Dissociation of brain activation in autism and schizotypal personality disorder during social judgements

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Abstract

Background

There are overlaps between autism and schizophrenia but these are particularly pronounced, especially in social domains, for higher functioning individuals with autism spectrum disorders (ASD) or schizotypal personality disorder (SPD). It is not known whether these overlapping social deficits result from shared or distinct brain mechanisms. We therefore compared social cognition in ASD and SPD using functional magnetic resonance imaging (fMRI).

Methods

21 individuals with SPD, 28 with ASD and 33 controls were compared with respect to clinical symptoms using the Positive and Negative Syndrome Scale; social cognition, using a social judgement task and Ekman 60 faces task; and brain activation using an fMRI task of social judgement.

Results

The ASD and SPD groups showed few differences in symptoms or social cognition. However, fMRI showed that, compared to ASD, the SPD group showed significantly greater activation during social compared to gender judgements in the amygdala and three clusters: right posterior cerebellum, extending into fusiform and inferior temporal gyri; left posterior cerebellum; and left intraparietal sulcus extending through medial portions of the temporal gyri into the fusiform gyrus (all $p<0.05$ family-wise error corrected). Control activations lay between the ASD and SPD groups.

Conclusions

Although social cognitive deficits in ASD and SPD appear superficially similar they are the result of different brain mechanisms. These findings have implications for therapeutic interventions targeted at social dysfunction in these conditions.

Keywords: social cognition, negative symptoms, imaging, fMRI

Introduction

The term autism was initially coined by Bleuler in 1911 to describe a characteristic symptom of people with schizophrenia, specifically 'detachment from reality, together with the relative and absolute predominance of the inner life.'[1] It was first used to describe a specific disorder by Kanner in 1943, when he presented a case series of children affected by 'autistic disturbance of affective contact.'[2] Although initially thought to be a distinct condition, autism soon came to be regarded as a form of early onset schizophrenia[3] and this continued until a series of studies differentiated the disorders on phenomenology, course and family history.[4-9]

With the advent of the autism spectrum concept, it is now recognised that there exist forms of both disorders which do not show such marked impairments. Although autism spectrum disorders (ASD) and 'schizophrenia spectrum disorders', such as schizotypal personality disorder (SPD), would be expected to differ on the level of mild psychotic symptoms and on restricted repetitive behaviours,[10] there are significant overlaps between the conditions: both occur in non-intellectually disabled people and are associated with social difficulties, idiosyncratic language and unusual behaviour, as well as showing common associated psychopathology.[11-24] Both conditions are also associated with deficits in social cognition.[25-31] Finally, the age of onset of SPD is unclear, while ASD may not become obvious until after early childhood, when social demands exceed ability.[10] Thus the distinction between ASD and SPD can be difficult;[32-34] indeed it has been proposed that the disorders should not be classified separately.[35]

Clinical and neuropsychological similarities therefore exist between ASD and SPD, but it is unclear whether these share a common pathophysiological mechanism, as direct comparisons have not been conducted. It has been suggested that, although ASD and schizophrenia show similar social deficits, the mechanisms through which these develop differ, with schizophrenia associated with hyper-mentalising (i.e. over-ascription of mental states to others) and ASD associated with hypo-mentalising.[36-40] To the authors' knowledge, three functional magnetic resonance imaging (fMRI) studies have directly compared ASD and schizophrenia using social cognition tasks;[41-43] these are broadly supportive of the hypo-/hyper-mentalising theory, particularly the most recent studies.[41, 44] However, it is also not clear whether these findings apply to higher functioning groups with ASD and SPD, in which fewer symptomatic differences are apparent.

We therefore compared social cognitive deficits in people with ASD and SPD and tested whether they are associated with different underlying brain activity using fMRI. We employed a social judgement task (assessing approachability from faces) on which we have previously shown impaired performance in ASD[27] and schizophrenia.[45] Making a judgement of approachability requires individuals to assess affective information from facial cues and to interpret this in relation to the threat or otherwise represented.[46] Using fMRI, we have also shown this task to activate social brain regions in typically developing individuals, including the medial and inferior prefrontal cortex, amygdala and cerebellum.[46] We hypothesised that individuals with ASD and those with SPD would show impaired social judgement compared to controls, but that, consistent with the literature on autism and

schizophrenia, those with SPD would show increased activation of these brain regions while making social judgements whereas the opposite pattern would be seen in ASD.

Methods

Participants

Individuals with ASD were recruited from clinical and support services in Southeast Scotland. All had a DSM-IV diagnosis of either autism or Asperger Syndrome and met ASD cut-offs on the Autism Diagnostic Observational Schedule (ADOS-G).[47]

Participants with SPD were recruited from non-psychotic people who had previously participated in the Edinburgh High Risk Study of schizophrenia (EHRS)[48] and from clinical services in Southeast Scotland. All met DSM-IV criteria for SPD using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II).[49]

Some individuals met criteria for both ASD (determined by DSM-IV and the ADOS) and SPD (determined by the SCID-II). These were analysed as a separate group, referred to as 'comorbid' (CM).

Controls were recruited from participant and investigator acquaintances and the Scottish Mental Health Network research register. Individuals with a history of, or first degree relative with, ASD, SPD or a psychotic illness were excluded.

General exclusion criteria were IQ<70, substance dependence or history of schizophreniform disorder, schizophrenia or bipolar affective disorder.

The study was approved by the NHS Lothian Research Ethics Committee. Written informed consent was obtained from all participants.

Assessments

In addition to the ADOS-G and the SCID-II, participants were assessed using the Positive and Negative Syndrome Scale (PANSS)[50] and the Wechsler Abbreviated Intelligence Scale.[51] For those on antipsychotic medication, doses were converted to chlorpromazine equivalents.[52, 53]

Social cognition was assessed outside the MRI scanner using the Ekman 60 facial emotion recognition test[54] and a Social Judgements Task.[45] In the Ekman 60 each face was presented for up to five seconds and participants selected the emotion displayed from a randomly ordered list consisting of fear, anger, disgust, sadness, happiness and surprise. Ten presentations of each emotion were shown in a random order. Performance was measured by totalling correctly identified emotion labels.

For the social judgement task, participants were shown six sets of thirty two faces for up to five seconds each. In each set they allocated the faces into one of the following binary characteristics: approachable-unapproachable, distinctive-not distinctive, young-old, trustworthy-untrustworthy, intelligent-not intelligent and attractive-unattractive. The stimuli for the social judgement task were the same as a previous study and ratings for each were scored as 'correct' when they agreed with predefined ratings for each stimulus.[45]

fMRI Image Acquisition

Details of image acquisition and preprocessing are given in the Supplement.

fMRI Approachability Task

The approachability component of the social judgement task was adapted for the scanner as previously described.[46] Face stimuli were presented in blocks of approachability judgements ('social' condition) and gender judgements ('gender' condition). Stimuli differed from those employed for the behavioural task. Two runs were presented, each lasting 240 seconds. Three blocks of each condition were shown; each lasted for 25 seconds, separated by a central fixation cross ('Baseline' condition). Each block began with a 1 second visual reminder of the task for the block ("Approachable?" or "Gender?"), followed by 6 faces, in a pseudorandom order, each presented for 3.5 seconds with a 0.5 second gap between stimuli. Underneath the faces, participants were shown their bivalent choice ("Approachable:Not approachable" or "Male:Female") and indicated their selection by pressing a button in the hand corresponding to their choice. The stimuli were counterbalanced for stimulus order, judgement order, and hand used to indicate choice.

Data analysis

Differences between demographic characteristics were determined using parametric or non-parametric tests. The PANSS, Ekman 60 and social judgement scores were not normally distributed and so were analysed using Kruskal-Wallis tests. When significant results were identified in the Kruskal-Wallis tests, follow-up Mann Whitney U tests were conducted. To assess the potential confounding effect of IQ, partial correlations between IQ and performance were conducted across all participants with group as a covariate.

Statistical analysis of fMRI data were conducted using the general linear model in SPM8. Data for individual participants were modelled with three conditions (social judgement, gender judgement and baseline). Parameters representing participant movement were entered as covariates of no interest. Contrast images were generated for each participant for two contrasts: social versus baseline and gender versus baseline. In the second level analysis, a 2 x 4 flexible factorial design matrix was constructed with the two contrasts (social versus baseline and gender versus baseline) as within subjects factors, and four groups (ASD, SPD, CM and control) as between-subjects factors, in addition to subject constants. Contrasts were constructed to test the main effect of condition (social or gender) across all four groups; the effect of condition within each group; and the group x condition interaction. Note that the group x interaction contrast essentially allows comparison of the social and gender conditions, with the gender condition acting as a 'high level' baseline to remove the effects of any differential face processing not related to affective content

Between group analyses were conducted using an initial height threshold of $p=0.005$ uncorrected. Cluster results were only considered significant at $p<0.05$ after family wise error (FWE) correction for multiple comparisons across the whole brain. A small volume correction (SVC) was applied to the amygdala bilaterally.

