



Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Dissociation of mirroring and mentalising systems in autism

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ARTICLE INFO

Article history:

Received 2 December 2010
Revised 31 January 2011
Accepted 1 February 2011
Available online xxxx

Keywords:

Autism
Social cognition
Theory of mind
Mirror neuron system
Action understanding

ABSTRACT

The role of mirror neuron systems and mentalising systems in causing poor social and communication skills in individuals with autistic spectrum conditions is hotly debated. We studied 18 adults with autistic spectrum conditions in comparison to 19 age and IQ matched typical individuals. Behavioural assessments revealed difficulties in mental state attribution and action comprehension in the autism sample. We examined brain responses when observing rational and irrational hand actions, because these actions engage mirror and mentalising components of the social brain respectively.

Both typical and autistic participants activated the left anterior intraparietal sulcus component of the mirror system when viewing hand actions compared to moving shapes. The typical but not autistic participants activated the posterior mid cingulate cortex/supplementary motor area and bilateral fusiform cortex when viewing hand actions. When viewing irrational hand actions, the medial prefrontal cortex of typical participants deactivated but this region did not distinguish the different stimuli in autistic participants. These results suggest that parietal mirror regions function normally in autism, while differences in action understanding could be due to abnormal function of cingulate, fusiform and medial prefrontal regions. Thus, brain regions associated with mirroring and mentalising functions are differentially affected in autistic spectrum conditions.

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Introduction

The ability to make sense of other people's actions is a fundamental social skill which enables learning about the world and interaction with other people. This action comprehension skill may be abnormal in autistic spectrum conditions (ASC), a neurodevelopmental disorder with a particular impact on social cognition. The paper aims to advance our knowledge of the different brain systems involved in action understanding and to determine which of these might function atypically in ASC.

We first summarise current knowledge of brain systems for simple and more complex action comprehension and their relationship to autism. Research in social neuroscience commonly distinguishes between mirror systems for comprehending basic actions, and mentalising brain systems for interpreting other people's beliefs and desires (Wheatley et al., 2007). Classically, the human mirror system is defined as inferior frontal and inferior parietal cortex, and these regions are believed to contain mirror neurons that respond to both performed and observed actions (Rizzolatti et al., 2001). We use the term 'mirror systems' as a compact way to describe this network without requiring the presence of mirror neurons themselves, and we use the term 'mirroring' to refer to activity within classic mirror system regions which is assumed to link representations of performed and observed actions. It

is argued that the human mirror system provides a 'direct' mechanism for understanding other people's actions and emotions, and could be the foundation of social cognition (Gallese et al., 2004).

In contrast, comprehension of beliefs and desires engages a mentalising network in medial prefrontal cortex and temporoparietal junction (Fletcher et al., 1995; Frith, 2001; Saxe et al., 2004). Assessment of other people's intentions from stories (Jenkins and Mitchell, 2010) and pictures of human actions (de Lange et al., 2008; Spunt et al., 2010) and even the movement of simple geometric shapes (Castelli et al., 2000) also engages the mentalising network. However, the relationship between these mirror and mentalising regions is undefined; some argue that the development and functioning of mirror regions is an essential precursor to mentalising (Gallese and Goldman, 1998; Rizzolatti et al., 2009) while others suggest that the two systems are independent (Saxe, 2005; Southgate et al., 2010).

Both mirror (Iacoboni and Dapretto, 2006; Rizzolatti and Fabbri-Destro, 2009; Williams et al., 2001) and mentalising (Frith, 2001) networks have been implicated in the abnormal development of social cognition in autistic spectrum conditions (ASC). The dominant explanation for action comprehension difficulties in autism is the broken mirror hypothesis, which claims that dysfunction of neural systems for mirroring is a primary cause of poor social skills in autism (Gallese et al., 2009; Iacoboni and Dapretto, 2006; Oberman and Ramachandran, 2007; Rizzolatti and Fabbri-Destro, 2009; Williams et al., 2001). Evidence for this theory is mixed. Individuals with autism show reduced imitation (Williams et al., 2004), reduced modulation

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of mu rhythms over motor cortex (Oberman et al., 2005) (but see Fan et al., 2010), abnormal MEG responses (Nishitani et al., 2004), reduced excitability of motor cortex (Theoret et al., 2005) and a failure of predictive muscle activation (Cattaneo et al., 2007) during action comprehension tasks. These results support the broken mirror theory but use methods which are only weakly localised in the brain. fMRI studies show that activation of inferior frontal gyrus is reduced when children with autism imitate emotional facial expressions (Dapretto et al., 2006) and observe emotional body actions (Grezes et al., 2009). However, no mirror system differences were reported in studies of hand action imitation (Williams et al., 2006), observation of unemotional whole body actions (Grezes et al., 2009) or selectivity of responses to performed and observed hand actions (Dinstein et al., 2010).

The mentalising hypothesis of autism claims that the failure to comprehend other people's beliefs is a key factor in poor social skills in autism. This hypothesis can account for poor performance on false-belief tasks (Baron-Cohen et al., 1985; Frith, 2001; Senju et al., 2009) and in everyday social situations (Frith, 2003). Participants with ASC show reduced activation of mentalising brain regions during the observation of animated shapes interpreted as having mental states (Castelli et al., 2002). This finding is consistent with the role of the mentalising system in interpreting intentions, and with poor understanding of intentions in autism. However, few studies have directly assessed the ability of individuals with autism to understand other people's goals and intentions, and results have been mixed. Good goal understanding (Aldridge et al., 2000; Carpenter et al., 2001; Hamilton et al., 2007) but poor comprehension of more complex action sequences (Zalla et al., 2006) has been reported. Thus, it is not yet clear whether goal and intention understanding is spared or impaired in autism, and what role the mentalising system might play in this (Hamilton, 2009).

