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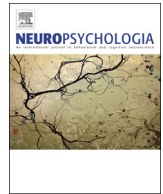
Reduced connectivity between mentalizing and mirror systems in autism spectrum condition

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A B S T R A C T

The mentalizing system and mirror system are thought to play important roles in inferring the internal mental states of others – a process known as mentalizing. Autism spectrum condition (ASC) is associated with difficulties in mentalizing. The aim of this study was to determine whether the behavioural difficulties in mentalizing associated with ASC can be explained by changes in functional connectivity between the mentalizing and mirror system. We recruited 40 adult participants (20 with ASC and 20 typically-developing). Brain activity was monitored using functional magnetic resonance imaging while participants watched videos in which actors performed hand actions. The videos were shown in separate mentalizing and non-mentalizing blocks. During mentalizing blocks, participants were asked to indicate whether hand actions were clumsy or spiteful (i.e. to judge the intent of the action). During non-mentalizing blocks, participants indicated whether the actions were successful or unsuccessful (i.e. to judge the outcome of the action). Higher activity during the mentalizing blocks compared to non-mentalizing blocks was found in regions associated with the mentalizing system: the dorsal medial prefrontal cortex (dmPFC) and the temporo-parietal junction (TPJ), as well as in regions typically associated with the mirror system: the inferior frontal gyrus (IFG) and the inferior parietal lobe (IPL). Next, functional connectivity between regions was evaluated as a function of task. During mentalizing blocks, there was increased functional connectivity between the dmPFC and the mirror system in typically developing participants. In contrast, there was no increase in functional connectivity between these regions in ASC participants. Connectivity between the dmPFC and IFG was negatively correlated with autistic traits. The reduced connectivity in ASC participants was consistent with behavioural performance on the mentalizing task, which was also negatively correlated with the level of autistic traits. Together, these data emphasise the importance of functional connectivity between the mentalizing and mirror systems when inferring social intentions and show that reduced connectivity between these systems may explain some of the behavioural difficulties experienced by adults with ASC.

1. Introduction

Inferring the internal mental states of others is critical for successful social interactions and is known as mentalizing (Chung et al., 2014; Frith and Frith, 2006). The actions of other individuals provide an important source of this social information (Grezes, 2004; Runeson and Frykholm, 1983; Sartori et al., 2009, 2011). Two neural systems, the mirror system and the mentalizing system have been shown to be active when making inferences about the internal mental states of others from their actions (Becchio et al., 2012; Ciaramidaro et al., 2014; de Lange et al., 2008; Spunt et al., 2011; Spunt and Lieberman, 2012b).

The main components of the mentalizing system are considered to be the medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ; Frith and Frith, 2006; Schurz et al., 2014). The dorsal sub-region of the mPFC (dmPFC), appears to be particularly involved in inferring internal states of others from their actions (Amodio and Frith, 2006; Frith and Frith, 2006; Sallet et al., 2013). The orbitofrontal cortex (OFC) is not considered a 'core' region of the mentalizing system but neuroimaging and lesion studies have shown the involvement of this region in mentalizing tasks (Mainieri et al., 2013; Stone et al., 1998; Stuss, 2001). The OFC is therefore considered to be a region of the extended mentalizing system (Gallagher and Frith, 2003). The core components of the mirror system are the inferior frontal gyrus (IFG) and the inferior parietal lobe (IPL; Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010). These regions show similar activation patterns during both the performance and observation of actions (Rizzolatti

et al., 1996) and it is thought that this pattern of activation reflects a simulation of observed actions within the observer's own motor system (Rizzolatti and Craighero, 2004).

A variety of evidence suggest that interactions between the mentalizing and mirror systems are important for mentalizing tasks involving action (Sperduti et al., 2014; Spunt and Lieberman, 2012b; Ciaramidaro et al., 2014; Arioli et al., 2017). For example, functional connectivity between the mentalizing and mirror systems has been shown to be higher when inferring internal mental states based on videos of actions compared to text descriptions of actions (Spunt and Lieberman, 2012b). It has been proposed that mentalizing tasks involving human action processing require increased connectivity in order to allow kinematic information from the mirror system to be interpreted by the mentalizing system (de Lange et al., 2008; Jacob and Jeannerod, 2005; Liew et al., 2011; Mainieri et al., 2013).

Individuals with autism spectrum condition (ASC) have difficulties mentalizing (Baron-Cohen et al., 1997; Castelli et al., 2002; Jolliffe and Baron-Cohen, 1999; Kana et al., 2014; Senju et al., 2009). The impairment on mentalizing tasks in adults with ASC is particularly evident in tasks involving action processing (Ponnet et al., 2004; Roeyers et al., 2001; Rosenblau et al., 2015). This is important, because difficulties inferring the social intentions of others (i.e. their intended impact on others, such as the intent to help or to harm) can lead to inappropriate social decisions, making them vulnerable to mistreatment (Fisher et al., 2013; The National Autistic Society, 2014). The neural correlates of the deficit in mentalizing tasks involving action are not clear. However, given the importance of interactions between the mirror and mentalizing systems on these tasks, it is possible that dysfunctional functional connectivity between these systems could explain the difficulties observed in ASC.

The aim of this fMRI study was: (1) to define regions in the mentalizing and mirror systems that respond more to actions that involve judging intention, (2) to measure functional connectivity between different regions of the mentalizing and mirror systems when inferring social intentions from actions in typically developing individuals (TD) and individuals with ASC. To address this issue, we recruited adults with and without a diagnosis of ASC. Neural responses were recorded using fMRI, while participants viewed videos in which actors performed actions. In the experimental condition, participants had to judge whether the actions were spiteful or clumsy. We labelled this condition 'mentalizing' because it involves making a judgement of the <u>intent</u> of the actor's movement. For example, in a spiteful trial, participants had to judge whether the actor had deliberately decided not to perform the task. They had to discriminate this from clumsy trials in which the participant did not complete the task, but this was not done deliberately. The actions in the videos were carefully matched and, in both trial types, the outcome is the same. Our mentalizing task was based on previous experiments that claim to measure the subjective state and mental processes of others (Behne et al., 2005; Call et al., 2004). In the control condition, participants were asked to indicate whether the action was successful or unsuccessful. We labelled this condition 'non-mentalizing' because it involves making a judgement of the *outcome* of the actor's movement rather than the intent. That is, the success or failure of the participant to post an object. Our non-mentalizing task is similar to previous control conditions in mentalizing studies, in which an action is viewed without requiring the participant to make an explicit judgement of mental state (Chambon et al., 2011; Chambon et al., 2017a, 2017b; de Lange et al., 2008; Spunt et al., 2011; Xu et al., 2009). The contrast between the mentalizing and non-mentalizing conditions was used to define regions of the mentalizing and mirror systems that are involved in making inferences about the intent of an action. This comparison was complemented by a connectivity analysis in which we asked whether there was an increase in functional connectivity between these regions during the mentalizing task. Finally, we asked whether there were differences in functional connectivity between individuals with ASC and typically developing individuals, and asked whether

Table 1
Participant demographic information; group mean (SD) values.