When clusters showed a significant group x condition interaction, eigenvariates were extracted and the difference value calculated by subtracting the value for the gender versus baseline contrast from the social versus baseline contrast. These difference values were regressed against PANSS scores to explore the relationship between brain activation and symptomatology. To assess the effect of potential confounding factors,

difference values were regressed against IQ, chlorpromazine equivalents and task performance. Regression analyses were conducted within IBM SPSS Statistics 19.0. Finally, to examine whether results related to differences in activation during the social or non-social condition, or both, eigenvariates for the social versus baseline and gender versus baseline conditions were compared between groups.

Results

Participants

Characteristics of the participants are given in Table 1.

INSERT TABLE 1 ABOUT HERE

No significant differences were seen with respect to gender, handedness, age or education (all $p>0.22$). IQ scores differed significantly ($F=4.12$, $p=0.009$) with the control group having significantly higher IQ than the SPD and the CM group (all $p<0.05$). The ASD, SPD and CM groups did not differ significantly on IQ (all $p>0.08$). Ten participants were taking antipsychotic medication in chlorpromazine equivalent doses ranging from 25mg to 400mg per day. The median chlorpromazine equivalent doses for those taking antipsychotics in each group were: ASD – 50mg, SPD – 100mg, CM – 150mg. The SPD and the CM groups were more likely to be taking antipsychotic medication than the ASD or control groups ($p=0.008$).

Clinical Features

Summary scores for PANSS positive and negative symptom scales are shown in Figure 1.

INSERT FIGURE 1 ABOUT HERE

Kruskal-Wallis tests showed significant differences between the groups for positive and negative symptoms ($chi^2=49.3$, $p<0.001$ and $chi^2=41.7$, $p<0.001$ respectively).

Follow-up Mann-Whitney tests showed that the ASD group scored less than the SPD and CM groups on positive symptoms ($Z=-3.34$, $p=0.01$; $Z=-3.7$, $p<0.001$ respectively). With respect to negative symptoms, there was no difference between the ASD and SPD group ($Z=-0.82$, $p=0.41$); however the CM group scored significantly more than the SPD group ($Z=-2.0$, $p=0.04$) and showed a trend towards a significantly higher score than the ASD group ($Z=-1.7$, $p=0.09$).

Social Cognition

The results for the out of scanner social cognition tasks are summarised in Table s1 in the supplement.

In the Ekman 60, there were no significant differences between the ASD, SPD and CM groups on any measure. The ASD group identified significantly fewer angry faces correctly than the controls ($p=0.002$), while the ASD, SPD and CM groups all identified significantly fewer fearful faces correctly than the controls (all $p<0.05$). A significant positive relationship was seen across the groups between IQ and anger recognition ($p<0.001$) suggesting differences in this measure may relate to IQ differences between the groups; no such relationship was seen for fear.

In the Social Judgements Task, the ASD, SPD and CM groups did not differ significantly from each other on any of the measures. The ASD and SPD groups both scored significantly less than the controls on judgements of approachability, attractiveness, distinctiveness and intelligence (all $p<0.05$). The CM group scored significantly less than controls on judgments of age and distinctiveness ($p<0.02$ for

both). IQ correlated positively with scores on age and distinctiveness (p=0.01 and p=0.03 respectively), suggesting differences in these measures may relate to IQ differences between the groups.

Functional MRI

Two individuals from the ASD group, one from the SPD group and one from the CM group did not participate in the imaging component due to fear of the scanner environment. Two individuals (one control, one ASD) were excluded due to technical issues such that meaningful data were not recorded. Finally, one individual with ASD was excluded due to imaging artefacts. Table s2 (Supplement) contains the details of those included in the scanning study.

Task performance and within group analyses

Details of in-scanner performance in the task and the within group analyses are in the Supplement (Table s3–s6 and Figure s1– s5). Within the whole study group combined, greater activations were found in the social compared to the gender condition in many regions previously associated with social brain function: inferior frontal gyri, medial prefrontal cortex, left anterior temporal lobe, left superior temporal sulcus, occipital gyri and the cerebellum. No regions showed greater activation in the gender versus the social condition.

ASD, SPD, CM versus Controls

There were no significant group x condition interactions in the ASD, SPD or CM versus control comparisons. However, in the ASD versus control comparison, two

trends towards significant group x condition interactions were observed, with the ASD group showing less increase in activation than the controls during the social condition compared to the gender condition in the posterior cerebellum bilaterally (cluster peaks (30 -58 -44), p=0.05; and (-45 -55 -41), p=0.07; (Table s7 and Figure s6 in Supplementary Material).

ASD versus SPD

A significant group x condition interaction was seen for the ASD versus SPD comparison. The SPD group showed significantly greater activation compared to the ASD group when making social compared to gender judgements in a voxel in the amygdala and in three clusters: the right posterior cerebellum, extending into the fusiform and inferior temporal gyri; the left posterior cerebellum; and the left intraparietal sulcus extending through the medial portions of the temporal gyri into the fusiform gyrus. For each of these regions the controls lay between the ASD and the SPD groups (Figures 2-3, Table s8 and Figure s7 in Supplement).

Due to recent concerns expressed about the possibility of false positives due to the use of cluster based statistics in resting state fMRI,[55] we also examined data for this comparison using voxel based inference with a height threshold of $p<0.05$ FWE corrected, which has not been found to show the same concerns.[55] In this case, in addition to the significant voxel in the amygdala, we identified significant voxels in the right cerebellum at the same location as in our main analysis (Z=4.54, p=0.03) and in the right inferior frontal gyrus (MNI = 51 35 25, Z=4.5, p=0.03).

INSERT FIGURE 2 ABOUT HERE

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ASD versus CM

A significant group x condition interaction was observed in the ASD versus CM contrast. During the social condition compared to the gender condition the CM group showed significantly greater increases in activation than the ASD group in left pre- and post-central gyri and right cerebellum (Table s9).

SPD versus CM

There were no significant group x condition interactions for the SPD versus control contrast.

Analysis of confounding factors

No significant relationships were seen between fMRI activations and IQ, antipsychotic use or within-scanner task performance suggesting that results are not confounded by these factors. To further explore the effects of antipsychotic medication on the fMRI results, the ASD versus SPD analysis was repeated after omitting those taking antipsychotic medication. In this analysis, greater activation was seen in the SPD then in the ASD group in the cerebellum bilaterally and in a new cluster in the ventromedial prefrontal cortex (Table s10–s11 and Figure s8 in Supplement).

Exploratory Symptom Analysis

A significant group x symptom interaction (p= 0.04) was seen for positive symptoms when regressed against the extracted value from the left amygdala (-18 -10 -14). The ASD group showed a significant negative relationship between positive symptom score and activation change during the social compared to the gender condition (r=-50, p=0.01) which was similar to the relationship in the CM group but different from the positive relationship in the SPD group (Figure s9a in Supplement). A significant group x symptom interaction (p= 0.01) was also seen for negative symptoms and the extracted value from the frontal cluster identified in the ASD < CM contrast (-18 -19 49). For this cluster the CM group showed a significant positive relationship with negative symptoms (r=0.76, p=0.02) while the SPD group showed a trend towards a significant negative relationship (r=-0.43, p=0.06) (Figure s9b in Supplement).

Analysis of gender versus baseline condition

Analyses of the extracted gender versus baseline eigenvariates showed significantly increased activation in the ASD group in the left amygdala (-18 -10 -14) compared to the SPD and control groups (p=0.003 and 0.01 respectively) and the left postcentral gyrus cluster (-18 -19 49) compared to the CM and control groups (p=0.02 and p=0.004 respectively). There were no instances of the SPD or CM groups showing greater activation than the other groups in the gender versus baseline analysis.

Discussion

To our knowledge this is the first study directly comparing ASD and SPD using fMRI. The clinical groups all showed similar patterns of impairment compared to controls in negative symptoms and the social cognition tests, but clear differences were seen between the ASD and SPD groups using fMRI during the social judgement task. Differences between the ASD and SPD groups were also seen in the relationship between amygdala activation and positive symptoms. Our findings demonstrate that apparently similar clinical and neuropsychological features may be associated with quite distinct underlying brain mechanisms.