The present study addresses two questions. First, are brain systems for action understanding abnormal in autism? Second, what is the relationship between mirroring and mentalising in autism (Hamilton, 2009; Southgate et al., 2010), and can these functions dissociate? We studied a large and well-characterised participant group using both behavioural and fMRI measures of action understanding in non-verbal situations to assess the functioning of mirror and mentalising brain regions.

Previous studies have rarely attempted to engage both mirror and mentalising systems within the same paradigm. This is likely because most traditional mentalising tasks involve verbal stories (Baron-Cohen et al., 1985), while mirror systems are assessed using imitation or action observation (Rizzolatti et al., 2001). Here we build on the recent discovery that observation of irrational actions engages mentalising brain regions in typical adults without any specific instructions to consider intentions or mental states (Brass et al., 2007). Rational actions are those which achieve their goal efficiently given the constraints of the environment, while irrational actions are inefficient. Studies of typically developing infants show sensitivity to action rationality from the first year of life, and this is believed to arise from teleological reasoning about the relationship between actions, goals and contexts (Csibra, 2003). The capacity for teleological reasoning is likely to provide a foundation for later mentalising skills.

In the present study, we examine responses in the typical and autistic brain when observing rational hand actions, irrational hand actions or simple moving shapes with no biological form or motion. In typical individuals, observation of hand actions compared to moving shapes should engage brain regions associated with mirroring including anterior intraparietal sulcus, inferior parietal cortex and inferior frontal gyrus (Buccino et al., 2001; Gazzola and Keysers, 2009; Hamilton and Grafton, 2006). The broken mirror hypothesis predicts that this activation should be lacking in those with autism. Furthermore, typical individuals should engage mentalising regions including medial prefrontal cortex and temporoparietal junction

when observing irrational actions compared to rational actions (Brass et al., 2007). The mentalising hypothesis of autism predicts that equivalent engagement should not be seen in participants with ASC. Thus, the present study uses distinct but closely matched stimuli (rational and irrational actions) to probe action comprehension throughout the autistic brain.

Materials and methods

Participants

18 adults with a clinical diagnosis of Asperger's syndrome or autistic spectrum conditions and 19 age and IQ matched typical adults were recruited via local autism support groups and local publicity. Participant characteristics are summarised in Table 1 and detailed in Table S1. An additional two adults with ASC took part in the study but were excluded from all analysis due to excessive head movement during fMRI. All participants with ASC completed the Autism Diagnostic Observation Schedule (ADOS) Module 4 with a qualified examiner (Lord et al., 2000). 8 participants met the criteria for autism, and 8 met the criteria for autistic spectrum conditions. All participants also completed the Autism Quotient and 16 participants in the ASC group scored above the autism threshold of 26 (Baron-Cohen et al., 2001; Woodbury-Smith et al., 2005). Note that the two autistic participants that did not meet criteria on the ADOS were clearly above threshold on the AQ and had an unchanged ASC diagnosis since childhood. An additional analysis excluding these participants is reported in supplementary information. IQ was assessed using the full scale Weschler Adult Intelligence Scale (WAIS) and all participants had IQ scores over 80. The groups were matched on verbal and non-verbal IQ. All participants gave written informed consent before taking part and the study was approved by the University of Nottingham Medical School ethics committee.

Behavioural tasks

To assess mentalising, all participants watched movies depicting two triangles engaged in different interactions (Abell et al., 2000). Interactions could be (a) no interaction (e.g. drifting or floating), (b) physical interaction (e.g. bouncing off each other or chasing) and (c) mentalising interaction (e.g. teasing or coaxing). After each clip, participants judged the type of interaction they had seen. For mentalising animations they also judged the mental state of the triangles. All judgements were forced choice questions with four options, which provides an accurate assessment of mentalising, without the difficulty of coding responses or participant's reluctance to speak (White et al., 2011). Two questions were asked for each of the four mentalising clips, giving a range of scores from 0 to 8 and a chance level of 2.

To assess action comprehension, all participants completed a computerised gesture recognition task (Hamilton et al., 2007; Mozaz et al., 2006). On each trial, a cartoon image of an action with the hands missing was shown on the screen for 3 s. Then, three photographs of human hands postures were shown. Participants were asked to select the posture which best filled the gap in the cartoon by pressing a

Table 1

This table summarises the characteristics of the participants in this study. See Table S1 for full details of each individual.