	ASC	TD	p	η_p^2
N	20	20		
Age	29.8(12.87)	29.6 (13.50)	0.96	0.00
Gender (m:f)	12:8	12:8	1.00 (X^2)	/
Years of formal Education	16.20 (1.42)	17.20 (1.88)	0.07	0.09

p values were obtained from a one-way MANOVA unless otherwise stated.

differences in connectivity can be predicted by the level of autistic traits.

2. Methods

2.1. Participants

Twenty adults with a diagnosis of Asperger's or Autism Spectrum Disorder (referred to collectively as Autism Spectrum Condition (ASC); 8 female) and twenty typically developing (TD) adults were recruited for this study. Diagnoses were issued by qualified clinicians external to this study and all participants in the ASC group met the DSM-5 criteria for ASD. Participants in the ASC group were either recruited from the University of York's student support services or a local support group. Participants were individually matched across groups on both gender and age and the groups did not significantly differ in years of formal education (demographic information is shown in Table 1). One participant from each group was left-handed. All participants had normal or corrected-to-normal vision. This research project was approved by the Ethics Committee at York Neuroimaging Centre and was performed in accordance with the ethical standards laid down in the 1990 Declaration of Helsinki. Six participants in the ASC group were taking psychotropic medication to treat depression or anxiety and one of these participants was additionally taking a very low dose of an antipsychotic (see Table 2). None of the participants in the control group were taking psychotropic medication for any psychiatric disorders.

2.2. Stimuli

The stimuli were action videos used in a previous behavioural study (Cole et al., 2018), and the videos are described in detail there. Videos were filmed at a resolution of 1080 × 1920 pixels and 50 frames per second. The videos showed actors either successfully or unsuccessfully passing a poker chip through slots in a white wooden board to another player on the other side that was out of view (Fig. 1). The actors in the unsuccessful videos either did not pass the poker chip to the other player deliberately ('spiteful' action) or accidentally ('clumsy' action). All action types (successful, spiteful and clumsy) were carried out by both pushing the poker chip (with the index finger) through a lower slot or by grasping the poker chip (with the index finger and thumb) and passing it through a higher slot. Eighteen different actors (9 female) were shown performing these actions and each video was four seconds long.

Table 2
Medication information for participants in the ASC group.

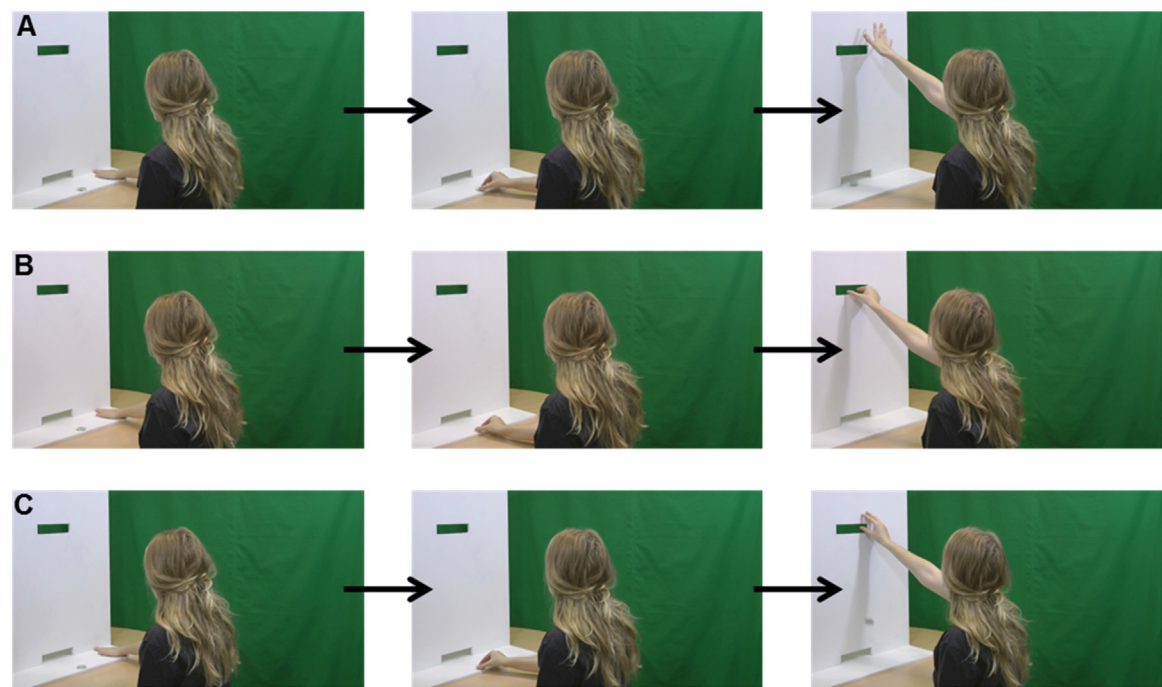| Participant	Medication (daily dosage)
1	Fluoxetine (20 mg)
2	Mirtazapine (30 mg)
3	Sertraline (200 mg)
4	Sertraline (200 mg)
5	Sertraline (200 mg)
6	Aripiprazole (2.5 mg), Citalopram (30 mg)

Fig. 1. Images showing frames of example videos during the mentalizing and non-mentalizing tasks: A. Spiteful action, B. Successful action, C. Clumsy action. In all videos the actor's hand started in the same stationary position (left panels), the poker chip was then grasped with the right hand (middle panels) before being either (right panels) deliberately dropped (A), passed through the board to another player who is out of view (B) or accidentally dropped (C).

2.3. Experimental design

We used a block-design with two conditions: mentalizing and non-mentalizing. In mentalizing blocks, participants were shown unsuccessful (clumsy or spiteful) actions and after each video a response screen, prompting participants to indicate whether the action was clumsy or spiteful. In the non-mentalizing blocks, participants were shown successful or unsuccessful (clumsy) actions and were asked to indicate whether the action was successful or unsuccessful. In both tasks, participants indicated their answers by pressing buttons on a response box placed in their right hand. Each block contained six videos (three of each type). Videos were counterbalanced, so that gender and identity of the actors were not predictive of the actions they were performing. These videos have been previously used in other experiments (Cole and Barraclough, 2018; Cole et al., 2018a, 2018b).

