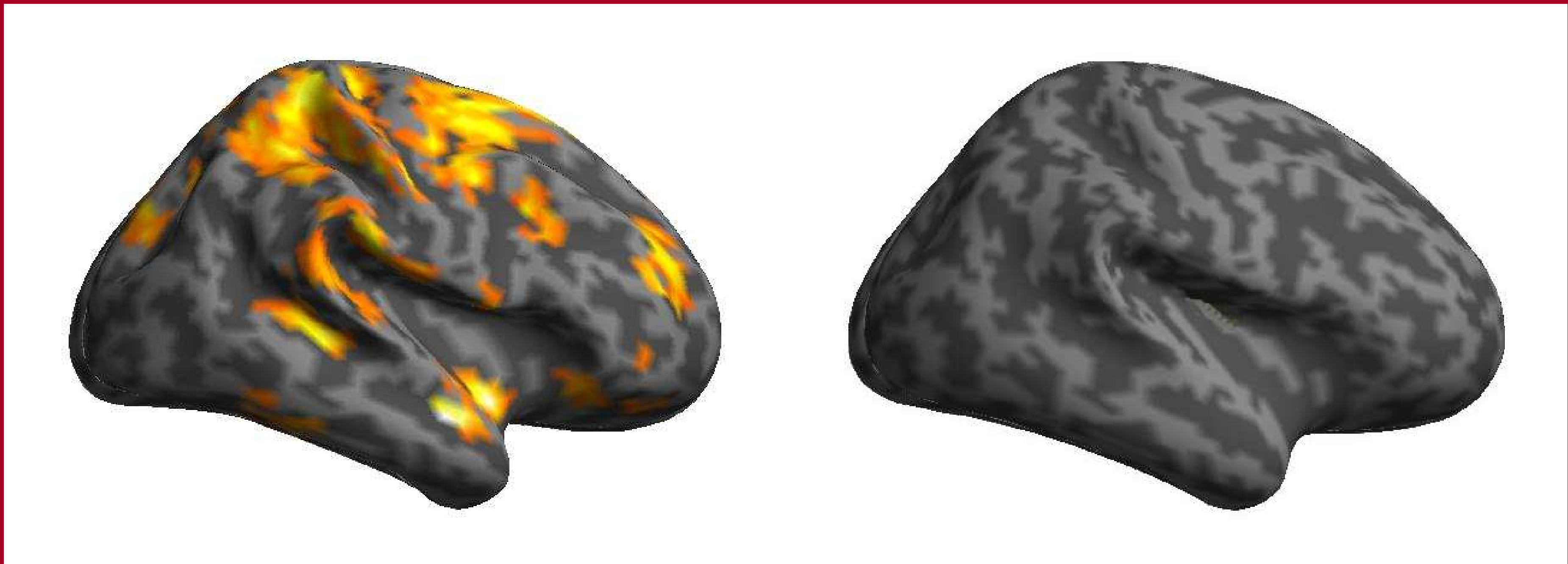
Controls **ASD**

Effect of Baseline (>Congruous) for faces > arrows



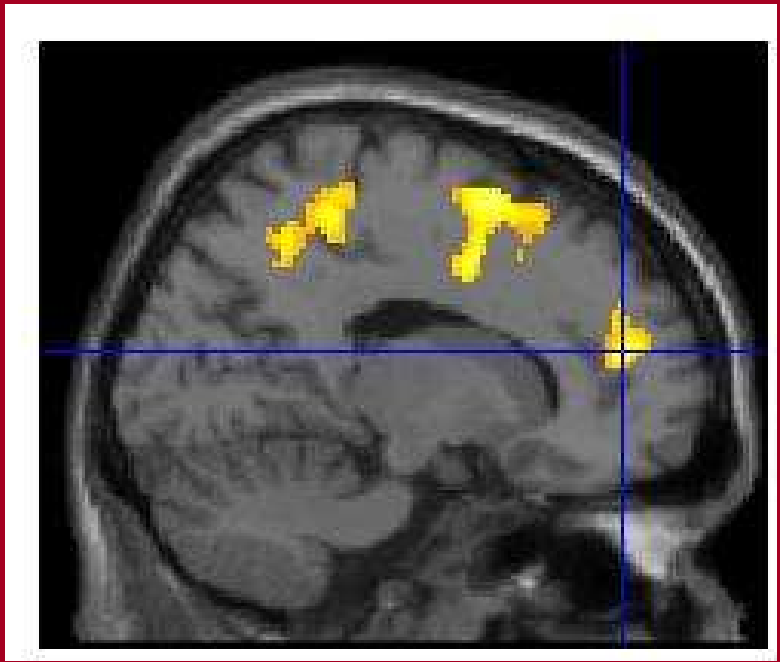
Controls

ASD

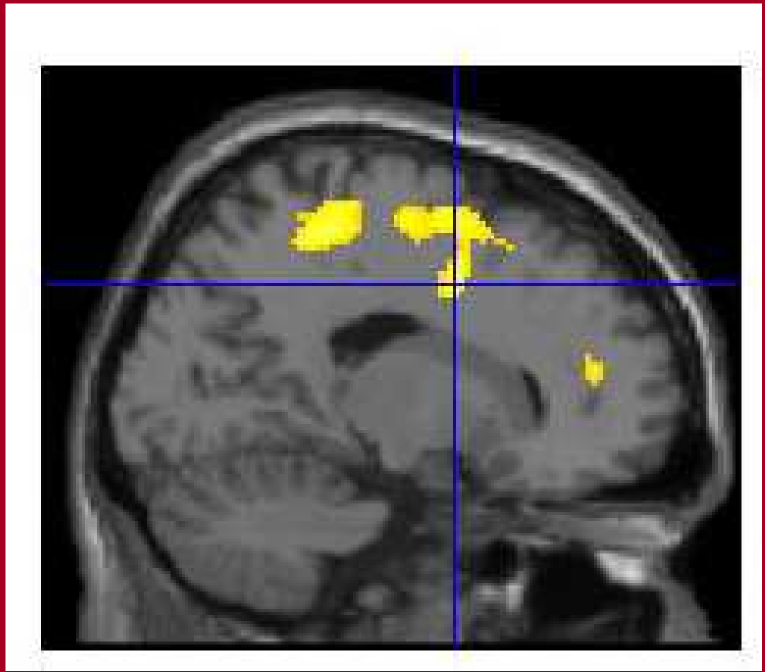
Controls: Cue type interacting with Congruity