	ASC	Typical	Statistical significance of group difference
N	18	19	
Age	33 ± 10.9	32.2 ± 10.1	0.820
Verbal IQ	112.9 ± 16.6	112.5 ± 13.8	0.935
Performance IQ	104.4 ± 18	113.4 ± 13.9	0.101
Autism quotient	36.1 ± 8.7	15.8 ± 7.2	0.000
Animations test	2.1 ± 2.1	3.7 ± 2	0.03
ADOS	8.7 ± 5		

response key. Participants completed 8 trials depicting transitive, tool-use actions (e.g. sew or draw) and 8 trials depicting intransitive, social actions (e.g. clap or wave) in a pseudorandom order. Reaction time and correct responses were recorded.

fMRI stimuli

Movie clips were prepared for each of the five conditions are illustrated in Fig. 1. In every clip two objects (one food and one tool) were present. The actor's hand started at rest in the lower right of the screen, then reached and took one of the objects, bringing it back to the start. Clips in set R1 showed the hand reaching with an efficient straight movement trajectory. Clips in set I1 showed the hand taking an inefficient irrational trajectory, going up and over an invisible barrier and returning the same way. These clips were filmed with invisible thread providing a barrier to enforce a natural trajectory. Clips in set R2 included a large red physical barrier and showed a hand reaching over it. Clips in set I2 were created by digitally manipulating clips from set R1 to impose a barrier on the action so that the hand moved through the barrier and returned the same way. This action is irrational from the point of view of the actor, who would hurt his hand

if the barrier were real. Clips in set S depicted three coloured shapes on a blue background; one of the shapes drifted steadily across the screen, while the others remained still. These clips provide a baseline for the perception of shape, colour and visual motion.

fMRI scanning and analysis

During fMRI scanning, participants viewed movie clips arranged in blocks of 8 movies (24 s per block). Each run of scanning contained 10 blocks (two of each type) presented in a pseudorandom order. Each participant completed four runs. To maintain alertness, participants were instructed to press a button when the movie froze in the middle of an action. Two freeze trials were present in each run, counter-balanced across blocks.

Embedded within each block of the experimental design, we ordered the video clips to measure repetition suppression for the goal of the action, as previously (Hamilton and Grafton, 2006, 2008). This means that it is possible to analyse the same dataset both as a traditional block-design study and also as an event-related repetition suppression study. For the repetition suppression component, video clips were ordered and classified in relation to the previous clip in the

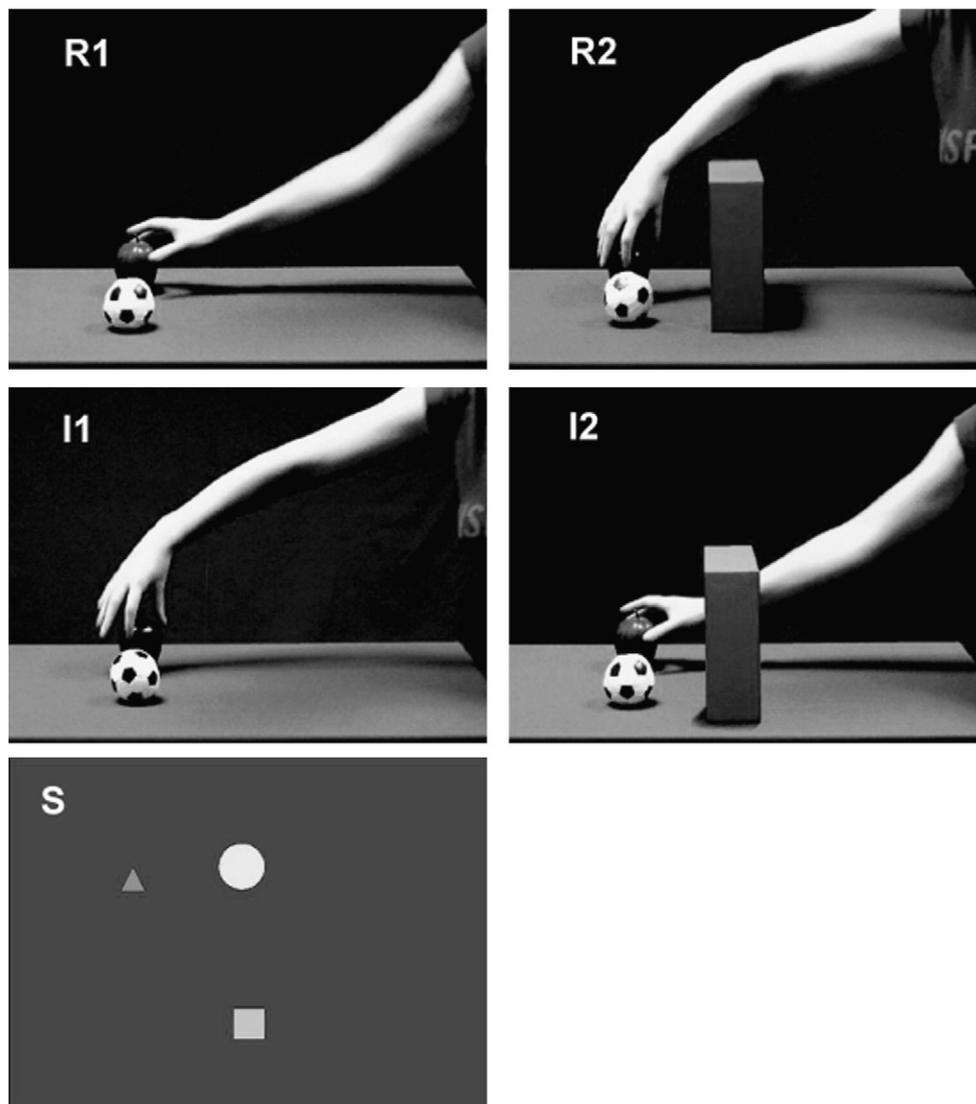


Fig. 1. Frames from the five types of movies shown during fMRI scanning. Each hand action movie was 2.5 s long and depicted a still hand on the right of the screen which reached out, picked up one of two objects and took the object back to the starting location. R1 – rational action, R2 – rational action with barrier, I1 – irrational action, and I2 – irrational action with barrier. The shape movies (S) showed three shapes on the screen, one of which moved linearly across the screen over 2.5 s. Throughout the text, the letter codes given here are used to refer to the different types of movies.