At the beginning of each block, an instruction screen was shown for nine seconds to make participants aware of the task they would be completing during the upcoming block. After each video the response screen was shown for five seconds and afterwards a central fixation cross was shown for one second before the next video in the block was shown. Participants completed twelve blocks (six mentalizing and six non-mentalizing) lasting a total of 12 min 36 s. The videos were projected onto a rear projection screen in the bore of the scanner using an Epson EB-G5900 projector with a long throw lens. Participants viewed the videos using a mirror attached to the head coil. Videos were shown full screen (subtending 40 × 23° of visual angle, 1920 × 1080 pixels).

Prior to scanning, participants completed practice trials (one mentalizing and one non-mentalizing block) on a laptop outside of the scanner in order to familiarise them with the structure of the task. The actors shown in the practice blocks were not shown in the main experiment to avoid previous experience with the actors influencing decisions in the main experiment.

2.4. Psychological assessments

We used standardised psychological assessments to measure the level of autistic traits displayed by all participants (both those with and

without a diagnosis of ASC). This was done so that behavioural and neural measures could be investigated in relation to the level of autistic traits displayed. This method complements the use of group differences based on diagnosis because of the high variability in levels of autistic traits known to exist within clinical and non-clinical populations (American Psychiatric Association, 2013; Robinson et al., 2011; van Boxtel and Lu, 2013; Von Dem Hagen et al., 2011). High variability in autistic traits within groups could generate high variability in behavioural and neural characteristics (Gökçen et al., 2014, 2016; van Boxtel and Lu, 2013) and thus prevent group differences being identified. Participants completed three psychological assessments after the scanning session: two self-report questionnaires and one interactive task. The questionnaires completed were the Autism Spectrum Quotient (AQ) scale and the Social Responsiveness Scale (SRS-2). The interactive task used was the Awareness of Social Inference Test (TASIT) which involves watching video clips of social interactions and subsequently answering questions about the thoughts and feelings of characters. These psychological tests have been shown to display good psychometric properties (Hurst et al., 2007; McDonald et al., 2006; Wigham et al., 2012). The AQ, SRS-2 and TASIT scores were calculated and a one-way MANOVA was used to identify group differences in these scores. The scores on all psychological tests significantly differed between groups (see Table 3). In all cases, scores in the ASC group indicated higher levels of autistic traits/greater degree of social impairment.

Table 3
Participants' psychological test scores; group mean (SD) values.

	ASC	TD	p	η_p^2
AQ	37.4 (8.04)	12.90 (6.23)	< .001***	0.75
TASIT[a]	46.35 (10.92)	58.20 (4.26)	< .001***	0.35
SRS[b]	114.75 (26.37)	35.85 (20.90)	< .001***	0.74

p values were obtained from a one-way MANOVA.
[a] Obtained from part 3 (social inference test), scores are out of 64.
[b] Unstandardized, raw scores, where scores above 75 reflect severe social impairment.

A principal components analysis (PCA) was then performed on all the psychological test scores in order to obtain a single score for each participant that reflected the level of autistic traits that they displayed. The psychological test scores correlated with each other (all rs > 0.6) meaning that they were suitable for PCA. The Kasier-Meyer-Olkin measure of sampling accuracy was above .6, Barlett's test of sphericity was significant $\chi^2(3) = 100.03$, p < .001 and the communalities were all .7 or above; this collectively supported the inclusion of all the psychological tests in the PCA. PCA with varimax rotation was used. Only one factor had an eigenvalue above Kaiser's criterion of 1 (2.51) and this factor explained 83.56% of the variance in psychological test scores. Consequently, only one factor was extracted and this factor was labelled 'autistic traits'.

2.5. Behavioural analysis

The numbers of correct responses on the mentalizing and non-mentalizing tasks were calculated for each participant (out of a total of 36). Data screening identified that the behavioural data were not normally distributed even after a log transformation had been applied so independent *t*-tests with bootstrapping were used to investigate potential group differences in behavioural performances. Linear regression analyses were used to investigate relationships between autistic traits and performance on both tasks.

2.6. Data acquisition and analysis

A 3 T GE HD Excite MRI scanner with an 8-channel phase array head coil tuned to 127.4 MHz was used to acquire fMRI data. A gradient-echo EPI sequence was used to collect data from 38 interleaved axial slices (TR = 3 s, TE = 35 ms, voxel size = 2.25 × 2.25, flip angle = 90°, FOV = 288 mm, matrix size = 128 × 128, slice thickness = 3 mm). High-resolution T1-weighted anatomical images (TR = 7.96 ms, TE = 3.05 ms, voxel size = 1.13 × 1.13 mm, FOV = 290 mm, matrix size = 256 × 256, slice thickness = 1 mm) were also obtained. T1-weighted fluid-attenuated inversion recovery sequence (T1-FLAIR) images with the same spatial prescription as the EPI data were collected to aid co-registration to structural images (voxel size = .56 × .56 mm, matrix size = 512 × 512).

fMRI analyses were conducted using FEAT v5.98 (http://www.fmrib.ox.ac.uk/fsl). The data were pre-processed with slice-timing correction, spatial smoothing (FWHM: 6 mm), motion correction (MCFLIRT, FSL) and temporal high-pass filtering. Brain extraction was conducted using the FSL brain extraction tool (BET). The individual data were then analysed using a general linear model (GLM) with two regressors: 'mentalizing' and 'non-mentalizing'. Parameter estimates were calculated for each condition by regressing the hemodynamic response against a box-car regressor showing the onset and offset of each video convolved with a gamma response function.

In order to identify areas that displayed higher levels of activation during the mentalizing blocks compared to the non-mentalizing blocks, statistical images were created for the mentalizing > non-mentalizing contrast. Functional data for each participant were first registered to the participant's high-resolution T1-image (using the T1-FLAIR image as an intermediate step to aid co-localisation) and then data were registered onto the standard MNI brain (ICBM152). Individual participant data were entered into a higher-level analysis using a mixed-effects design (FLAME; http://www.fmrib.ox.ac.uk).