Although this is the first fMRI study comparing ASD and SPD, our findings are consistent with the three previous imaging studies which compared ASD and schizophrenia. Pinkham et al[42] reported greater activation in right amygdala and left ventrolateral prefrontal cortex in non-paranoid individuals with schizophrenia compared to people with ASD during a trustworthiness judgement. In addition, a meta-analysis combining various mentalizing tasks showed greater activation in people with schizophrenia compared to those with ASD, albeit in different brain regions than we identified.[56] Pinkham et al also reported qualitatively different factors underlying paranoia in ASD and schizophrenia,[57] consistent with the opposing correlations between amygdala activation and positive symptoms that we report. This is also in keeping with a study showing that psychosis in autism was associated with different structural brain changes than psychosis alone.[58]

Recently, Ciaramidaro et al[41] identified opposing patterns of brain activation in ASD and schizophrenia during intentionality assessment. Specifically, using stimuli which

didn't require the assessment of intention they identified hyperactivation in schizophrenia compared to controls in VMPFC and left posterior superior temporal sulcus. In contrast, using stimuli requiring an assessment of intention they found hypoactivation in the right posterior superior temporal sulcus in ASD. Similarly, Eack et al also identified increased ventromedial prefrontal and temporo-parietal junction activity in patients with schizophrenia compared to those with ASD during a visual perspective taking task.[43] These findings are comparable to ours in that we also found opposing patterns of activation between groups in left temporoparietal regions and in the VMPFC, although the latter was only apparent in unmedicated individuals. However, Ciaramidaro et al's findings also differ from ours in that they identified hyperactivation to a non-intentional stimulus in the schizophrenia group, whereas our findings are limited to explicit social judgements (i.e. hyperactivation in the SPD group was not seen in the gender versus baseline analysis). This disparity between studies could relate to task differences, or to the difference between schizophrenia and SPD. It is possible that in people with SPD, this hyperactivation is limited to explicit social judgments, as opposed to also being inappropriately present during non-social judgements in schizophrenia.[41, 59] This may represent the mechanism by which individuals with SPD are spared some of the more severe symptomatology associated with schizophrenia.

We found hyperactivation in SPD compared to ASD in two regions we previously found to be activated in controls using the same task: the amygdala and the cerebellum. The amygdala has a range of functions in socio-emotional processing which include the detection of threat,[60] so the increase in activation may represent an exaggeration of this response in SPD; with a relatively reduced response to such

stimuli in the ASD group. However, we have previously found that the amygdala is activated by both affective and non-affective judgements, suggesting that the hyperactivation observed here may relate to a broader role of the amygdala in inferring the traits of others.[46] Consistent with this, a recent meta-analysis found that activations in posterior cerebellum, which overlap strongly with those identified here, are also associated with tasks requiring participants to draw inferences about traits of others.[61]

We also identified increased activation in participants with SPD compared to those with ASD in the fusiform gyrus, a region strongly associated with face processing.[62] On the left side we also identified a cluster in the intraparietal sulcus extending through the temporal gyri, including the superior temporal sulcus. The intraparietal sulcus and the superior temporal sulcus are known to be involved in assessing the intent of others,[63, 64] although more usually in the context of biological motion perception. Interestingly, increased activity in these regions has been reported in people with schizophrenia compared to controls when making judgements of a non-social, but not a social, nature[59] and was also identified as hyperactive in schizophrenia compared to ASD by both Ciaramidaro et al[41] and Eack et al.[43]

Although we did not identify clear group differences between either the ASD or SPD groups and the controls, results in the controls tended to lie between the two clinical groups, as did the findings for the CM group (Figures 2 and 3). Given this, and the above, we suggest that our findings are consistent with the hypo- and hyper-mentalizing theory of ASD and schizophrenia.[36-38] Further evidence for distinct patterns of pathophysiology comes from our finding that increased activation in the

left amygdala is associated with increased positive symptoms in SPD, whereas the reverse is true in ASD. These opposite patterns of correlation are consistent with the hypo- and hyper-mentalising theory of the autism and schizophrenia spectrums with the SPD group developing psychotic symptoms due to over-activation of amygdala, whereas the ASD group develop such symptoms due to under-activation of this region. It should be noted however that we made no attempt to correct for multiple comparisons for these exploratory analyses and therefore further research is required to confirm the differential symptom-function relationships which we report. At present however, our results are in keeping with the idea that the schizophrenia and autism spectrums represent diametrical disorders of brain development, at least in regard to social cognition.[36, 39, 40] Future studies investigating brain activation during other aspects of brain function known to be impaired in both conditions are required to determine if similar patterns are seen for other cognitive domains

Irrespective of the exact nature of the underlying process, the differences we report carry important implications for clinical practice and classification. In particular it is important to note that clinical phenotypes can appear similar but arise from very different mechanisms and may therefore require quite different treatment approaches. This raises the prospect of developing treatments targeted at mentalizing styles, as opposed to clinical symptoms, an idea in keeping with the RDoC proposals.[65] These findings also highlight the importance of considering SPD as a differential diagnosis for ASD and vice versa; it is therefore important that diagnostic services where these conditions may be met, especially those working with adults, contain access to skilled professional assessment of both sets of disorders.

We also identified people who met criteria for both ASD and SPD. This is consistent with previous work which reported that 23% of people with ASD met criteria for SPD.[32] These 'comorbid' individuals were more symptomatic than those with either condition alone, highlighting the importance of their identification. Interestingly, the fMRI findings for the CM group showed differences compared to the ASD group suggesting that they do not simply suffer from severe ASD. In contrast, there were no significant differences between the CM and SPD groups, which may indicate that they have a form of SPD. However, the numbers in this group are small making it difficult to draw firm conclusions. It is also possible that the definition of the CM group is reflective of the diagnostic tools that we employed and that more detailed clinical investigation could allocate members of this group more confidently into either one category or the other.

A number of limitations of the current study merit mention. The sample size is relatively small, especially the CM group, and a larger population may have identified more subtle differences. IQ differences were apparent between the groups, although the lack of correlation between IQ and the fMRI results suggests that this did not confound the results. In addition, ASD diagnoses were based upon DSM-IV criteria, and confirmed using the ADOS; we would ideally also have included a standardised developmental history but this was not practicable in this adult sample. In terms of the image analysis, the choice of threshold for our fMRI may be considered to be quite lenient raising the risk of type I error; however, we note that some differences between the groups were still apparent using the more stringent[55] voxel based inference. Finally, it is likely that the gender judgement condition, although intended

to remove non-affective face processing related activations, also contained an element of implicit social judgements, which may have reduced the differences between our groups when compared to the explicit judgement of approachability. The addition of a gender judgement using neutral stimuli with no affective content would perhaps have revealed greater differences between the groups

Notwithstanding these limitations, we report marked overlaps between ASD and SPD in negative symptoms and social cognitive difficulties, but significant differences on examination of social brain activity using fMRI, consistent with the idea that these superficially similar conditions are associated with distinct underlying mechanisms.

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Table 1: Participant characteristics

	ASD	***SPD***	***CM***	***Controls***
N	28	21	10	33
M:F	22:6	14:7	7:3	23:10
Age	39.5 (11.6)	37.1 (9.2)	34.9 (9.9)	36.5 (9.3)
Handedness	27:1	19:2	8:2	31:2
Yrs. education	16.2 (1.7)	15.2 (2.0)	16.2 (2.3)	16.5 (1.9)
*Full-scale IQ**	113.1 (17.3)	106.4 (10.7)	103.5 (22.5)	118.1 (9.9)
*Antipsychotic use (yes:no)**	2:26	5:16	3:7	0:33

*differed significantly between groups ($p<0.05$)

Figure Legends

Figure 1: Median PANSS positive and negative symptom scores

Error bars represent 95% confidence intervals

Figure 2: Clusters projected onto a rendered brain demonstrating regions of greater increase in activation in SPD compared to the ASD group using the social > gender contrast in: (A) left temporo-parietal cluster (-24 -52 31); (B) left cerebellum (-15 -40 -38); (C) right cerebellum (33 -64 -44). All clusters were significant at an initial height threshold of $p<0.005$ uncorrected with a cluster significance of $p<0.05$ FWE corrected. Graphs underneath show difference values of extracted eigenvariates for each cluster.

Figure 3: Location of peak voxel (p=0.03 FWE corrected) of increased amygdala activation (-18 10 14) and graph of difference values of extracted eigenvariates for social > gender contrast in SPD versus ASD.

Supplementary Material

Image Acquisition and Preprocessing

All participants were scanned on a 1.5T GE Medical Systems Signa Scanner (GE Medical, USA). Axial, gradient-echo planar images (EPI) were acquired with repetition time (TR) of 2.5s, echo time (TE) of 40ms, matrix 64 x 64, field of view (FOV) of 240mm x 240mm and flip angle of 90 degrees. Thirty contiguous 5mm slices were acquired in an interleaved fashion within each TR. A T1 structural image was obtained using an MPRAGE sequence: 180 contiguous 1.2mm thick coronal slices were obtained in an interleaved fashion (TR 9.7ms, TE 4.0ms, matrix 192 x 192, FOV 240mm x 240mm, flip angle 8 degrees).

Image data were converted to NIfTI format and preprocessed using Statistical Parametric Mapping 8 software (SPM8 – www.fil.ion.ucl.ac.uk/spm/) running in MATLAB 2011b (The MathWorks, Inc). In each task the first four volumes of each run were discarded to avoid T1 equilibrium effects. The images were realigned to the mean EPI image and co-registered to the T1 structural image for each participant. The T1 and the functional images were then normalised to the standard Montreal Neurological Institute (MNI) template with a voxel size of 3mm x 3mm x 3mm and the functional images smoothed using an 8mm full width at half maximum Gaussian kernel.