sequence (one-back design). For example, a take-ball clip which followed a take-apple clip would be classified as a 'novel goal', while a take-ball clip which followed another take-ball clip would be classified as a 'repeated goal'. This repetition suppression is specific to the goal of the action, rather than hand trajectory, because the locations of objects on the tables and hence the precise hand trajectory varied randomly from trial to trial. This method has been used previously to identify repetition suppression for goals in left anterior intraparietal sulcus (Hamilton and Grafton, 2006) and the logic of the present approach is identical.

Whole brain images were collected in a 3 T Phillips Achieva scanner using an 8 channel-phased array head coil with 40 slices per TR (3 mm thickness); TR: 2500 ms; TE: 40 ms; flip angle: 80°; FOV: 19.2 cm, matrix: 64×64. 136 brain images were stored on each of 4 functional runs. High resolution anatomical images were also collected. Data were realigned and unwarped and the mean EPI image was normalised to the standard SPM EPI template (MNI space) with a resolution of 2×2×2 mm using SPM2 software.

Two different design matrices were fitted for each participant. The block design matrix modelled the blocks of movies in each of the five categories as a box-car of a 24 second duration convolved with the standard hemodynamic response function. Regressors were included for freeze trials. The repetition suppression design matrix modelled the movies within each block as events which were classified as 'first' (the first movie in a block), 'novel' (an action with a different goal relative to the previous movie), or 'repeated' (an action with the same goal as the previous movie). This design did not distinguish different action types. Regressors were included for freeze trials and for shape movies. These two design matrices are independent of one another, and allow us to ask different questions from the same dataset. For both design matrices, at estimation every raw image was weighted according to its overall variability to reduce the impact of movement artefacts (Diedrichsen and Shadmehr, 2005). After estimation, 9 mm smoothing was applied to the beta images.

Statistical analysis

Contrasts were calculated for the following effects in the block design: all hands>shapes (R1 + R2 + I1 + I2>S), rational actions>irrational actions (R1 + R2>I1 + I2), and irrational actions>rational actions (I1 + I2>R1 + R2). In the repetition suppression design matrix, contrasts were calculated for novel goals>repeated goals. In both designs, contrast images were taken to the second level for a random effects analysis and were analysed first within each group and then between groups.

All results were first thresholded at $p<0.01$ uncorrected and 50 voxels, and all figures are shown at this threshold. Only clusters which met the $p<0.05$ cluster corrected threshold (Friston et al., 1996), either over the whole brain or within a small volume correction, are reported and discussed. Thus, all reported results met correction for multiple comparisons. Small volume corrections were applied to the medial prefrontal cortex (based on mentalising coordinates from papers listed in Amodio and Frith, 2006) and to the left anterior intraparietal sulcus (based on coordinates from Tunik et al., 2007), and are noted in the results tables.

Results

Behavioural assessment

As expected, the ASC group scored higher than the typical group on the autism quotient (Baron-Cohen et al., 2001) ($t=7.75$, $df=35$, $p<0.0001$). Assessment of mentalising ability in the triangles task revealed that participants in the autism group were less able to select appropriate mental state descriptions than typical participants (Mann-Whitney $U=93.5$, $p=0.03$).

In the action comprehension task, all participants made more errors on transitive trials than intransitive trials ($F=22.4$, $df=1,34$, $p<0.001$) and the ASC group made more errors overall ($F=4.8$, $df=1,34$, $p=0.035$) but there was no interaction ($F<1$). Analysis of correct reaction times revealed no effect of trial type ($F<1$) and a trend towards an effect of group ($F=3.0$, $df=1,34$, $p=0.091$). A significant group by trial type interaction was found ($F=4.33$, $df=1,34$, $p=0.045$). A post-hoc t -test confirmed that the autism group took significantly longer to respond to intransitive trials than the typical group ($t=2.33$, $df=34$, $p=0.026$), see Supplementary Fig. S1. These results show that the ASC group had subtle difficulties with action comprehension, in particular with intransitive social actions. All of these analyses were repeated using performance IQ (PIQ) as a covariate to ensure that the trend towards a group difference in PIQ did not have a bearing on task performance. The pattern of results was comparable to those reported above.

Brain responses to observed actions

Brain activation when viewing all goal directed actions (R1, R2, I1, and I2) was contrasted with activation when viewing moving shapes (S). Typical participants showed robust activation of occipito-temporal cortex, middle cingulate cortex, pulvinar and left anterior intraparietal sulcus (aIPS) (Fig. 2A). Similarly, autistic participants activated middle and inferior occipital gyrus and left aIPS (Fig. 2A). Thus, both groups showed similar response profiles in the parietal component of the mirror system.