Location	x,y,z	Cluster size	P(cluster) FWE-corr	Z (peak voxel)
Left Sup'r Frontal Gyrus	-12,22,54	2639	0.000	4.37
R.IPS	40,-46,-48	3055	0.000	3.91
Ant'r right MFC	16,48,16	955	0.035	3.60
Ant'r left Insula	-34,0,0	1073	0.021	3.44

Symbol-arrow interactions in medial frontal cortex



Incongruous



baseline

Medial prefrontal cortex locations in relation to Amodio & Frith (2006)

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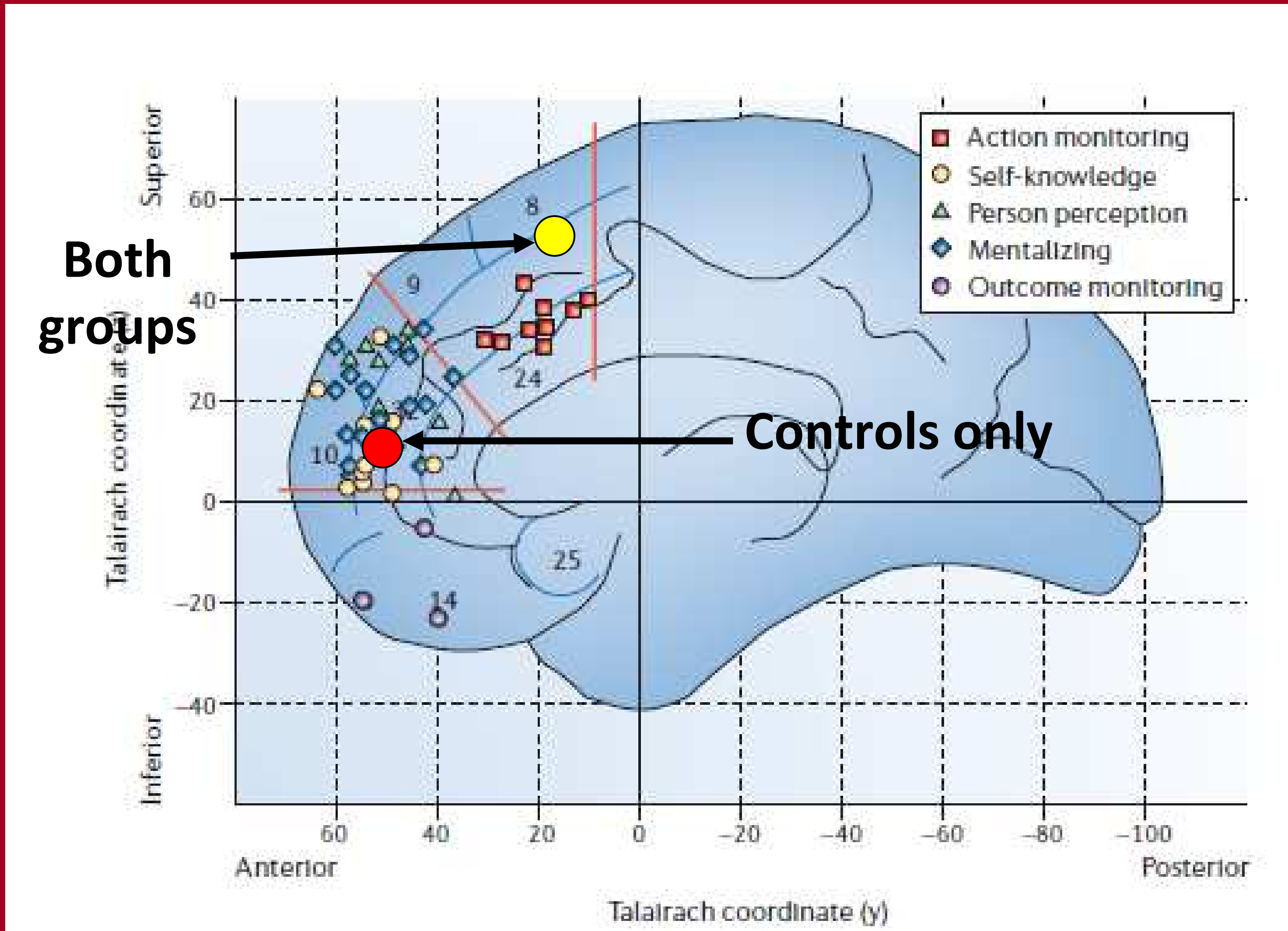

- In controls, interaction between self-related cue-direction and cue-type indicated that BOTH conditions modulated activity in aMFC, AI, R.IPS and L.FG.
- Both populations showed equally differential responses in face-processing areas to social vs non-social stimuli
- BUT Participants with ASD did not show evidence of modulating response to social stimuli according to self-related cue-direction.

Conclusions

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- 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

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