Regions of interest (ROIs) were defined using the peak activations for the mentalizing > non-mentalizing contrast. ROI masks were drawn using fslview and fslmaths (http://www.fmrib.ox.ac.uk/fsl) commands were used to restrain the masks to voxels which were active (z > 3.1) for the mentalizing > non-mentalizing contrast. ROIs were labelled based on regions identified in existing fMRI studies (Becchio et al., 2012; Liew et al., 2011), meta-analyses (Schurz et al., 2014; Van Overwalle and Baetens, 2009) and using the Juelich histological atlas

from the FSL anatomy toolboxes as a reference (Eickhoff et al., 2005). This process of defining ROIs based on peak activation using our data and confirming the location of these ROIs using previously reported co-ordinates is consistent with previous studies (Kana et al., 2009; Libero et al., 2014; Sperduti et al., 2014; Spunt and Lieberman, 2012b). The ROIs defined included: bilateral inferior frontal gyrus (IFG), bilateral inferior parietal lobe (IPL), bilateral temporoparietal junction (TPJ), bilateral orbitofrontal cortex (OFC) and dorsal medial prefrontal cortex (dmPFC).

In each participant, the timecourse of activation was extracted from each ROI for both mentalizing and non-mentalizing blocks. Timecourses were based on the 6 blocks (6 min and 18 s) of data from each task. Alternating block designs like ours have been shown to produce equivalent functional connectivity results as continuous data collection (Fair et al., 2007). The advantage of using alternating blocks is that it limits the impact of factors such as participant inattention/boredom, learning or repetition effects influencing the data. Previous fMRI studies investigating functional connectivity during mentalizing tasks have used comparable alternating block designs (Ciaramidaro et al., 2014; Damarla et al., 2010; Libero et al., 2014; Spunt and Lieberman, 2012a, 2012b; Xu et al., 2009).

To measure functional connectivity between and within regions, we correlated the time series from different ROIs. Our aim was to determine if there was greater connectivity during the mentalizing compared to the non-mentalizing blocks. This comparison of connectivity according to task is similar to PPI (O'Reilly et al., 2012) and has been used in a number of previous fMRI studies (Damarla et al., 2010; Fishman et al., 2014; Libero et al., 2014; Mason et al., 2008; Neufeld et al., 2017; Von Dem Hagen et al., 2014). A mixed model ANOVA was used to explore task and regional differences in connectivity both within each system individually and between the mentalizing and mirror systems, we performed mixed model ANOVAs. Prior to statistical analysis, correlations were transformed using a Fisher's z transform.

3. Results

3.1. Behavioural performance

Performance on the mentalizing and non-mentalizing tasks was measured during the fMRI scan. Individuals in the ASC group displayed poorer performances (M = 31.25, SD = 4.96) on the mentalizing task than the TD group (M = 33.65, SD = 2.30). This group difference in behavioural performance on the mentalizing task (−2.4, BCa 95% CI [−4.85, −.081]) was close to significance (t(26.81) = −1.96, p = .06). The difference in behavioural performance on the non-mentalizing task (−1.15, BCa 95% CI [−2.90, .31]), between the ASC (M = 33.95, SD = 3.47) and TD (M = 35.1, SD = 1.86) groups was not significant (t(38) = 1.31, p = .20). Using linear regression, scores on the mentalizing [M = 32.45, SD = 4.0] and non-mentalizing [M = 34.53, SD = 2.81] tasks were examined to see how they related to the level of autistic traits. The level of autistic traits predicted performance on the mentalizing task [F(1,38) = 5.50, p = .02, R^2 = 0.13, 95% CI [−2.65, −0.20]; see Fig. 2A], but did not predict performance on the non-mentalizing task [F(1,38) = 0.01, p = .94, R^2 < 0.001, 95% CI [−0.96, 0.89]; see Fig. 2B].

3.2. Neural responses during mentalizing and non-mentalizing tasks

A group analysis across all participants was performed on the response to either the mentalizing or non-mentalizing tasks relative to baseline. Similar patterns of activation were elicited in primary sensory and motor regions of the brain during both mentalizing and non-mentalizing tasks (see Fig. 3), indicating that our stimuli were well matched across the experimental and control conditions on basic sensorimotor properties. During both mentalizing and non-mentalizing tasks, activity was evident in regions of visual (posterior occipital lobe, lateral
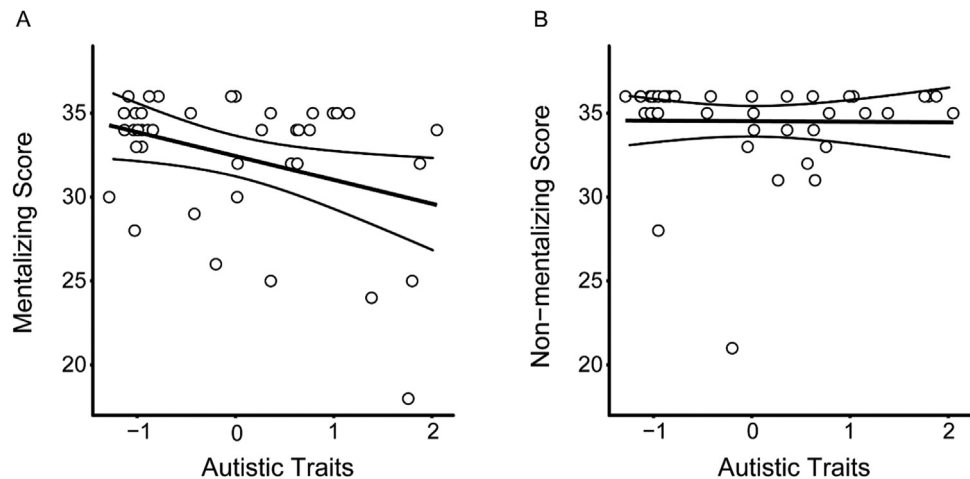
Fig. 2. A) Relationship between the level of autistic traits of each individual and performance on the mentalizing task. B) Relationship between level of autistic traits of each individual and performance on the non-mentalizing task. The curved lines represent 95% confidence intervals.

occipital lobe, fusiform gyrus) and motor cortex (pre-central gyrus, supplementary motor area), reflecting the visual and motor components of the tasks. There was also activity in the inferior frontal gyrus (IFG), inferior parietal lobe (IPL), temporoparietal junction (TPJ), superior parietal lobe (SPL), and posterior cingulate cortex (PCC), reflecting regions that form the mentalizing and mirror systems (Van Overwalle and Baetens, 2009). The coordinates of the peak activation are shown in Table 4.

Next, we contrasted the brain responses during the mentalizing and non-mentalizing tasks. Significantly higher activation during the mentalizing task was evident in regions associated with the mentalizing system, including bilateral dorsal medial prefrontal cortex (dmPFC), TPJ and orbitofrontal cortex (OFC; Fig. 4A; Frith and Frith, 2006; Schurz et al., 2014). Significantly higher activation during the mentalizing task was also evident in regions associated with the mirror system, including bilateral inferior frontal gyrus (IFG) and inferior parietal lobe (IPL; Fig. 4B; Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010). Higher activation during the non-mentalizing task was found in the left primary somatosensory cortex and the cingulate gyrus. The co-ordinates of peak activation for the mentalizing > non-mentalizing and non-mentalizing > mentalizing contrasts are shown in Table 5.