An interaction contrast was calculated to localise brain regions with stronger responses to hand actions (R1, R2, I1, and I2) than moving shapes (S) in the typical group compared to the autistic group. A large cluster in the posterior mid cingulate cortex (pmCC) extending to the supplementary motor area (SMA) (Fig. 3A) and a diffuse cluster spanning bilateral fusiform cortex through occipital cortex and lingual gyrus (Fig. 3B) both showed this pattern of activation. The pmCC cluster found in this interaction contrast closely overlaps with the pmCC cluster found when typical participants observed hand actions, confirming that this region is specifically engaged by action observation in typical participants. Furthermore, this activation is robust when PIQ is included as a covariate. Though the figures suggest that pmCC was more activated in the autism group for observation of shapes compared to hand actions, this contrast did not yield significant results.

The fusiform cluster partly overlapped with the extensive occipital cluster found when typical participants observed hand actions, with the largest overlap region falling in the right fusiform cortex (Fig. 3B). However, when including PIQ as a covariate, this cluster is more diffuse and does not meet cluster corrected thresholds. The reverse interaction contrast did not yield any significant clusters. These results show that there are clear differences in how the typical and autistic brain responds to observed action outside the classic mirror system.

Repetition suppression analysis

A separate event-related repetition suppression analysis was used to test for selectivity to action goals (Hamilton and Grafton, 2006). In the typical group, a cluster of 185 voxels within left aIPS showed a stronger response to novel than repeated goals but did not meet corrected statistical thresholds. In the autistic group, robust repetition suppression ($p<0.05$ whole brain cluster corrected) was found in left aIPS and middle frontal gyrus. The left aIPS clusters in both groups overlapped (Fig. 2B), demonstrating that participants with ASC encoded the goal of the observed hand action (take-ball or take-apple) in the same brain regions and showing the pattern of same trial-to-trial repetition suppression as the typical individuals. No group differences were found in the repetition suppression analysis.

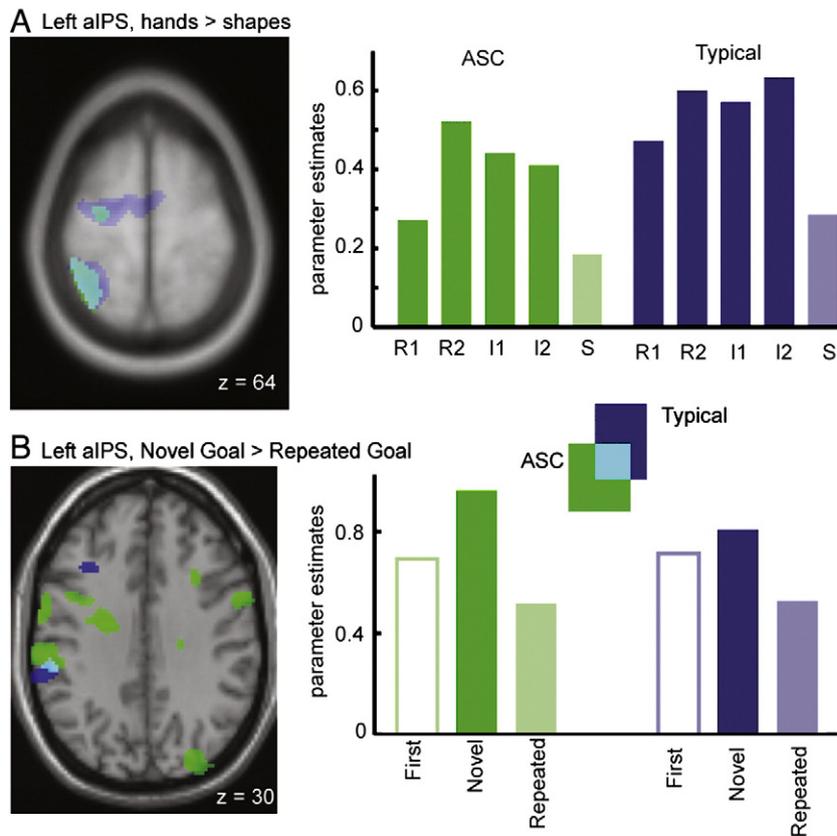


Fig. 2. Goal directed hand actions. A. Both typical and autistic participants activated anterior intraparietal sulcus when viewing hand actions compared to viewing moving shapes. Coordinates for all clusters are given in Table S2a and b. Coordinates for the contrast of rational goal directed hand actions only (movie set R1) compared to shapes were very similar and are given in Table S5a and b. B. Both typical and autistic participants showed repetition suppression in left anterior intraparietal sulcus, with stronger responses to novel goals than to repeated goals. Coordinates are given in Table S3.