Summary of Social Cognition Results

	ASD(1)	*SPD(2)*	*CM(3)*	*Controls(4)*	*Between group differences*
Ekman 60					
Anger	8 (1.5)	8 (2)	8 (3)	9 (1)	1<4*
Disgust	8 (4)	8 (2.5)	8 (2)	8 (2)	
Fear	6.5 (4)	6 (3.5)	7 (4)	8 (2)	1,2,3<4**
Happiness	10 (0)	10 (0)	10 (0)	10 (0)	
Sadness	7 (3)	8 (2)	8 (2)	8 (2)	
Surprise	8.5 (3)	9 (3)	9 (1)	9 (2)	
Social judgements					
Age	31 (1.5)	31 (2)	30 (2)	31 (1)	3<4**
Approachability	24.5 (8.5)	26 (8.5)	27 (9)	29 (5)	1,2<4**
Attractiveness	26.5 (6.5)	26 (5)	28 (3)	29 (3)	1,2<4**
Distinctiveness	23 (3.5)	22.5 (6.5)	21 (5)	25.5 (3.5)	1,2,3<4**
Intelligence	26 (4)	27 (6.5)	28 (3)	28 (3)	1,2<4**
Trustworthiness	25.5 (4)	23.5 (7)	24 (5)	25.5 (4)	

Table s1: Median (IQR) scores for each group for Ekman 60 and social judgement tasks

*p<0.01; **p<0.05

Participant Characteristics for Imaging Component

	ASD	*SPD*	*CM*	*Controls*
N	24	20	9	32
M:F	19:5	14:6	6:3	22:10
Age	40.5 (11.9)	37.3 (9.4)	35.8 (10.0)	36.6 (9.5)
Handedness	23:1	18:2	7:2	30:2
Yrs. education	16.4 (1.6)	15.4 (2.0)	16.1 (2.4)	16.4 (2.0)
*Full-scale IQ**	113.9 (17.1)	106.4 (10.7)	102.4 (23.6)	117.9 (10.0)
*Antipsychotic use (yes:no)**	2:22	5:15	3:6	0:32
*CPZ equivalents**	0 (50)	0 (25-200)	0 (25-400)	0(0)

Table s2: Characteristics of participants for fMRI study.
*differed significantly between the groups

Participant performance during fMRI approachability task
The mean scores for in-scanner performance for each group were: ASD=27.8, SPD=27.3, CM=29.4 and controls=30.7. Although these differences were not significant overall (F=1.9, p=0.13) there was some evidence that the ASD and SPD groups were more impaired than controls (p=0.06 and p=0.04 respectively).

fMRI analysis: main effect of condition

The main effect of condition shows the activation for the social versus gender contrasts when all four groups are considered together.

Significantly greater activation was found during the social > gender contrast bilaterally in the inferior frontal gyrus, superior medial prefrontal gyrus, insula, temporal poles, occipital regions and posterior cerebellum as well as in the left temporoparietal junction and right amygdala (Table s3 and Figure s1). No significant clusters were seen for the reverse contrast.

Locations of cluster peaks	**MNI of peak**			**Extent**	**P_{FWE}**	**Z_{peak}**
Social > Gender						
L inferior frontal gyrus - p orbitalis and p triangularis	-54	32	-2	218	0.01	3.99
R. inferior frontal gyrus - p triangularis	51	29	-5	237	0.01	4.57
L. & R. superior medial gyrus	-9	-32	58	1121	<0.001	5.88
L. ant. inferior temporal gyrus	-48	2	-35	146	0.048	5.11
L. post. middle temporal gyrus	-57	-43	1	346	0.002	4.43
L. & R. calcarine gyrus	-9	-85	1	1953	<0.001	∞
L. cerebellum	-39	-67	-44	245	0.009	5.74
R. amygdala	15	-4	14		0.01 ^{SVC}	3.52
Gender > Social						
No significant clusters						

Table s3: Brain activations during social versus gender contrast across all groups
Significance values reported are cluster values FWE-corrected for whole brain volume unless indicated using ^{SVC} when significance is reported at voxel level FWE corrected for amygdala volume; L. = left; R. = right; ant. = anterior; post. = posterior

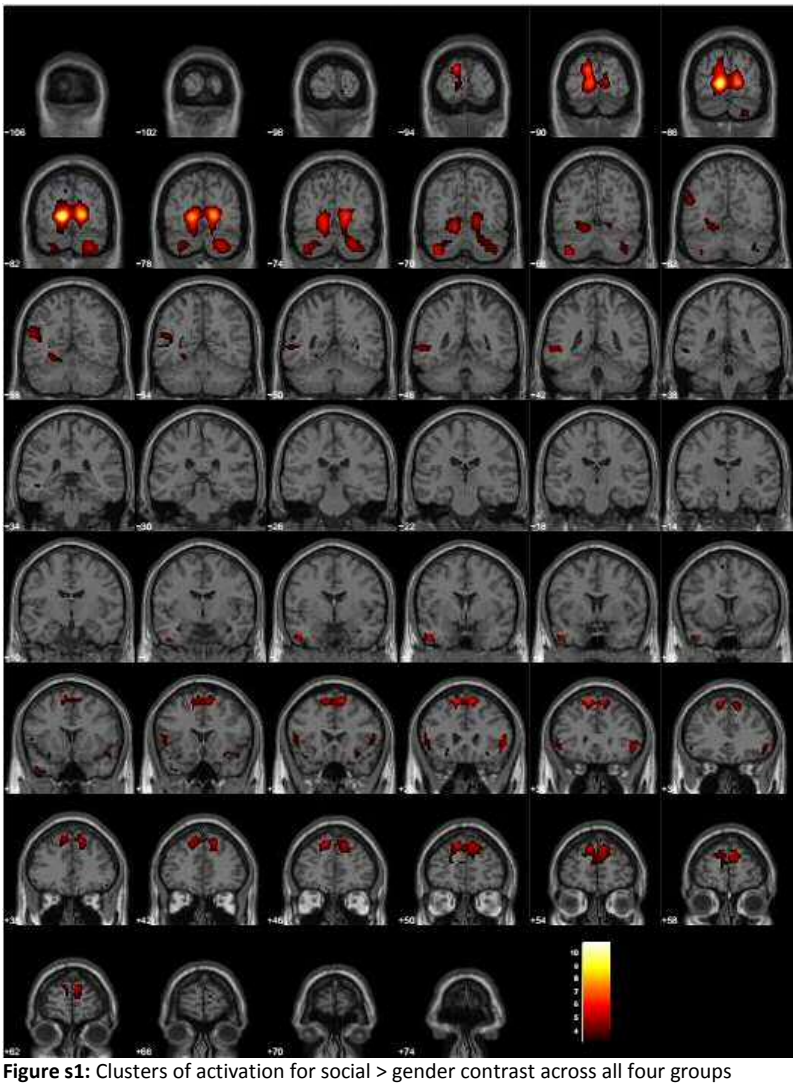

Figure s1: Clusters of activation for social > gender contrast across all four groups
No significant clusters were seen for gender > social

fMRI analysis: Within group activations

Within Controls

Locations of cluster peaks	MNI of peak			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L. & R. superior medial gyrus	9	32	58	183	0.02	4.19
L. & R. superior medial gyrus	12	56	34	202	0.02	3.76
L. & R. lingual gyrus	12	-82	1	472	<0.001	5.86
L. cerebellum - VIIa Crus II	-36	-70	-44	201	0.02	4.24
R. cerebellum - VIIa Crus II	30	-82	-44	114	0.09	3.97
Gender > Social						
No significant clusters						

Table s4: Brain activations during social versus gender contrast for control group