3.3. Functional connectivity within the mentalizing system

We compared functional connectivity between regions of the mentalizing system. For each participant, the time-course of responses in each region of the mentalizing system (dmPFC, TPJ, OFC) was correlated with the time-course of each of the other regions within the mentalizing system. To determine whether connectivity during the mentalizing task was higher than during the non-mentalizing task,

Table 4
Peak areas of activation during the mentalizing and non-mentalizing tasks compared to baseline.

Anatomical region	Peak MNI co-ordinates				
	BA	x	y	z	z-value
EVC	18	−6	−82	−6	8.50
Left LOC	18	−22	−92	12	8.33
Right LOC	37	48	−70	−2	8.13
Left M1	6	−26	−10	52	8.13
Right M1	6	24	−8	54	6.62
Left ventral stream	18	−14	−76	−14	7.64
Right ventral stream	37	30	−52	−14	6.90
Left SPL	7	−34	−48	54	7.53
Right SPL	7	16	−66	58	6.71
Left SMA	6	−6	0	52	6.35
Right SMA	6	8	6	52	5.38
Left PCC	31	−14	−26	40	6.08
Right PCC	31	14	−28	42	4.03
Left IPL	40	−54	−28	36	5.92
Right IPL	40	54	−26	36	4.26
Right TPJ	39	62	−44	20	5.08
Left TPL	22	−44	−40	18	4.25
Left IFG	44/6	−54	4	28	5.03
Right IFG	44/6	−48	0	28	4.90

Abbreviations: EVC - early visual cortex, LOC - lateral occipital cortex, M1- primary motor cortex, SPL - superior parietal lobe, SMA - supplementary motor area, PCC - posterior cingulate cortex, IPL - inferior parietal lobe, TPJ - temporoparietal junction, IFG - inferior frontal gyrus.

these correlations were calculated separately for each task. Table 6 shows the average connectivity within the mentalizing systems during both the mentalizing and non-mentalizing tasks for each group.
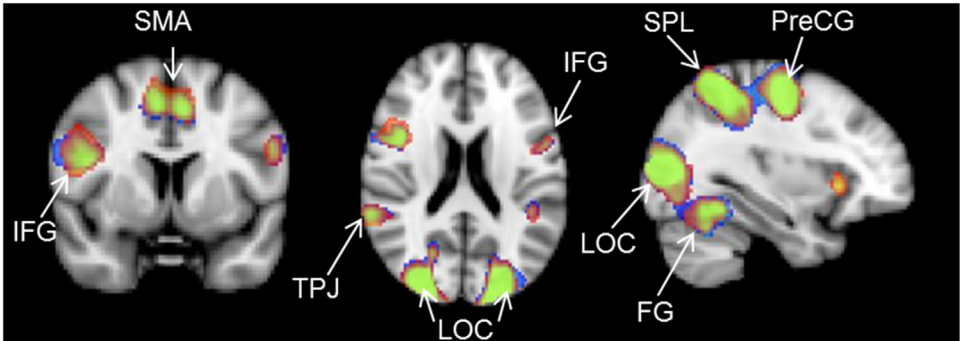

Fig. 3. Whole-brain group analysis showing regions that were active during the mentalizing (red) and non-mentalizing (blue) tasks compared to baseline. The overlap in activation is shown in yellow. Both tasks elicited bilateral activation in inferior frontal gyrus (IFG), supplementary motor area (SMA), temporoparietal junction (TPJ), fusiform gyrus (FG), lateral occipital cortex (LOC), precentral gyrus (preCG) and the superior parietal lobe (SPL). Images thresholded at z > 3.1, p < 0.001. MNI co-ordinates of images (x, y, z): −32, 6, 20.
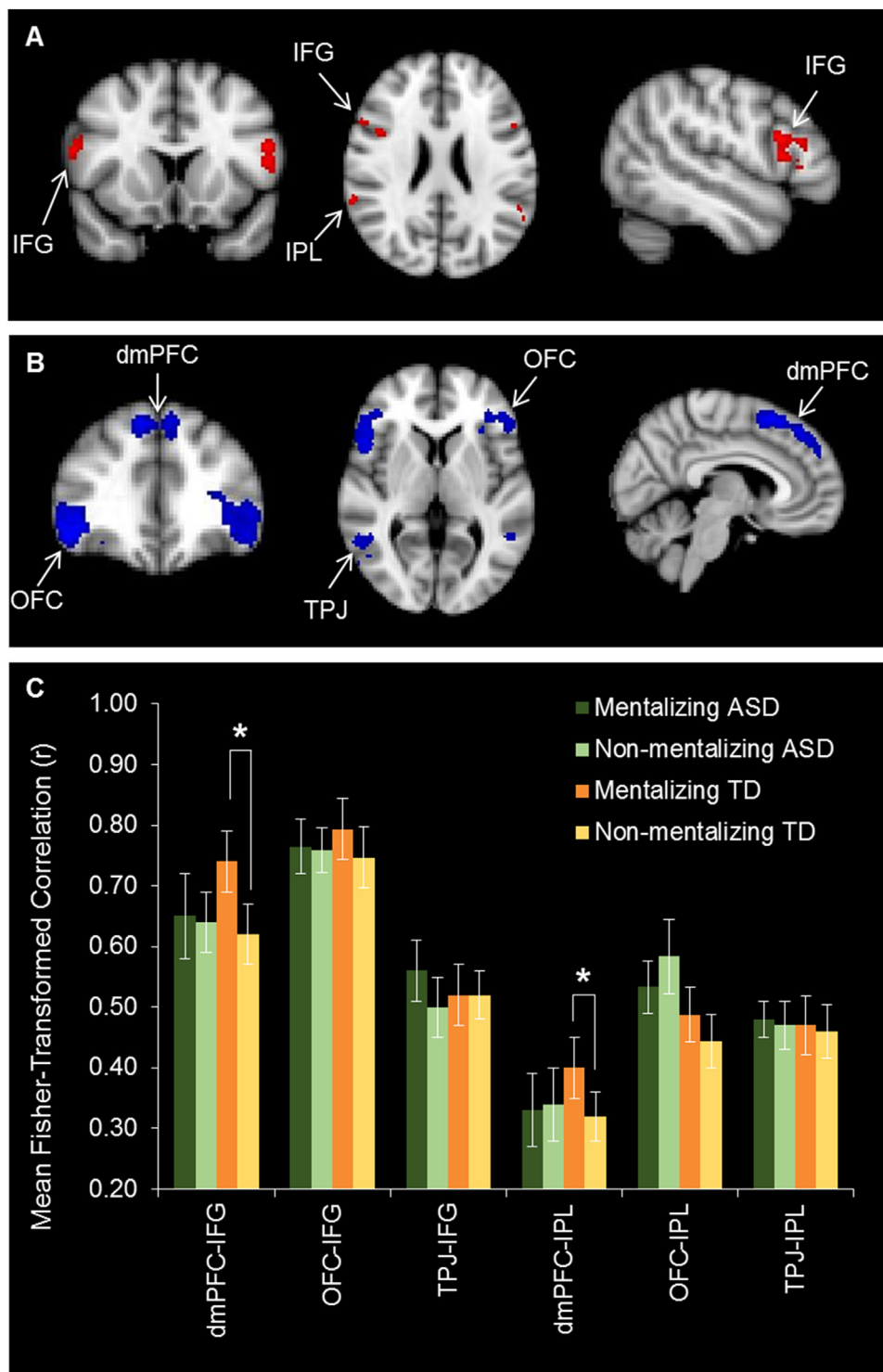
Fig. 4. A) Regions associated with the mirror system which showed higher activity during the mentalizing task compared to the non-mentalizing task: bilateral inferior frontal gyrus (IFG) and bilateral inferior parietal lobe (IPL). MNI co-ordinates of images: − 50, 14, 24. B) Areas associated with the mentalizing system which displayed higher activity during the mentalizing task compared to the non-mentalizing task: dorsal medial prefrontal cortex (dmPFC), bilateral temporoparietal junction (TPJ) and bilateral orbitofrontal cortex (OFC). MNI co-ordinates of images: 6, 36, 4. Images are thresholded at z > 3.1, p < 0.001. C) Mentalizing-induced changes in functional connectivity between mentalizing and mirror system regions shown in A and B. Asterisks indicate significant (p < .05) task-related changes in functional connectivity. Error bars indicate SEM.