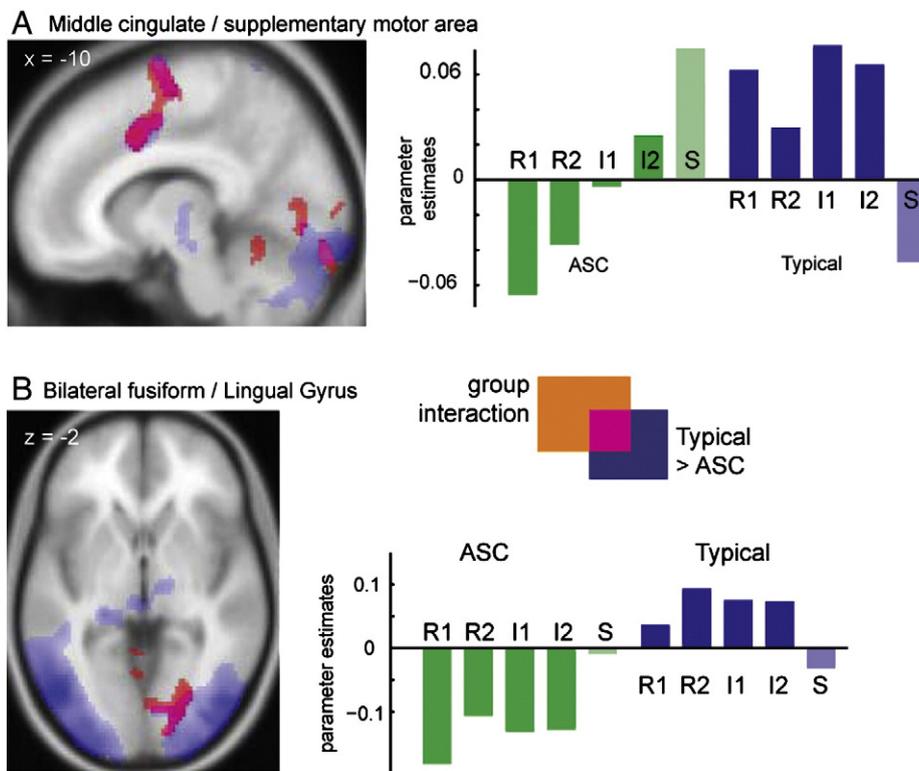


Fig. 3. Group differences in responsiveness to hands > shapes. The group by hands > shapes interaction analysis revealed clusters in posterior mid cingulate cortex extending to SMA and in bilateral fusiform cortex. Coordinates for all clusters are given in Table S2c. Coordinates for the contrast of rational goal directed hand actions only (movie set R1) compared to shapes were very similar and are given in Table S5c.

Observation of irrational actions

When viewing irrational actions (I1 and I2) compared to rational actions (R1 and R2), typical participants showed greater activation of right aIPS (Fig. 4A) and reduced activation of mPFC (Fig. 4B). The ASC group also activated right aIPS when viewing irrational actions (Fig. 4A) and this cluster overlapped substantially with the equivalent contrast in typical participants. However, the ASC group did not show differential activation of medial prefrontal cortex when viewing irrational actions. To directly test for group differences, we calculated the interaction between participant group and action rationality. This revealed that mPFC (Fig. 4B) differentiates between rational and irrational actions in typical individuals but not in those with autism. The region identified in this contrast overlapped substantially with the region identified when contrasting rational and irrational actions in typical individuals only, confirming that the interaction is driven by a rationality effect in the typical participants. This finding is also robust when including PIQ as a covariate.

General discussion

This paper aimed to further our understanding of the role of mirroring and mentalising brain systems in action understanding in autism. Our results shed light on this complex topic in several ways. We demonstrate reduced comprehension of actions and poor mentalising in a group of participants with autism. These same participants showed typical activation of the aIPS component of the human mirror system when viewing hand actions, but group differences in pMCC/SMA and fusiform cortex. Furthermore, mPFC distinguished irrational from rational actions in typical but not autistic participants. The full implications of these results for our neurocognitive theories of autism and social interaction are discussed below.

Action comprehension and the autistic brain

The current data compared responses in the typical and autistic brain when participants observed hand actions rather than moving shapes. We found that both typical and autistic participant groups activated left aIPS when viewing hand actions compared to moving shapes and both showed repetition suppression in left aIPS tied to the goal of the action on a trial-by-trial basis. This repetition suppression analysis, closely based on previous studies (Hamilton and Grafton, 2006) demonstrates that aIPS responses in both groups are selective for the goal of the observed action. The results cannot be accounted for by selectivity to hand motion or direction because these features did not vary systematically from trial to trial as the goal did. In addition to these group similarities, we found differences between typical and autistic brains observing actions outside the classic mirror system, in pMCC/SMA and in fusiform cortex.

Previous fMRI studies of action processing in ASC have reported no group differences during imitation of hand actions (Williams et al., 2006) or observation of unemotional whole body actions (Grezes et al., 2009). Using a repetition suppression approach similar to the current paper, Dinstein and colleagues showed that selectivity of responses to performed and observed hand shape in aIPS is normal in ASC (Dinstein et al., 2010). The present data confirms this result and extends it to goal directed hand actions in a larger participant sample. The finding of normal responses in the aIPS component of the mirror system is critical because aIPS encodes goal directed hand actions (Hamilton and Grafton, 2006; Tunik et al., 2007). Stroke damage to the parietal mirror system impairs imitation and action comprehension (Buxbaum et al., 2005). Normal aIPS brain responses in autism may provide an explanation for behavioural results demonstrating intact comprehension of goal directed action in autism (Aldridge et al., 2000; Carpenter et al., 2001; Hamilton et al., 2007). Furthermore, the finding that one key part of the mirror system is intact in autism