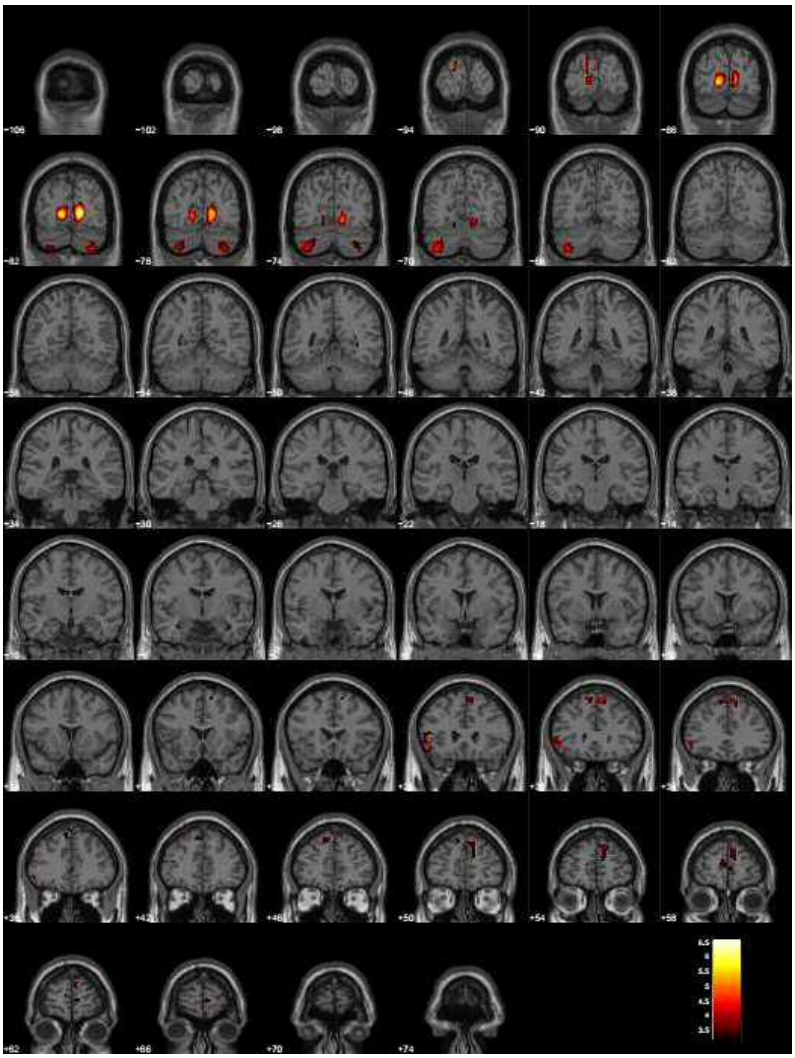

Figure s2: Activations within control group for social > gender contrast
No significant clusters were seen for gender > social

Within ASD group

Locations of cluster peaks	MNI			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L. calcarine gyrus	-9	-85	4	118	0.08	5.77
Gender > Social						
No significant clusters						

Table s5: Brain activations during social versus gender contrast for ASD group

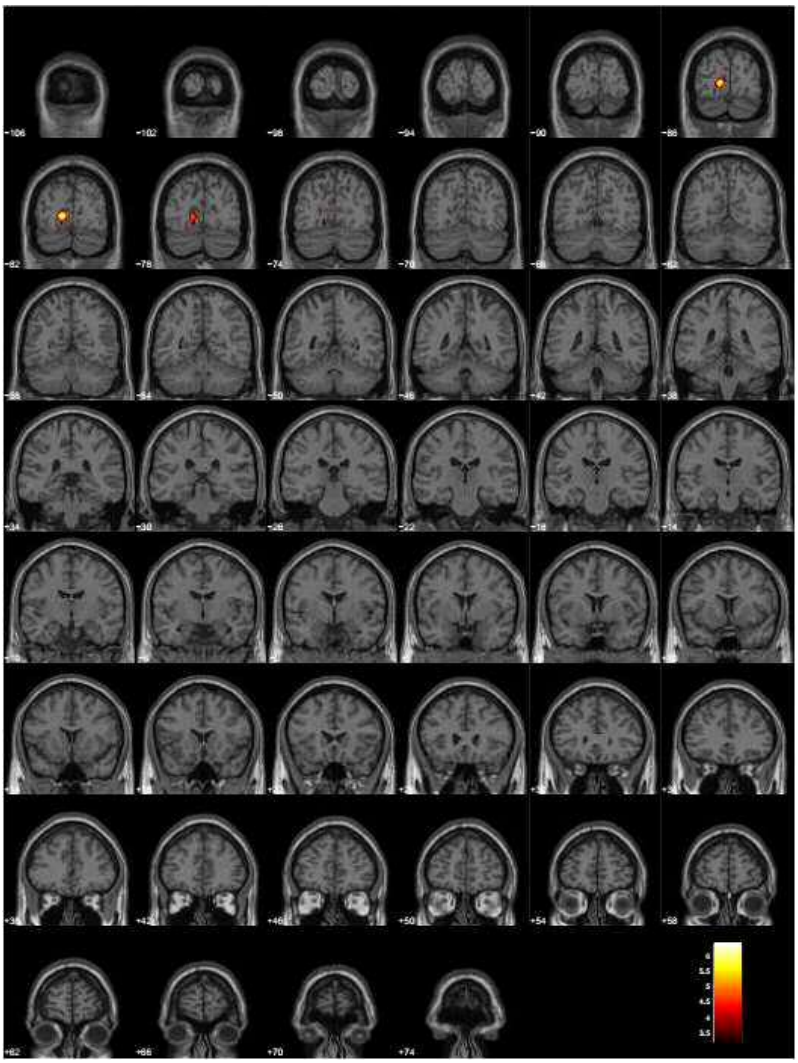

Figure s3: Activations within ASD group for social > gender contrast
No significant clusters were seen for gender > social

Within SPD group

Locations of cluster peaks	**MNI of peak**			**Extent**	**P_{FWE}**	**Z_{peak}**
Social > Gender						
L. superior frontal gyrus	-12	32	58	233	0.01	4.48
L. & R. superior medial gyrus	-6	56	34	155	0.04	4.33
L. inferior frontal gyrus - p. orbitalis and p. triangularis	-54	17	4	200	0.02	4.6
R. inferior frontal gyrus - p. triangularis	51	35	25	232	0.01	5.52
L. inferior temporal gyrus	-48	-1	-38	135	0.06	4.61
L. middle temporal gyrus	-63	-40	1	110	0.096	4.68
L. & R. calcarine gyrus	-9	-85	1	2422	<0.001	5.62
L. caudate & pallidum	-15	5	-5	136	0.058	3.86
L. hippocampus	-3	-25	-26	139	0.054	4.49
R. amygdala	15	-4	-14		0.02^{SVC}	3.38
Gender > Social						
No significant clusters						

Table s6: Brain activations during social versus gender contrast for SPD group

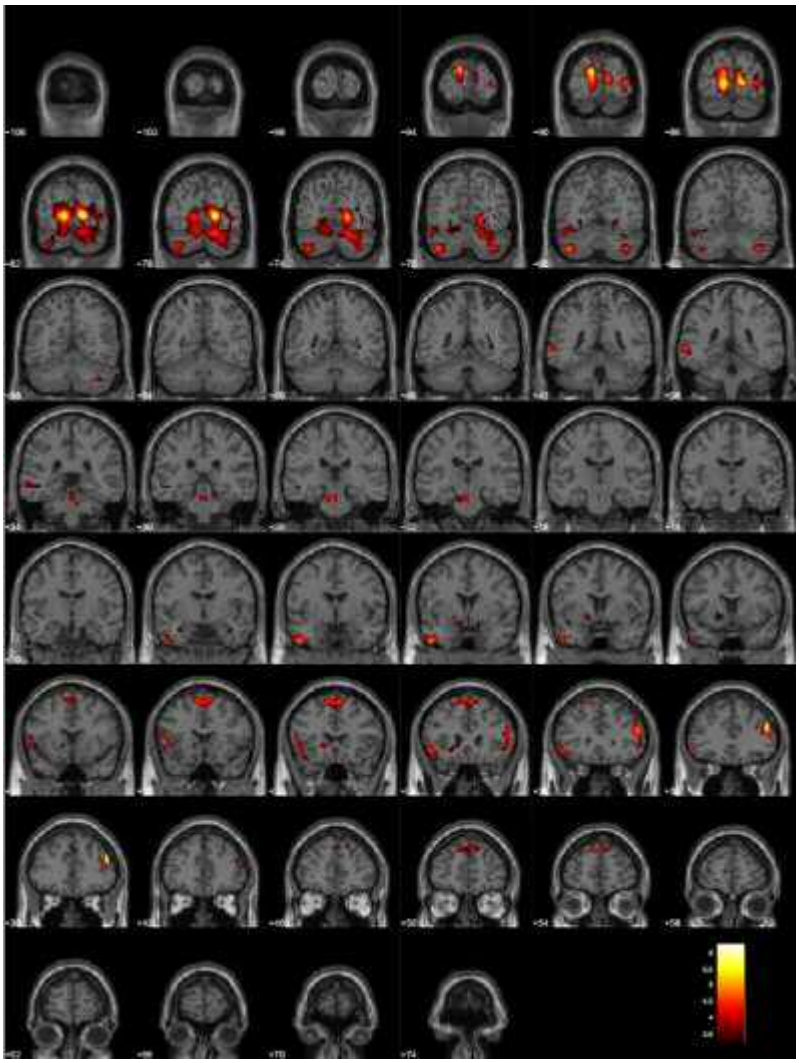

Figure s4: Activations within SPD group for social > gender contrast
No significant clusters were seen for gender > social

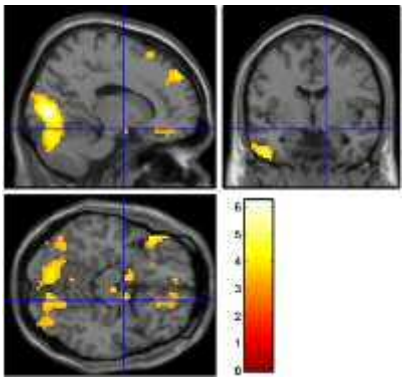

Figure s5: Location of right amygdala activation (MNI: 15 -4 -14) within SPD group for social > gender contrast