Connectivity within the mentalizing system was investigated using a mixed ANOVA with Task (mentalizing, non-mentalizing) and Connection (dmPFC-TPJ, dmPFC-OFC, TPJ-OFC) as within subject variables and Group (TD, ASC) as the between subject variable.

There was a significant main effect of Connection [$F_{(2,76)} = 55.92$, $p < .001$, $\eta_p^2 = 0.56$]. This shows that functional connectivity differs between different regions of the mentalizing system. However, there was no effect of Task [$F_{(1,38)} = 1.79$, $p = .19$, $\eta_p^2 = 0.05$]. There was also no effect of Group [$F_{(1,38)} = 0.09$, $p = .77$, $\eta_p^2 = .002$]. There were also no other interactions between Connection, Task and Group [Task × Connection interaction: $F_{(2,76)} = 1.20$, $p = .31$, $\eta_p^2 = 0.03$;

Task × Group interaction: $F_{(1,38)} = 0.001$, $p = .97$, Task × Connection × Group interaction: $F_{(2,76)} = 1.55$, $p = .22$, $\eta_p^2 = 0.04$, Task × Group interaction: $F_{(2,76)} = 1.73$, $p = .18$, $\eta_p^2 = 0.04$].

3.4. Functional connectivity within the mirror system

Connectivity within the mirror system was investigated using a similar ANOVA but without Connection as a factor as there was only one connection (IFG-IPL). Connectivity within the mirror system was not significantly influenced by Task [$F_{(1,38)} = .86$, $p = .36$, $\eta_p^2 = 0.02$]. There was also no main effect of Group [$F_{(1,38)} = 0.54$, $p = .47$, $\eta_p^2 =$

Table 5
Areas of peak activation for the mentalizing > non-mentalizing contrast ($p < .001$ uncorrected for multiple comparisons).

Contrast	Anatomical region	BA	x	y	z	z-value
		Peak MNI co-ordinates					
Mentalizing > non-mentalizing	Right OFC	47	52	32	−8	5.72
	Left OFC	47	−50	24	−4	5.60
	Right SMA	6	6	18	56	4.71
	Left SMA	6	−6	12	60	3.51
	Right IFG	44	52	20	12	4.36
	Left IFG	44	−52	14	20	3.79
	Right TPJ	37	56	−52	10	4.19
	Left TPJ	21	−52	−50	4	3.47
	dmPFC	9	4	48	38	4.11
	Right IPL	40	62	−42	24	3.53
	Left IPL	39	−62	−46	28	3.54
Non-mentalizing > mentalizing	CG	23	0	−42	36	4.65
	Left S1	1	−52	−22	46	3.93

OFC - orbitofrontal cortex, SMA - supplementary motor area, IFG - inferior frontal gyrus, TPJ - temporoparietal cortex, dmPFC - dorsomedial prefrontal cortex, IPL - inferior parietal lobe, CG – cingulate gyrus, S1-primary somatosensory cortex.

0.01] or any Task $\times$ Group interaction [$F(2,76) = 2.29$, $p = .14$, $\eta_p^2 = 0.06$].

3.5. Functional connectivity between the mentalizing and mirror systems

Finally, we asked whether there was a difference in functional connectivity *between* the mirror and mentalizing systems. Fig. 4C shows the measures of functional connectivity between each of the mentalizing and mirror system regions in TD and ASC adults. These differences in functional connectivity were investigated using a mixed ANOVA with Task (mentalizing, non-mentalizing), mentalizing system region (dmPFC, TPJ, OFC) and mirror system region (IFG, IPL) as within subject variables, and Group (TD, ASC) as a between subjects variable.