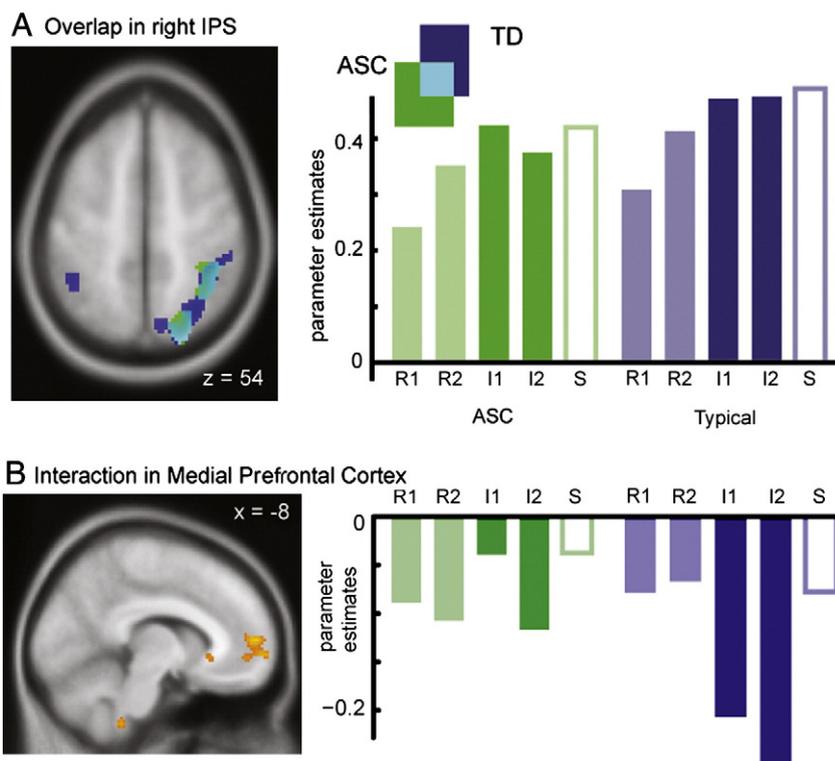


Fig. 4. Group similarities (A) and differences (B) in responsiveness to irrational and rational actions. A. Both typical and autistic participants activated right intraparietal sulcus when viewing irrational actions compared to rational actions. Coordinates for all clusters are given in Table S4e and f. An additional analysis to compare possible and impossible irrational actions did not yield any group differences. The clusters are reported in Table S6 and Fig. S1. B. Typical but not autistic participants differentiate between irrational and rational actions in medial prefrontal cortex. Coordinates of clusters are given in Table S4a and c.

means that theories proposing a global mirror system deficit in autism are not plausible.

However, our data also contrasts with other studies. Group differences between ASC and typical participants have been reported in inferior frontal gyrus during imitation of emotional facial expressions (Dapretto et al., 2006) and in premotor and inferior frontal regions during observation of emotional body actions (Grezes et al., 2009). These results might differ from ours because our stimuli did not involve emotional actions. Inferior frontal gyrus is considered a classic mirror system region, and was not engaged in either typical or autistic participants in our study. This might seem problematic, but a recent meta-analysis suggests that engagement of premotor cortex is more common than inferior frontal gyrus during action observation tasks which do not involve imitation (Caspers et al., 2010). Both our participant groups showed sub-threshold activation of premotor cortex in the action observation task. Future studies could use methods (e.g. Kilner et al (2009)) which more specifically test the integrity of inferior frontal regions in ASC.

The present paper also reports group differences during action observation in brain regions beyond the classic mirror system. A large cluster spanning posterior mid cingulate cortex and supplementary motor area (pMCC/SMA) showed a stronger response to hand actions than moving shapes in typical but not autistic participants. Some studies suggest that the SMA has mirror properties (Gazzola and Keysers, 2009; Mukamel et al., 2010) and a role in action prediction (Ramnani and Miall, 2004). An extended mirror model could plausibly claim the SMA as part of the human mirror system, and argue that dysfunction of this component is central to the broken mirror in autism, but such a model has not yet been proposed.

An alternative is to consider the pMCC part of this cluster. Nomenclature for this region is mixed, with some studies terming it posterior mid-cingulate (Vogt, 2005; Yu et al., 2010) and others terming it middle cingulate cortex (Chiu et al, 2008 and Lombardo et al, 2010). Typical participants engage pMCC for self-related mentalising, while autistic participants engaged pMCC for other-related mentalising (Lombardo et al., 2010). In an economic game, middle cingulate activity during the 'self' phase of the game distinguished autistic and typical participants (Chiu et al., 2008). It is possible that observation of hand actions requires a degree of self-other processing, leading to group differences in this area. As the cluster we report here is large and spans more than one cortical region, we cannot distinguish between these different functions. However, the finding of group differences in this region suggests the need for a broader consideration of action understanding in autism, beyond the current dichotomy of mentalising and mirror systems. Further investigation of the role of pMCC/SMA in social cognition and in autism would be essential.

A difference between typical and autistic groups was also found in bilateral fusiform cortex, which responds to observation of hand actions in typical participants and observation of moving shapes in autistic participants. This finding was less robust as the cluster was diffuse and did not meet thresholds after covarying PIQ. However, previous studies also report group differences in fusiform in autism. (Dinstein et al., 2010) found stronger fusiform responses to action observation in typical than autistic participants. A meta-analysis of autism fMRI studies highlights fusiform cortex as a region which tends to be more activated in typical than autistic participants (Di Martino et al., 2009). Fusiform cortex is linked to face (Kanwisher et al., 1997) and body (Peelen and Downing, 2005) perception, and it is likely that differences in body perception in autism underlie the activation differences we report.

Our fMRI results are also important in relation to behavioural data on action understanding in autism. In our participant sample, the typical and ASC groups differed in error rates and reaction times in an action comprehension task. The interaction effect in reaction time is critical, because outliers or generally slower reaction times in the ASC group cannot account for this group by condition interaction. Thus, our data shows that weak performance on a task involving understanding of

intransitive, social actions can co-occur with normal engagement of the parietal mirror system.