Within CM group
No significant regions of activation were seen in the CM group in either the social > gender or the gender > social contrast.

fMRI analysis: Group x condition interaction between ASD and control groups

Locations of cluster peaks	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > Control						
No significant clusters						
ASD < Control						
R. cerebellum - VI, VIIa Crus I and II	30	-58	-44	126	0.050	4.16
L. cerebellum - VI, VIIa Crus I and II	-45	-55	-41	329	0.07	3.52

Table s7: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and control groups

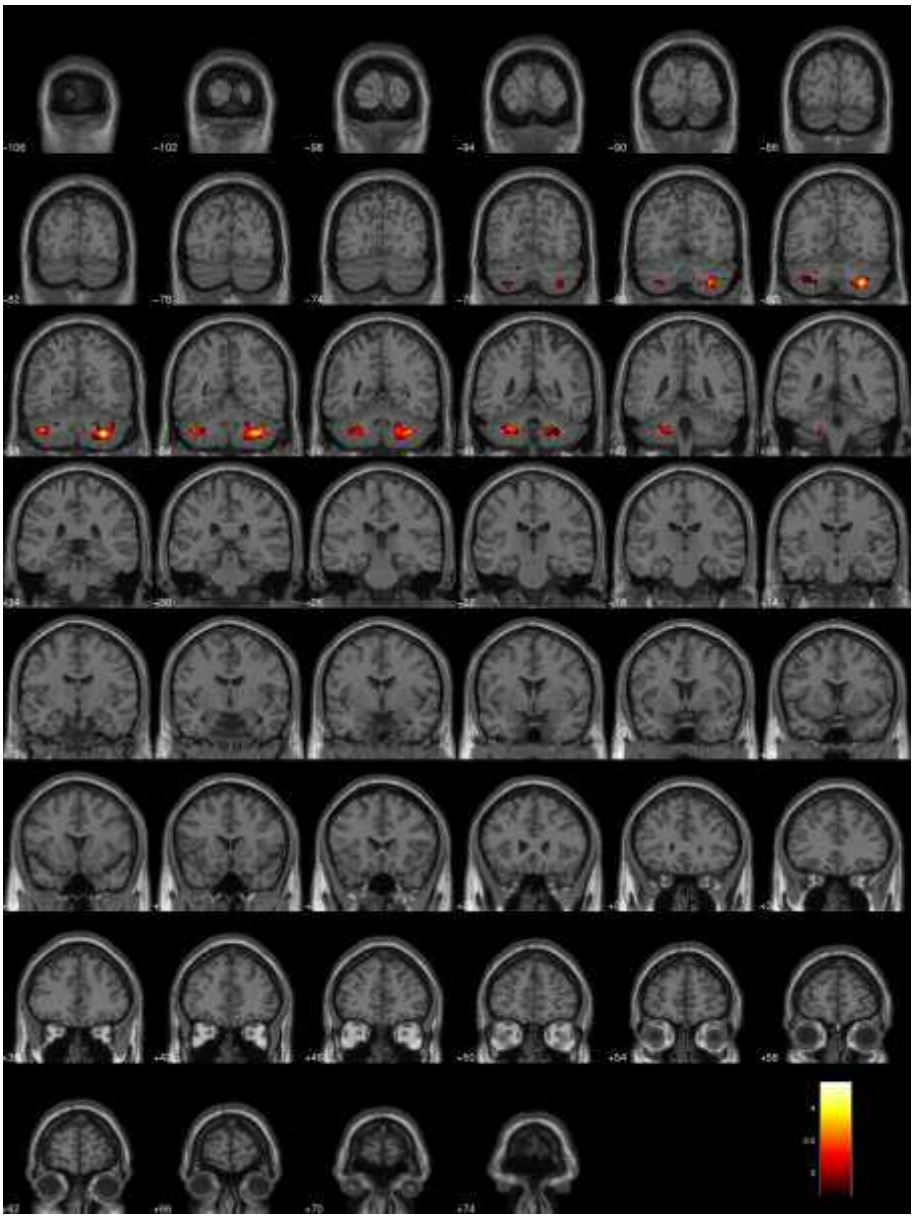

Figure s6: Clusters showing less increase in activation in the ASD group compared to controls in the social > gender contrast.

fMRI analysis: Group x condition interaction between ASD and SPD groups

Location of cluster peaks	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > SPD						
No significant clusters						
ASD < SPD						
L. intraparietal sulcus	-24	-52	31	403	0.04	3.55
L. cerebellum - anterior, VI, VIIa Crus I&II, VIIb	-15	-40	-38	652	0.005	4.18
R. cerebellum - VI, VIIa Crus I, VIIIb	33	-64	-44	1554	<0.001	4.54
L. amygdala	-18	-10	-14		0.046^{SVC}	3.00

Table s8: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and SPD groups.

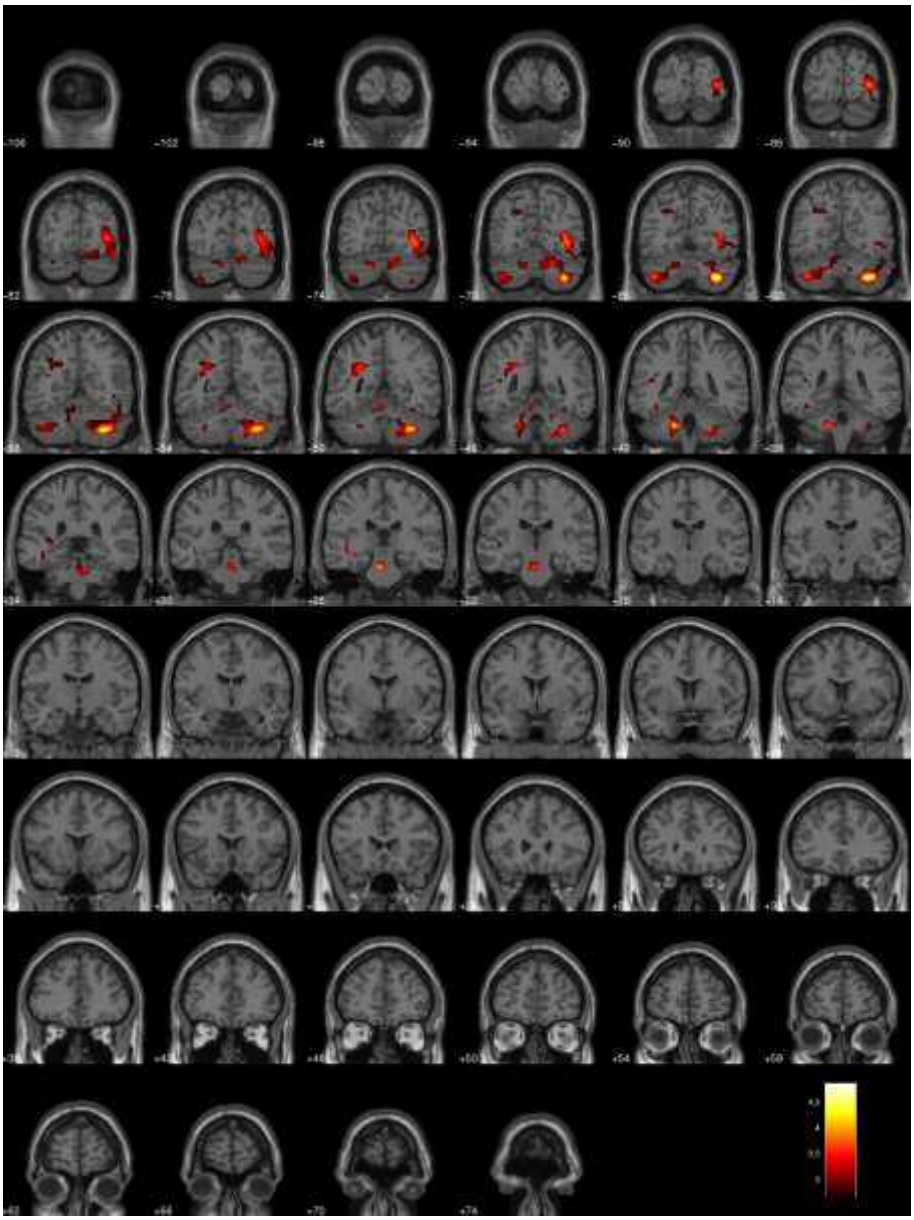

Figure s7: Clusters showing greater increase in activation in the SPD group compared to the ASD group using the social > gender contrast

fMRI analysis: Group x condition interaction between ASD and CM groups

Locations of cluster peaks	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > CM						
No significant clusters						
ASD < CM						
L. postcentral gyrus	-18	-19	49	844	0.001	3.94
R. cerebellum (VI, VIIa, VIIb)	24	-55	-41	404	0.04	3.84

Table s9: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the CM and the ASD groups.