There were significant main effects of Mentalizing system region [$F(1,38) = 17.50$, $p < .001$, $\eta^2 = .32$] and mirror system region [$F(1,38) = 94.28$, $p < .001$, $\eta_p^2 = .71$]. There was also an interaction between mentalizing system region and mirror system region [$F(2,76) = 31.12$, $p < .001$, $\eta_p^2 = 0.45$]. This shows that regions of the mentalizing system were more strongly connected to some regions of the mirror system than to others. There was no main effect of Task [$F(1,38) = 1.35$, $p = .25$, $\eta^2 = 0.03$] or Group [$F(1,38) = 0.03$, $p = .86$, $\eta_p^2 = 0.001$]. However, there was a significant interaction between mentalizing region $\times$ Task $\times$ Group [$F(1,38) = 5.78$, $p < .01$, $\eta_p^2 = 0.13$]. This shows that functional connectivity of different regions in the mentalizing system was significantly dependent upon the task and the diagnosis of the individual. This effect was not dependent upon the connectivity to a specific mirror system region [mentalizing system region $\times$ Group $\times$ Task $\times$ mirror system region: $F(2,76) = 1.01$, $p = .37$, $\eta_p^2 = .03$]. No other interactions were significant [mentalizing

system region $\times$ Group: $F(2,76) = 8.07$, $p = .45$, $\eta_p^2 = 0.02$; mentalizing system region $\times$ Task: $F(2,76) = 2.14$, $p = .13$, $\eta_p^2 = 0.05$; mirror system region $\times$ Group: $F(2,76) = .70$, $p = .41$, $\eta_p^2 = 0.02$; mirror system region $\times$ Task: $F(1,38) = 1.47$, $p = .23$, $\eta_p^2 = 0.04$; Group $\times$ Task: $F(1,38) = .89$, $p = .35$, $\eta_p^2 = .02$; mentalizing system region $\times$ mirror system region $\times$ Group: $F(2,76) = 5.78$, $p = 0.27$, $\eta_p^2 = .03$; mentalizing system region $\times$ mirror system region $\times$ Task: $F(2,76) = 0.006$, $p = .99$, $\eta_p^2 < 0.001$; mirror system region $\times$ Group $\times$ Task: $F(1,38) = 0.65$, $p = .43$, $\eta_p^2 = 0.02$].

The significant 3-way interaction between Mentalizing system region $\times$ Task $\times$ Group was investigated further by comparing connectivity across tasks for each group (TD, ASC) and mentalizing region separately. As the significant 3-way interaction was not dependent upon the connected mirror system region, timecourse correlations were averaged across mirror system regions. In the TD group, connectivity of the dmPFC with the mirror system was significantly higher during the mentalizing task compared to the non-mentalizing task [$t(19) = 2.78$, $p = .01$]. Connectivity of both TPJ and OFC with the mirror system did not significantly differ across tasks [TPJ: $t(19) = 0.11$, $p = .91$, OFC: $t(19) = 1.10$, $p = .29$]. The increased connectivity between dmPFC and the mirror system survived correction for multiple comparisons (Bonferroni corrected p value: $.05/3 = .017$). For the ASC group, there were no task-related differences in functional connectivity between mentalizing regions (dmPFC, TPJ, OFC) and the mirror system [dmPFC: $t(19) = .04$, $p = .97$, TPJ: $t(19) = 1.15$, $p = .27$, and OFC: $t(19) = −0.65$, $p = .53$].

Finally, we asked whether functional connectivity between dmPFC and mirror system regions is predicted by autistic traits. During the mentalizing task, high levels of autistic traits significantly predicted decreases in connectivity between dmPFC and IFG [$F(1,38) = 7.23$, $p = .01$, $R^2 = 0.16$], but not between dmPFC and IPL [$F(1,38) = 2.67$, $p = .11$, $R^2 = 0.07$]. Autistic traits did not predict functional connectivity between dmPFC and either region of the mirror system during non-mentalizing tasks [dmPFC and IFG: $F(1,38) = 0.04$, $p = .84$, $R^2 = 0.001$; dmPFC and IPL: $F(1,38) = 0.14$, $p = .71$, $R^2 = 0.004$].

4. Discussion

This study aimed to identify whether functional connectivity between different regions of the mirror and mentalizing systems is higher when inferring the social intentions of others from their actions, and whether functional connectivity between these systems is different in individuals with ASC. We found an increased neural response in regions associated with the mentalizing and mirror systems when participants were making inferences about the intent underlying an action (mentalizing) compared to when they were viewing an action without an explicit judgement of intent (non-mentalizing). We also found higher levels of functional connectivity between the mentalizing system (dmPFC) and the mirror system (IFG, IPL) in TD adults. However, the functional connectivity between these regions did not increase during the mentalizing task in adults with ASC. Across all participants, higher levels of autistic traits significantly predicted reduced functional connectivity between dmPFC and IFG during the mentalizing task and a reduced ability to infer social intentions.

Table 6
Average measures of connectivity (mean r value and SE in brackets) within mentalizing system and mirror systems during mentalizing and non-mentalizing tasks for TD and ASC individuals.

Connection	Mentalizing TD	Non-mentalizing TD	Mentalizing ASC	Non-mentalizing ASC
Mentalizing system				
dmPFC-TPJ	0.50 (.05)	0.47 (.03)	0.49 (.08)	0.48 (.06)
dmPFC-OFC	0.94 (.05)	0.91 (.05)	0.82 (.09)	0.83 (.08)
TPJ-OFC	0.59 (.05)	0.56 (.04)	0.66 (.05)	0.57 (.05)
Mirror system				
IFG-IPL	0.48 (.05)	0.41 (.04)	0.48 (.05)	0.50 (.05)

These results provide insights into the way that the mentalizing and mirror systems interact during mentalizing tasks. Increased connectivity between dmPFC and IFG has previously been shown when inferring intentions from actions (Spunt and Lieberman, 2012b). Together, these findings support the important role of the connectivity between the dmPFC and the IFG when making inferences about the internal mental states of others based on their actions. In contrast to TD adults, adults with ASC did not show a similar increase in connectivity between the mentalizing and mirror systems during the mentalizing task. This difference in connectivity in adults with ASC is consistent with the difficulties that they have inferring internal states from actions (Kana et al., 2009; Kirkovski et al., 2016; Ponnet et al., 2004; Roeyers et al., 2001; Rosenblau et al., 2015; Spek et al., 2010). Our results also show that adults with higher levels of autistic traits showed reduced abilities to infer the intentions of others from their actions, supporting the findings of a previous behavioural study using this paradigm (Cole et al., 2018b). Higher levels of autistic traits were also correlated with reduced functional connectivity between dmPFC and IFG. This suggests that, in adults with high levels of autistic traits, there is a disruption to the functional connectivity between mentalizing and mirror systems and a reduced ability to infer the intentions of others from their actions.

A key feature of our design was that the mentalizing task involved making an inference about a person's intent (clumsy or spiteful), whereas the non-mentalizing task just required making an observation of the outcome (successful or unsuccessful). The outcome of the mentalizing task was always failure, so outcome could not be used to perform the task. However, it is possible that the difference between clumsy and spiteful trials could be discriminated by lower-level information in the actions rather than higher-level information about the inference (Michael and De Bruin, 2015; Catmur, 2015; Herschbach, 2015). Although we cannot rule out this possibility, the contrast between the mentalizing and non-mentalizing conditions did not show any differences in sensory regions, particularly those involved in action perception.