Finally, our fMRI results, with a pattern of group similarity in the parietal component of the mirror system and group differences beyond the mirror system, may be able to account for some previous mixed results in behavioural studies of action understanding in autism. We found normal responses in the parietal mirror system which encodes action goals. This can be linked to good comprehension of action goals by individuals with autism (Aldridge et al., 2000; Carpenter et al., 2001; Hamilton et al., 2007) and normal predictive eye movements when observing goal-directed actions (Falck-Ytter, 2009). In contrast, we found reduced activation of MCC/SMA and fusiform in ASC brains. This might account for some previous reports of abnormal prefrontal/premotor brain responses during action understanding in autism (Cattaneo et al., 2007; Nishitani et al., 2004; Oberman et al., 2005; Theoret et al., 2005). Given the link between SMA and motor sequencing (Hazeltine et al., 1997), SMA dysfunction might provide an explanation for reported difficulties in understanding and performing chained action sequences in autism (Cattaneo et al., 2007; Fabbri-Destro et al., 2009; Zalla et al., 2006).

Overall, our results implicate brain regions beyond the classic parietal mirror system in abnormal action comprehension in autism. We suggest that future studies of autism should be cautious in attributing behavioural differences to specific brain regions without direct neuroimaging evidence. The present results suggest that behavioural action understanding differences between typical and autistic participants are more likely to result from differences in visual (fusiform) or motor-cognitive (pMCC/SMA) processing of observed actions, than from parietal mirror systems.

Mirroring and mentalising

The second aim in our study was to address the relationship between neurocognitive systems for mirroring and mentalising. We compared brain responses during observation of irrational actions to observation of rational actions to address this question. Detection of action irrationality requires teleological reasoning, a precursor to full mentalising (Csibra, 2003) and in typical adults engages mentalising brain regions including medial prefrontal cortex (mPFC) and temporoparietal junction (TPJ) (Brass et al., 2007). In the present study, we found that typical participants engaged right aIPS and disengaged mPFC when observing irrational actions. The autistic participants also engaged right IPS, but did not differentiate the stimulus types within mPFC.

Considering only the typical participant group, our results differ from the two previous studies of observation of irrational actions. Brass and colleagues reported stronger engagement of mPFC during irrational actions while we report reduced engagement of the same area during irrational actions. Brass also reported engagement of TPJ; we did not find TPJ activation but did find engagement of right aIPS. Another recent study (Jastorff et al., 2010) found sensitivity to rationality only in the middle temporal gyrus, and not in mentalising brain regions. This could be due to the smaller number of participants and use of a functional localiser approach. All three studies used very different stimulus sets, so it is likely that some differences in the stimuli can account for these very different results. The actions tested by Brass were all unusual and irrationality was defined by the environmental constraints, whereas in our study the actions were common and irrationality was defined by movement path. As right aIPS is engaged when observing more complex actions (Hamilton and Grafton, 2008; Hartmann et al., 2005), the change of movement paths and contexts in our study could account for the activation of right aIPS. Our paradigm included impossible irrational actions (Fig. 1, condition I2) unlike either previous study. However, additional analysis (supplementary info) rules out the possibility that our effect is driven by brain responses to these impossible irrational actions. One possible explanation of the cross-study difference lies in the recent finding (Jenkins and Mitchell, 2010) that mPFC is sensitive to

ambiguity in intention-mentalising tasks, and that different regions within mPFC have slightly different response profiles. All irrational action tasks involve somewhat ambiguous situations, but this has not yet been explicitly controlled. Further studies could test this possibility.

The results from the ASC group observing irrational actions show different response patterns in mirroring and mentalising brain systems. Like the typical participants, those with autism engaged right aIPF when observing irrational actions, which could reflect the sensitivity of this mirror region to complex actions (Hamilton and Grafton, 2008; Hartmann et al., 2005). However, the ASC group did not engage or disengage mPFC in any of the different stimulus conditions, and a group by condition interaction was found in mPFC. The lack of sensitivity to action rationality in this key mentalising brain region parallels the behavioural finding that the ASC group found it hard to interpret the intentions of animated triangles in a nonverbal mentalising task (Abell et al., 2000; White et al., submitted). Because the typical participants deactivated mPFC in the irrational action condition, we cannot suggest that they engaged in more mentalising than the ASC group when viewing irrational actions. However, our data does show a clear dissociation between parietal mirror systems and frontal mentalising regions, with the former functioning normally in autism and the latter not responding. Further study will be needed to understand the cognitive and behavioural consequence of this dissociation.

Conclusions

This paper describes a detailed assessment of neural responses to observed rational and irrational goal directed hand actions in the typical and autistic brain. Our results show that the parietal mirror system is intact in autism but that dysfunction of other regions, some that may have mirror roles and others that do not, may have an important role in action comprehension failures in autism. Furthermore, our data suggest that brain systems associated with mirroring and mentalising have different response profiles in autism.

Funding

This work is supported by a pilot grant from Autism Speaks (#1925) and by the School of Psychology, University of Nottingham.

Acknowledgments

We thank Uta Frith, Dana Samson, Steve Jackson and Tom Nielsen for helpful comments on earlier versions of the manuscript. We thank the SPMRC for assistance with scanning and all the participants for their time.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.02.003.

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