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fMRI analyses incorporating only participants naïve to antipsychotic medication

	ASD	*SPD*	*CM*	*Controls*
N	22	15	6	32
M:F	18:4	9:6	5:1	22:10
Age	41.2 (11.9)	37.5 (8.9)	35.9 (10.7)	36.6 (9.5)
Handedness	21:1	13:2	5:1	30:2
Yrs. education	16.5 (1.5)	15.8 (1.9)	16.5 (2.3)	16.4 (2.0)
Full-scale IQ	115.0 (17.1)	103.5 (10.7)	102.5 (23.6)	117.9 (10.0)

Table s10: Participant characteristics for individuals who were antipsychotic naïve

For the ASD versus SPD analysis, the cluster in the right cerebellum remained significant and stretched across the midline into the left cerebellum, and a new significant cluster in the ventromedial prefrontal cortex (VMPFC) extending into the left putamen was found to be significantly more activated in the SPD group than the ASD group when making social as compared to gender judgements (Table s11 and Figure s8)

Locations of cluster peaks	**MNI of peak**			**Extent**	**P_{FWE}**	**Z_{peak}**
ASD > SPD						
No significant clusters						
ASD < SPD						
R & L superior orbital gyri	18	35	-17	470	0.02	3.80
R. cerebellum - VI, VIIa Crus I, VIIIb L. cerebellum - VI, VIIa Crus I and II	33	-64	-44	438	0.03	3.87

Table s11: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and SPD groups when only antipsychotic naïve participants included

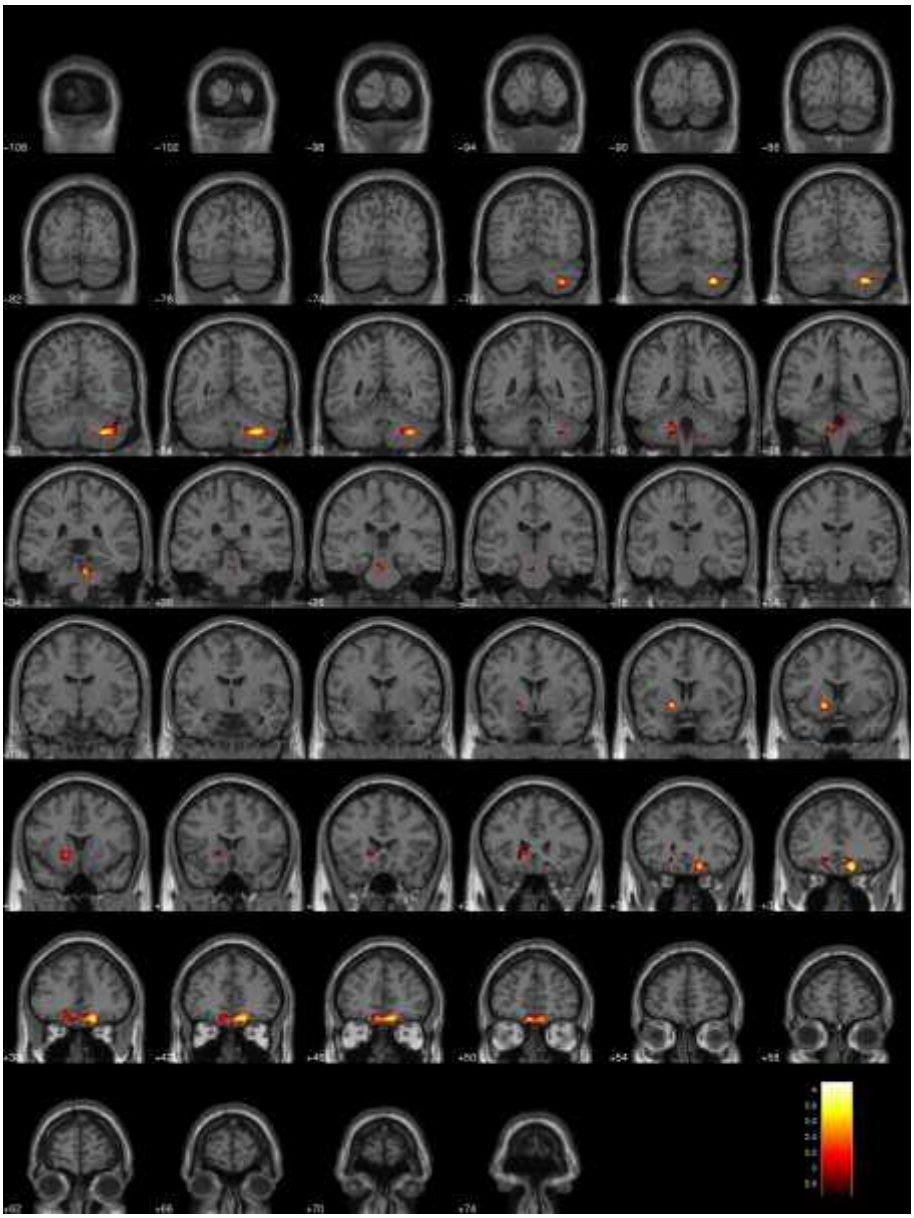
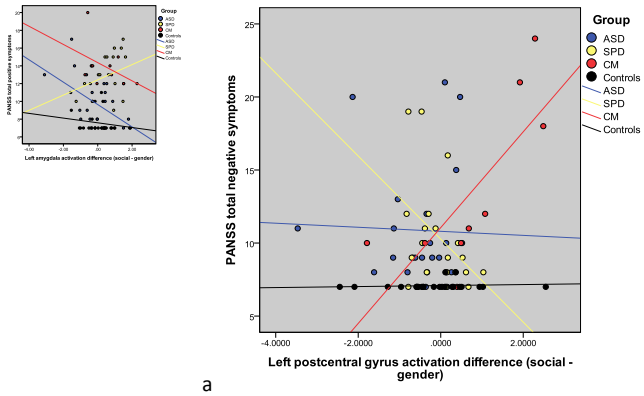


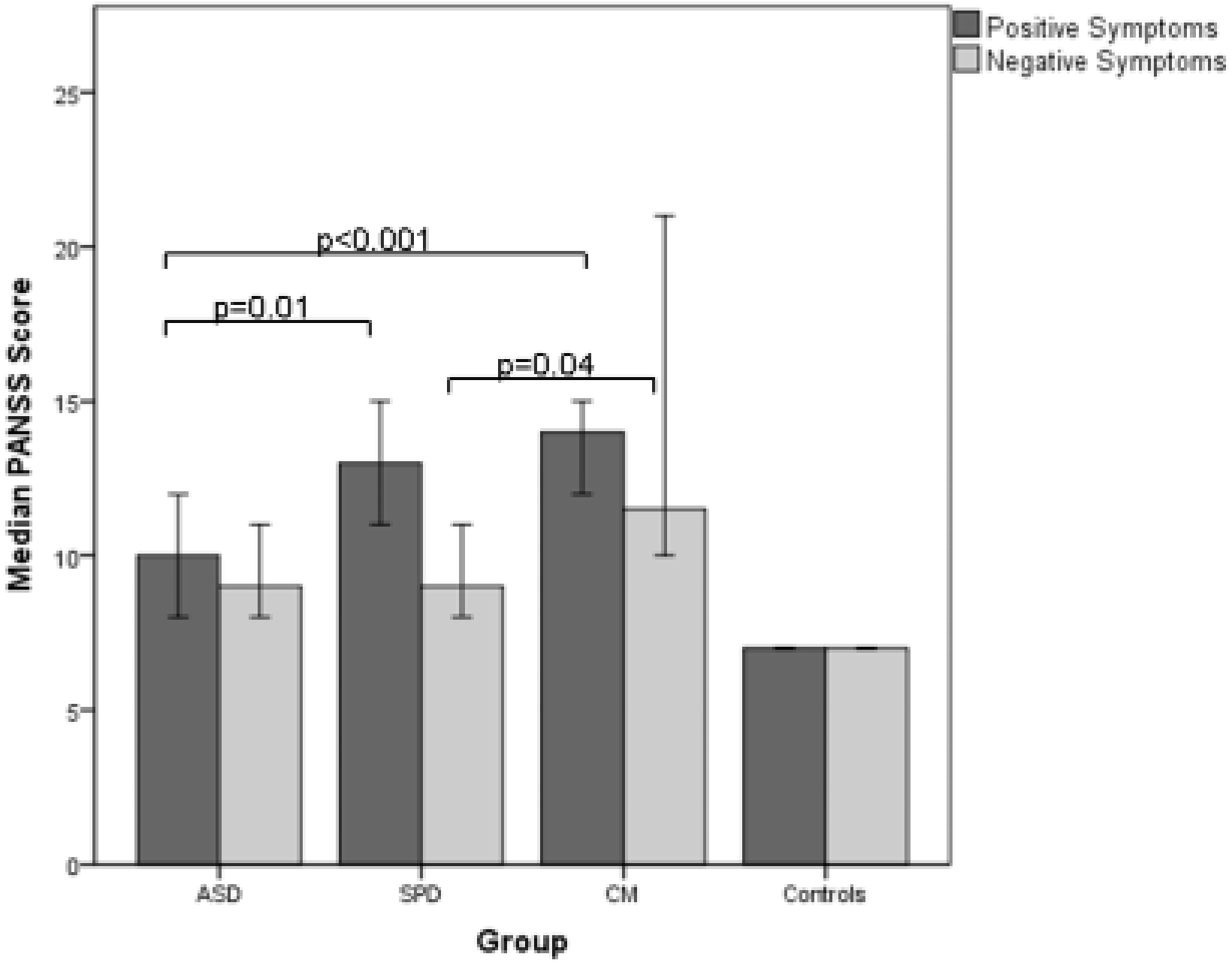
Figure s8: Clusters showing greater increase in activation in the SPD group compared to the ASD group using the social > gender contrast in antipsychotic naïve participants only