It could be argued that successful observation of the videos in both conditions could involve similar levels of mentalizing. For example, higher-level inferences (e.g. reward/punishment) might be associated with successful/unsuccessful judgements on the non-mentalizing task. The reason for the difference in response between the mentalizing and non-mentalizing conditions is that the response options in the mentalizing condition contain the word 'spiteful', which implies intent. In contrast, the response options for the non-mentalizing condition contain words that do not imply intent, or at least not to the same degree ('successful', 'unsuccessful'). Therefore, the difference between conditions could reflect differential activity to the text when participants are asked to make a response. The change in connectivity observed between the mentalizing and non-mentalizing conditions need not be explained by the demands of mentalizing. Rather, they could be explained by sensorimotor learning – participants push a button in response to a word that is associated with a mental state that implies intent. One way to differentiate between these different explanations is to compare (in the absence of the video) the response to words that imply intentional mental states (e.g. spiteful) with words that do not imply intentional mental states or at least to a lesser extent (e.g. successful) in the same regions. Although our data does not allow us to make this comparison, previous studies have found a lack of mirror system activation during mentalizing tasks using passages of text (Gallagher et al., 2000; Schurz et al., 2014; White et al., 2014). Moreover, a previous study also found greater connectivity between the dmPFC and IFG when inferring intent from videos compared to inferring intent from passages of text (Spunt and Lieberman, 2012b).

It has been proposed that inferring the social intentions of others from their actions requires the integration of contextual information and action kinematics (Chambon et al., 2017a; de Lange et al., 2008; Jacob and Jeannerod, 2005; Liew et al., 2011; Mainieri et al., 2013). Existing fMRI studies have provided evidence that context and

expectations about an upcoming action are processed in the mPFC (Alexander and Brown, 2011; Becchio et al., 2012; Chambon et al., 2017a; Cooper et al., 2010; Fogelson et al., 2009; Forster and Brown, 2011). Activity in the IFG, on the other hand, has been associated with processing intentional information portrayed by kinematic cues (Becchio et al., 2012; Buccino et al., 2007; Ciaramidaro et al., 2014; Herbet et al., 2014). Therefore, the reduced connectivity between the dmPFC and IFG found in adults with ASC may result in a reduction in the integration of kinematic and contextual information, leading to difficulties inferring social intentions (de Lange et al., 2008; Keysers and Gazzola, 2007; Spunt and Lieberman, 2012c; Uddin et al., 2007). The idea that there is a reduced integration of action context and kinematic information occurs in ASC is supported by a meta-analysis that showed adults with ASC are significantly impaired on mentalizing tasks that involve integrating information regarding others' internal states with surrounding context (Baez et al., 2012). Behavioural studies have also found atypical utilisation of prior experience relative to incoming sensory information in adults with ASC when inferring social intentions from actions (Chambon et al., 2017b) and children with ASC show impaired abilities to infer intentions when this requires processing of both contextual information and kinematic information (Boria et al., 2009). These data imply that integration of prior expectations and incoming sensory information is atypical in ASC during action observation. This reduced integration may result from reduced functional connectivity between IFG and dmPFC and consequently give rise to a poorer ability to infer social intentions from actions.

Some evidence has suggested that reduced mirror system (Cole et al., 2018a; Iacoboni and Dapretto, 2006; Oberman and Ramachandran, 2007; Ramachandran and Oberman, 2006) or reduced mentalizing system function (Baron-Cohen et al., 1999; Happé et al., 1996; Holt et al., 2014; Kana et al., 2009) underlies the social impairments associated with ASC. We found no evidence of reduced activation or functional connectivity within either the mirror or mentalizing systems. This is consistent with a number of previous studies that have also reported typical mirror system activation (Kana et al., 2009; Kirkovski et al., 2016; Marsh and Hamilton, 2011; Vander Wyk et al., 2014) or typical mentalizing system activation (Ciaramidaro et al., 2015; Kirkovski et al., 2016; Vander Wyk et al., 2014) in adults with ASC. Behavioural studies have shown that adults with ASC do not display consistent impairments on mentalizing tasks, which do not involve observing human action (Ammons et al., 2018; Kana et al., 2009; Kirkovski et al., 2016; Murdaugh et al., 2012; Ponnet et al., 2004; Roeyers et al., 2001; Spek et al., 2010) and neuroimaging studies have shown that the mirror system is not reliably activated during these tasks (Castelli et al., 2000, 2002; Gallagher et al., 2000; White et al., 2014). These data suggest that mentalizing system activation, without mirror system involvement, is sufficient to perform mentalizing tasks that do not involve human action (Castelli et al., 2000, 2002; Gallagher et al., 2000; White et al., 2014). In contrast, both mirror system and mentalizing system activation are reliably found during mentalizing tasks involving the observation of human actions (Becchio et al., 2012; Ciaramidaro et al., 2014; de Lange et al., 2008; Hooker et al., 2010; Spunt and Lieberman, 2012a, 2012b) and connectivity between these cortical systems has been shown to increase during these tasks (Rudie et al., 2012; Spunt and Lieberman, 2012a, 2012b; Tettamanti et al., 2017). The observed behavioural deficits in adults with ASC therefore support our finding that functional connectivity between mentalizing and mirror systems is reduced in individuals with ASC rather than dysfunction in either system alone.

It was perhaps surprising that we did not observe an increase in connectivity between the TPJ and the mirror system when deriving intentions from actions. The right TPJ has been shown to be involved in attributing thoughts to other individuals (Saxe and Powell, 2006). However, increased functional connectivity between dmPFC and areas of the mirror system has been more commonly reported when inferring others internal states from their actions (Ciaramidaro et al., 2014;

Spunt and Lieberman, 2012a, 2012b; Rudie et al., 2012) than increased connectivity between TPJ and mirror system areas (Spunt and Lieberman, 2012a). The TPJ is associated with self-referential processing (Andrews-Hanna et al., 2010; Blanke, 2005; Molnar-Szakacs and Uddin, 2013). It is possible that if a mentalizing task was used which elicited greater self-referential processing then increased connectivity may have been found between TPJ and mirror system areas.

In conclusion, increased connectivity between areas of the mirror and mentalizing systems was found when inferring the intentions of others from their actions in TD adults. This increased connectivity between the mirror and mentalizing systems was not evident in adults with ASC. The level of autistic traits predicted behavioural performance on mentalizing and the connectivity between the mirror and mentalizing regions. Our data highlight the possibility that reduced connectivity between the mirror and mentalizing systems could underlie difficulties adults with ASC experience in inferring social intentions.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.11.008.

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