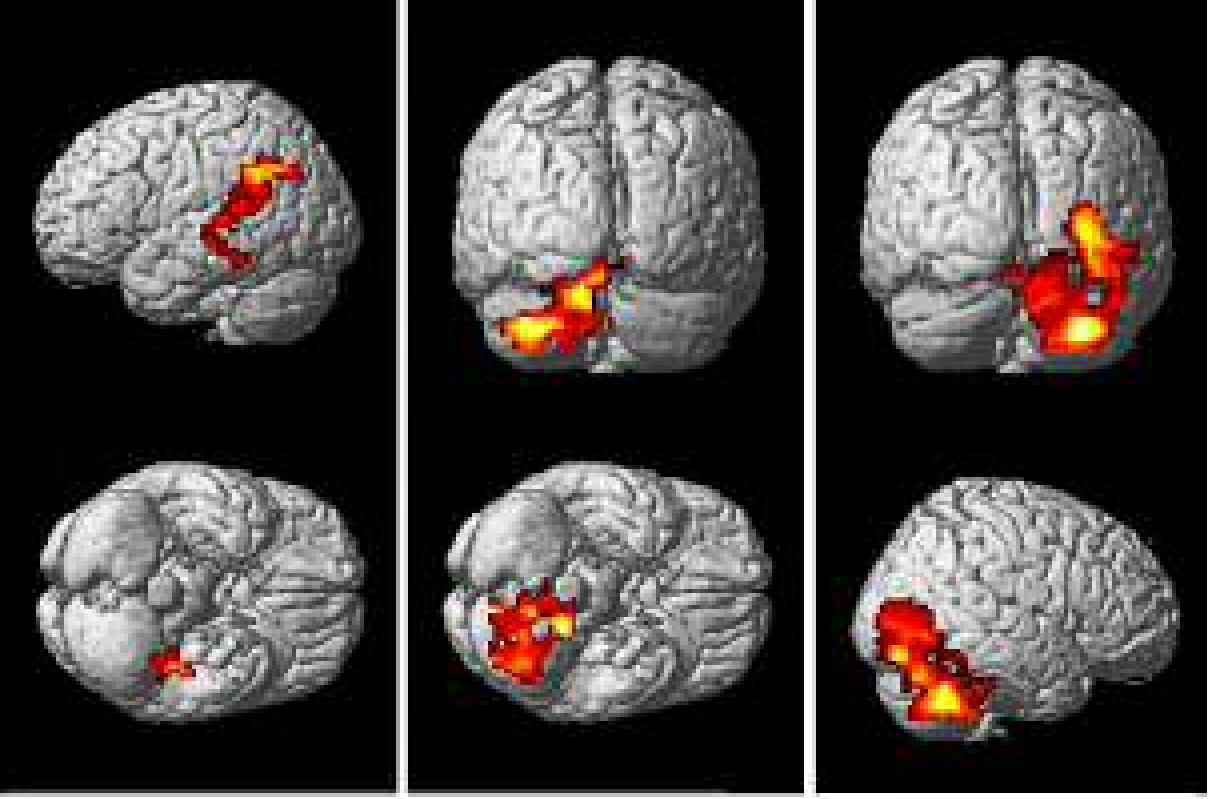
Exploratory Symptom Analysis

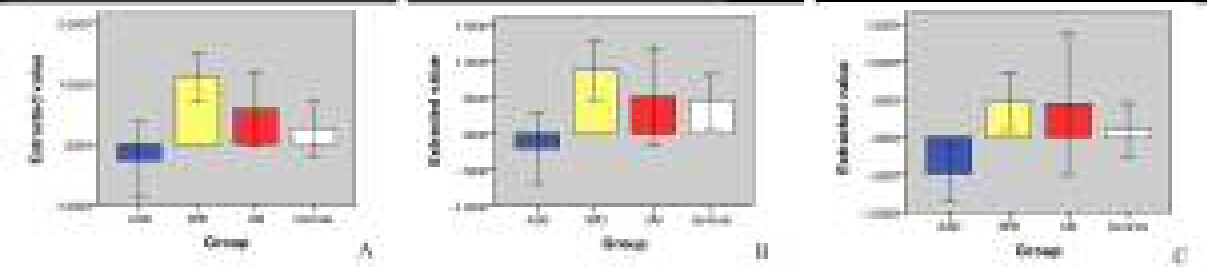


a b

Figure s9: Relationship between (a) left amygdala activation and positive symptoms; and (b) left postcentral gyrus activation and negative symptoms


Positive Symptoms
Negative Symptoms
Median PANSS Score
25
20
15
10
5
0
p<0.001
p=0.01
p=0.04
ASD
SPD
CM
Controls
Group

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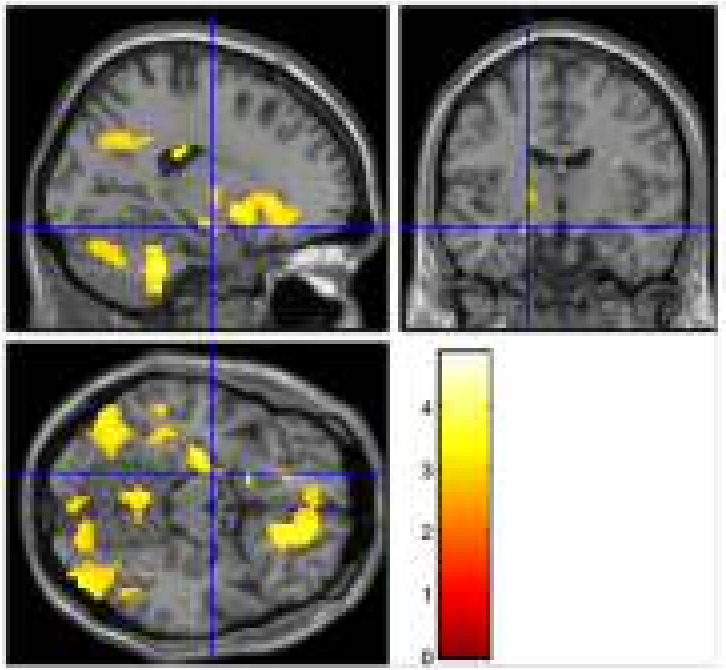
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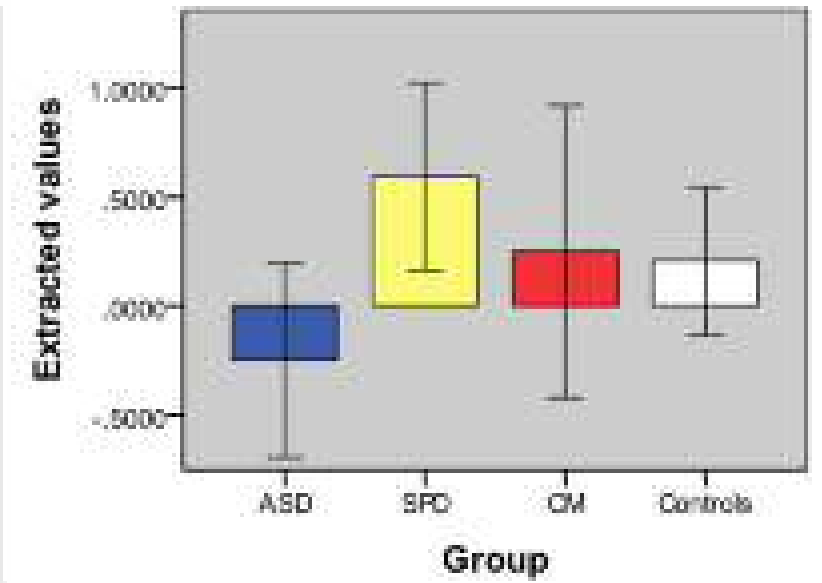
Extracted values
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ASD
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